

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Elosulfase alfa for treating mucopolysaccharidosis type IVa

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using elosulfase alfa in the context of national commissioning by NHS England. The Highly Specialised Technologies Evaluation Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this evaluation (see section 10) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Evaluation Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the Committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of elosulfase alfa in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

- If the technology were to be recommended, would an extension to the normal period of guidance implementation be appropriate? That is, given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 6.1), would an extension be needed because any of the following circumstances apply?
 - The health technology cannot be appropriately administered until training is in place?
 - The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?
 - The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?
- If so, please specify the reasons and an estimate of the time period within which the recommendation could be complied with.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Evaluation Committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final evaluation determination (FED).
- Subject to any appeal by consultees, the FED may be used as the basis for NICE's guidance on using elosulfase alfa in the context of national commissioning by NHS England.

For further details, see the [Interim Process and Methods of the Highly Specialised Technologies Programme](#).

The key dates for this evaluation are:

Closing date for comments: 23 June 2015

Second Evaluation Committee meeting: 21 July 2015

Details of membership of the Evaluation Committee are given in section 9, and a list of the sources of evidence used in the preparation of this document is given in section 10.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Evaluation Committee's preliminary recommendations

- 1.1 The Committee is minded not to recommend elosulfase alfa, within its marketing authorisation, for treating mucopolysaccharidosis type IVa.
- 1.2 The Committee requests that the company provides a further explanation of the cost of elosulfase alfa, in the context of development and manufacturing costs, the benefits it provides to people with the condition, and the budget impact on the NHS and Personal Social Services.
- 1.3 The Committee requests that the company provides additional economic analyses exploring:
- plausible rates of disease progression in 'single- and multi-domain responders', with appropriate sensitivity analyses
 - alternative estimates for the utility benefit (increment) associated with elosulfase alfa in each health state
 - exclusion of the VAT waiver for home care
 - alternative modelling of mortality to accurately reflect the mortality risks associated with mucopolysaccharidosis type IVa (excluding the double-counting of the mortality benefit associated with elosulfase alfa).
- 1.4 The Committee requests that the company provides an analysis of the budget impact for the NHS and Personal Social Services of administering elosulfase alfa at people's homes.
- 1.5 The Committee requests that the company and NHS England provide further details of the criteria for starting and stopping elosulfase alfa treatment in clinical practice.

2 The condition

- 2.1 Mucopolysaccharidosis type IVa (also known as MPS IVa and Morquio A syndrome, and referred to in this document as MPS IVa) is an inherited lysosomal storage disease caused by a lack of the enzyme N-acetylgalactosamine-6-sulfatase. The enzyme deficiency leads to accumulation of glycosaminoglycans, such as keratan sulphate, in the cells of several tissues and organs, causing progressive tissue damage.
- 2.2 MPS IVa causes a wide spectrum of symptoms that worsen over time, including joint and skeletal abnormalities, hearing loss, corneal clouding and heart valve disease. The joint and skeletal abnormalities lead to short stature, difficulties with breathing and movement, and spinal problems. MPS IVa also causes pain, fatigue, progressive loss of endurance and increasing dependence on wheelchairs. It leads to reduced life expectancy, primarily through respiratory failure and heart problems (63% and 15% of deaths respectively). Some people have a particularly severe form of the disease, with early onset, high morbidity and rapid progression, although others have a more attenuated form. The signs and symptoms typically appear in early childhood, with more than 70% of people presenting before age 3 years. At the time of the evaluation, there were 88 people living with MPS IVa in England, and about 3 new diagnoses made per year. The company and patient group noted that, of these 88 people, 74 were anticipated to be eligible for enzyme replacement therapy and may want treatment with elosulfase alfa.
- 2.3 Managing MPS IVa involves a multi-disciplinary approach to treat the symptoms and address the complications; before elosulfase alfa became available, there were no treatments that address the underlying disease. Because of the rarity and heterogeneity of this condition, there is no standard treatment or pathway of care. Management may include surgery for skeletal problems, respiratory support, drugs to manage heart disease, dental and eye care, pain relief, and hearing aids and ventilating tubes to manage deafness and middle ear effusions. The lysosomal storage

disorders expert group is developing a standard operating procedure for England to guide the management of this condition. Most people with MPS IVa are treated at 1 of 8 specialist centres (3 paediatric centres and 5 adults centres).

3 The technology

- 3.1 Elosulfase alfa (Vimizim, BioMarin) is a recombinant form of the human N-acetylgalactosamine-6-sulfatase enzyme. It is intended to replace the enzyme lacking in people with mucopolysaccharidosis type IVa (MPS IVa). Elosulfase alfa has a marketing authorisation in the UK for treating MPS IVa in people of all ages. It is given by intravenous infusion, over 4 hours, once a week. The recommended dosage is 2 mg/kg body weight each week, and is anticipated to continue lifelong.
- 3.2 The summary of product characteristics lists the following adverse reactions for elosulfase alfa: anaphylaxis, hypersensitivity, headache, dizziness, shortness of breath, diarrhoea, vomiting, nausea, sore throat, abdominal pain, muscle pain, chills and fever. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.3 Elosulfase alfa is available in 5 ml vials containing 5 mg of elosulfase alfa, at a net price of £750 per vial (excluding VAT). NICE estimates that the average cost per year for elosulfase alfa is £394,680 per patient (based on the recommended dosage of 2 mg/kg/year and an average body weight of 25.3 kg). The company has proposed a patient access agreement, in which elosulfase alfa would be provided at a discounted cost; the discount is commercial in confidence and so cannot be reported here.

4 Evidence submissions

The Evaluation Committee (section 9) considered evidence submitted by the company of elosulfase alfa, a review of this submission by the

Evidence Review Group (ERG; section 10) and evidence submitted by clinical experts, patient experts and NHS England.

Nature of the condition

4.1 Patient experts and patient groups highlighted the substantial impacts of mucopolysaccharidosis type IVa (MPS IVa) on the quality of life of people with the condition and their families.

- Most people with MPS IVa have seriously reduced mobility and stamina, making many daily activities challenging and leading to dependence on a wheelchair.
- Spinal instability puts people at a high risk of injury and medical complications, and often needs high-risk surgery. In particular, compression of the spinal cord needs surgical management by highly experienced surgical teams. Without careful monitoring, or because of an accident, patients can become paralysed or die.
- Bone and joint problems often cause chronic pain.
- Progressive hearing loss and frequent periods of diarrhoea can be debilitating and isolating.
- MPS IVa causes reduced life expectancy; the average life expectancy in people with this condition is about 25 years.
- The combination of symptoms in MPS IVa, including physical features and short stature, can cause considerable anxiety, depression and low self-esteem.
- Expensive wheelchairs and home adaptations carry a financial burden, which can be exacerbated by limitations on income caused by difficulty working.
- MPS IVa also significantly affects the families of people with the condition. Many parents struggle to continue working as care needs increase.
- Patient groups highlighted testimonies from families involved in clinical trials of elosulfase alfa. They describe substantial improvements in quality of life, and anticipate that stabilising disease progression and

maintaining mobility and stamina could have a particularly important impact.

- 4.2 The company also presented evidence from an observational study of the natural history of MPS IVa (MOR-001), which followed 325 people with MPS IVa for up to 10 years. This study suggested that the progression of MPS IVa over time leads to decline in endurance, restricted growth and limitations in the activities of daily living. Evidence was also presented from cross-sectional surveys of 63 people with the condition and of 56 families. The results showed that the effect of MPS IVa on quality of life and its effect on carers are both related to how much the person relies on a wheelchair. Quality of life is also correlated with endurance, pulmonary function and height. The survey of families found that people with the condition need up to 15 hours of care per day. Carers often report stress, lack of sleep, back pain, anxiety and depression, as well as effects on family and social life and finances.

Clinical evidence

- 4.3 The testimonies from families of children and adults who took part in clinical trials of elosulfase alfa gave individual illustrations of the benefits of treatment. They noted that children who had elosulfase alfa continued to grow, experienced less physical deterioration, avoided surgery and did not become dependent on wheelchairs. Adults experienced a significant increase in energy levels and reduction in pain, enabling them to work and have a more normal life. Patient groups emphasised the positive impact of stabilisation of the disease symptoms on quality of life and life expectancy. They highlighted the importance of outcomes such as improved energy levels, reduced disability and wheelchair dependence. They acknowledged that elosulfase alfa will not cure MPS IVa nor undo existing skeletal damage and disability, and stated that it is unknown how well the short-term benefits seen in clinical trials predict long-term outcomes. Clinical experts noted that elosulfase alfa is expected to slow the progression of disease, reduce the need for surgery and improve

quality of life. Elosulfase alfa is unlikely to reduce certain complications, such as spinal cord damage, and may not remove the need for supportive interventions.

4.4 The company identified 7 clinical studies of elosulfase alfa for MPS IVa, involving 255 patients. These included 1 randomised, placebo-controlled phase III trial (MOR-004) and its long-term extension (MOR-005), 1 open-label ascending dose study (MOR-002) and its long-term extension (MOR-100), 1 randomised phase II trial (MOR-008), and 2 single-arm studies in specific population groups (people under 5 years old and people with limited mobility; MOR-006 and -007).

4.5 The pivotal clinical effectiveness trials for elosulfase alfa were the MOR-004 and -005 studies; the MOR-002, -100, -007 and -008 studies provided supportive evidence, and no results were available from MOR-006 at the time of the evaluation. On enrolment into study MOR-004, 176 patients were randomised (1:1:1, stratified by age and endurance) to elosulfase alfa 2 mg/kg/week every week (licensed dose; n=58), elosulfase alfa 2 mg/kg/fortnight (unlicensed dose; n=59) or placebo (n=59), all for 24 weeks. Patients and investigators were blinded to treatment allocation. After 24 weeks, patients could enter the long-term extension, MOR-005 (n=173). At this stage, patients in the placebo group were randomised to elosulfase alfa 2 mg/kg/week or 2 mg/kg/fortnight; patients in the elosulfase alfa groups continued with their original treatment assignment, which remained double-blind. When the primary efficacy analysis of MOR-004 was complete (based on week 24 data), all patients in MOR-005 switched to open-label elosulfase alfa 2 mg/kg/week for the rest of the study (up to 240 weeks). Outcomes included endurance (measured using the 6-minute walk test [6MWT, primary outcome measure] and 3-minute stair climb test [3MSCT]), urine keratan sulphate, pulmonary and cardiac function, anthropometric measures, vision and hearing. The baseline and disease characteristics were broadly comparable between treatment groups in MOR-004 and -005, although

there were some small differences between groups, particularly in endurance scores in MOR-005.

- 4.6 The primary efficacy analysis of MOR-004 showed that elosulfase alfa 2 mg/kg/week was associated with a statistically significant improvement in 6MWT at week 24 compared with placebo. Patients treated with elosulfase alfa 2 mg/kg/week had a mean improvement from baseline in 6MWT of 23.7 metres at week 12 and 36.5 metres at week 24, equating to a mean difference between elosulfase alfa and placebo of 22.5 metres at week 24 (95% confidence interval [CI] 4.0–40.9 metres, $p=0.017$). A pre-specified subgroup analysis showed consistent improvements in 6MWT with elosulfase alfa 2 mg/kg/week compared with placebo across subgroups based on age, sex, endurance at baseline, geographical region and race.
- 4.7 Longer-term analyses of endurance were presented from MOR-005, -002 and -100. In the interim analysis of MOR-005 at week 72 (that is, 72 weeks after enrolment to study MOR-004, 48 weeks after enrolment to MOR-005), continuous treatment with elosulfase alfa 2 mg/kg/week was associated with a sustained increase from baseline in 6MWT distance (week 72: 30.1 metres and 46.0 metres in the intention-to-treat and per protocol analyses respectively). In MOR-002 and -100, elosulfase alfa appeared to be associated with improvements in 6MWT, although analyses were based on small patient numbers and had wide confidence intervals.
- 4.8 The company presented analyses of secondary and tertiary outcomes from studies MOR-004, -005, -100, -007 and -008. The results of MOR-004 suggested that elosulfase alfa 2 mg/kg/week provided improvements in endurance, pulmonary function, anthropometrics and quality of life compared with placebo at week 24. Statistical significance was not reached, although the company noted that the study was not powered to detect differences in secondary or tertiary outcomes. In this study, no substantial changes in corneal clouding were seen with

elosulfase alfa compared with placebo, whereas the hearing results showed some numerical changes based on a small population (n=6–9 per group). The number of people using a wheelchair at week 24 increased by 5 in the placebo group but did not increase in the elosulfase alfa 2 mg/kg/week group (although fewer people in the placebo group used a wheelchair at baseline than in the elosulfase alfa 2 mg/kg/week group). In MOR-005, there was a reduction in wheelchair dependency at week 72 with elosulfase alfa 2 mg/kg/week compared with baseline. Patients treated continuously with elosulfase alfa 2 mg/kg/week had fewer surgical operations and those that did had them later in the study, compared with the other treatment groups. In children under 5 years (MOR-007), the mean height z-score showed no significant change from baseline to week 52 (–2.0 at baseline and –2.2 at week 52). The company noted that, in untreated patients of a similar age in the observational study MOR-001, the mean height z-score decreased from –2.3 to –3.1 over 52 weeks. Evidence for the effect of elosulfase alfa on sleep apnoea was collected in study MOR-008, and the results show no clear trends in the change from baseline to week 24. Analyses of urine keratan sulphate levels showed a consistent decrease from baseline associated with elosulfase alfa treatment across the clinical studies. The decrease was about 40% over 24 weeks, and was statistically significantly larger than with placebo (MOR-004). The company stated that this confirms the biological activity of the enzyme replacement. In analyses of the effect of treatment on a combination of multiple endpoints in MOR-004, the results were statistically significantly or borderline significantly in favour of elosulfase alfa 2 mg/kg/week compared with placebo (p values from 0.002 to 0.053).

- 4.9 The company presented a responder analysis for endurance and pulmonary outcomes at week 72 in people treated with elosulfase alfa 2 mg/kg/week throughout MOR-005. Patients were classed as ‘multi-domain responders’ if they had any improvement from baseline in endurance (measured using 6MWT or 3MSCT) and any improvement from baseline in pulmonary function, as ‘single-domain responders’ if they

had improvements in either endurance or pulmonary function, and as 'non-responders' if they had no improvement in either outcome. Most patients treated with elosulfase alfa 2 mg/kg/week were 'multi-domain responders', and the remainder were 'single-domain responders'. The number of 'single- and multi-domain responders' were reported as academic-in-confidence and so cannot be reported here.

- 4.10 The company presented adverse event data from 235 people who had elosulfase alfa during the clinical trial programme, of whom 222 had it at the licensed dose of 2 mg/kg/week. Of people who had elosulfase alfa 2 mg/kg/week, 77% reported at least 1 adverse event; the most common included vomiting (35%), fever (34%) and headache (34%). Serious adverse events occurred in 29% of people who had elosulfase alfa 2 mg/kg/week; in the MOR-004 trial most adverse events were mild (48%) or moderate (45%). The company reported that most serious adverse events were related to the underlying disease or the intravenous administration of elosulfase alfa. There were no adverse events that led to the treatment being permanently stopped, and there were no deaths during the clinical trials. About 20% of people taking elosulfase alfa 2 mg/kg/week had a hypersensitivity reaction, and 71% had an infusion-associated reaction, the most common of which included fever, vomiting and headache. These infusion-associated reactions decreased in frequency with longer-term treatment. Three infusions were interrupted or stopped because of hypersensitivity reactions, and 14% of people had their infusions interrupted or stopped because of infusion-associated reactions. Clinical experts stated that infusion-associated reactions are an accepted complication of enzyme replacement therapy and respond to treatment.

Economic evidence

- 4.11 The company presented a cost–consequence analysis comparing elosulfase alfa 2 mg/kg/week with established clinical management. The analysis was based on a Markov model with 7 states, representing the

progression of MPS IVa based on increasing use of a wheelchair. The model included people with MPS IVa, with the demographic and disease characteristics (for example, body weight) based on the population in the MOR-001 observational study. The company noted that this was a younger group with less-advanced disease than people with MP IVa in England. The model had a lifetime time horizon (that is, it simulated costs and benefits over a maximum of 100 years) and a 1-year cycle length. The analysis was conducted from the perspective of the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 1.5% per year.

- 4.12 At the start of the model, patients were distributed between the 7 health states according to the range of symptoms and wheelchair use seen at the start of MOR-001. Patients then progressed through the model. Patients who started in the 'asymptomatic' state transitioned to the 'no wheelchair' state at age 3 years if treated with established clinical management (the 'established management group'), and 5 years later if treated with elosulfase alfa (the 'elosulfase alfa group'). This assumption was based on expert opinion. Patients then moved between health states at a rate based on changes in wheelchair use, 6MWT and forced vital capacity (FVC) seen in MOR-001 and -005. In the elosulfase alfa group, people whose disease responded in both endurance and pulmonary domains ('multi-domain responders'; see section 4.9) were assumed not to have any progression in wheelchair use, 6MWT or FVC score. This assumption was based on expert opinion and experience of the effect of enzyme replacement therapy in related disorders such as MPS VI. People whose disease responded in 1 domain ('single-domain responders'; see section 4.9) had a slowing of progression to 50% of the rate in the established management group. In each state, some patients had surgery, and either recovered (after a recovery period with lower quality of life), developed paraplegia because of complications (and transitioned to the 'paraplegic' state) or died (and transitioned to the 'death' state). Mortality was based on the assumption that people treated with elosulfase

alfa have the same mortality risk as the general population, and that people in the established management group have a 3.03-fold greater risk of death than those in the elosulfase alfa group.

- 4.13 Quality of life was captured in the model by assigning utility scores to each health state, and a utility decrement in the recovery period after surgery. The utility scores in the established management group were based on the general population (asymptomatic state) and the surveys of the people with the condition and their families (see section 4.2). In addition, each health state included an effect of the disease on carers' quality of life (a disutility). An increase in utility score (utility increment) was applied to the elosulfase alfa group in each health state. This utility increment was based on the improvement in 6MWT and FVC seen in clinical trials of elosulfase alfa, combined with the correlation between 6MWT and FVC and quality of life seen in the survey of people with MPS IVa (see section 4.2). The model did not include any effect of adverse events on quality of life.
- 4.14 The model included costs associated with treatment (acquisition cost of elosulfase alfa 2 mg/kg/week and infusion-related costs) and the disease (health-state costs). The acquisition cost of elosulfase alfa was based on the list price and the discount agreed in the patient access agreement; the discount is commercial in confidence and so cannot be reported here. Because elosulfase alfa is dosed on a per-kilogram basis, the cost of elosulfase alfa was also influenced by patient weight. The model took this into account by assigning an average weight to people in each health state (based on MOR-001) and assuming that weight stayed the same throughout each health state (that is, patients' weights changed only when they transitioned between health states). The health-state costs included primary and secondary care appointments, emergency treatment and surgery. The frequency of these appointments was based on expert opinion. In addition, each health-state cost included costs for daily care, based on the number of hours of care reported in the survey of the parents of people with MPR IVa (see section 4.2); the company assumed

that 50% of this care was given by professional carers. No costs associated with adverse events were included. NHS costs were taken from the Personal and Social Services Research Unit, NHS reference costs and literature sources.

- 4.15 In the base case, established clinical management was associated with £618,812 in costs and 9.75 quality-adjusted life years (QALYs) over the lifetime of the model. Elosulfase alfa was associated with 27.93 QALYs, amounting to 18.18 additional QALYs compared with established clinical management. The acquisition cost of elosulfase alfa over the lifetime of the model was £14,014,636 (based on the list price). The total costs in the elosulfase alfa group were provided as commercial in confidence and so cannot be reported here.
- 4.16 The company presented a one-way (deterministic) sensitivity analysis and probabilistic sensitivity analysis to assess the uncertainty in the model. The deterministic sensitivity analysis showed that the results were most sensitive to the discount rate for benefits and costs, body weights, and utility scores in the 'no wheelchair', 'sometimes wheelchair' and 'wheelchair-dependent' states and the progression of disease in 'single-domain responders'.
- 4.17 The company also presented scenario analyses to explore the effects of assumptions about the population, perspective, effect on carers, mortality, utilities and the treatment benefit associated with elosulfase alfa. The incremental costs and QALYs were most influenced by the use of a 'birth cohort' (that is, modelling patients from birth rather than their current health state), the modelling of mortality and the assumptions about the effect of elosulfase alfa on disease progression.
- 4.18 The company presented a budget impact analysis to predict the costs of elosulfase alfa in the NHS and PSS. The company stated that, of the 88 people living with MPS IVa in England, 74–77 would want to have elosulfase alfa treatment. The company assumed 50 people would have

treatment in the first year and the remainder would start in the second year. The results of the budget impact analysis suggested that the net budget impact of elosulfase alfa (based on the list price) would be £17,310,564 in the first year. The analysis suggested that the net budget impact would rise to £28,823,649 in year 5.

Impact of the technology beyond direct health benefits and on delivery of the specialised service

- 4.19 The company stated that people with MPS IVa can gain high achievements in education and employment, but may be limited by progression of the disease. It also emphasised the effects of the MPS IVa on the parents, siblings and carers of people with the condition, and suggested that elosulfase alfa may provide benefits in quality of life, education and employment for families and carers.
- 4.20 The company anticipated that treatment with elosulfase alfa could result in cost savings outside the NHS. These could include savings in the education, local government and welfare budgets, for example through reductions or delays in school and home adaptations and reduced welfare payments. In addition, if people with MPS IVa remain in employment for longer, they may contribute more income tax.
- 4.21 The company noted that people with MPS IVa incur substantial personal costs. These include adaptations of their homes and cars, bespoke clothes and specialist mobility equipment (including wheelchairs). In addition, families may incur costs for travelling to hospital appointments, time off work to care for their family, privately funded care or treatment, and special help with schooling.
- 4.22 The company described the Morquio A Registry Study (MARS), an ongoing registry of people with MPS IVa collecting natural history data, and clinical and patient-reported outcomes. The registry will also collect long-term efficacy and safety outcomes for elosulfase alfa. The company

stated that this registry represents a significant development for strengthening the evidence base in this condition.

- 4.23 The company stated that no additional infrastructure is needed to ensure the safe and effective use of elosulfase alfa in centres with experience in diagnosing and treating lysosomal storage disorders. It noted that there are 8 designated national centres for the diagnosis and management of lysosomal storage disorders, 7 of which have been involved in clinical studies of MPS IVa. The company highlighted that the specialist centres have extensive experience of enzyme replacement therapies. NHS England also anticipated that the service impact of the technology would be small, although clinical experts noted that giving the drug outside specialist centres may need additional staff training.

Evidence Review Group review

- 4.24 The ERG considers that, although there were some methodological shortcomings, the systematic review captured all relevant evidence including several good quality clinical studies. It noted some challenges in interpreting the clinical trial data including: the limited number and relatively short duration of randomised trials; heterogeneity in the natural history of MPS IVa and the observed treatment effect; limitations in the outcome measures; an apparent beneficial effect associated with placebo in MOR-004; and a potential confounding effect of surgical interventions during MOR-005. Nevertheless, the ERG noted that there was a statistically significant benefit in 6MWT associated with elosulfase alfa in MOR-004. The ERG understood that the observed benefit is also clinically significant (although there is no empirical evidence for this).
- 4.25 The ERG commented that the longer-term data from MOR-005 suggest that improvements with treatment are sustained (although the gains in 6MWT decline with time, as may be expected in a progressive condition). However, the possible placebo effect and the lack of a comparator group suggest the results should be interpreted with caution. The ERG also noted that the company presented an analysis of the per protocol group to

minimise the confounding effect of surgery. This excluded people who needed surgery and the ERG considered that the intention-to-treat group was more representative of the patient population.

- 4.26 The ERG noted that the 6MWT is a surrogate outcome, but accepted that it is appropriate for this condition. However, it highlighted limitations in this outcome about the meaningfulness of observed changes, sensitivity to improvements, validity of the test and potential for confounding. Similar limitations were noted for the 3MSCT. In addition, the ERG noted that both the 6MWT and 3MSCT may be affected by the test conditions, but that the 3MSCT was not standardised across centres and studies. Clinical experts noted in their submissions that the surrogate and composite measures used in trials were not satisfactory but were the only available options. A patient expert noted in its submission that the improvement in quality of life associated with elosulfase alfa might be greater than the increase in 6MWT, and noted that even a small improvement in endurance could make a substantial difference to the quality of life of a person with MPS IVa.
- 4.27 The ERG highlighted that the responder analysis for studies MOR-004 and -005 (see section 4.9) included no statistical comparisons, and that it was unclear whether the changes in 'responders' were clinically significant. The ERG noted that the change in FVC in 'single-domain responders' was counterintuitive. The clinical significance of the changes in height and growth rate were unknown, and the analyses of wheelchair use and audiometry were limited by small population sizes. The ERG noted that urine keratan sulphate may be a useful surrogate outcome as a marker of lysosomal function, but that it is not correlated with clinical outcomes.
- 4.28 The ERG considered that the company's economic model was broadly appropriate and followed methodological guidance and the NICE reference case. The progression of disease was coherently modelled and reflected the natural history, and the time horizon and cycle length were

appropriate. The ERG noted that the discounting rate of 1.5% per year might be considered reasonable, but explored this in a scenario analysis.

- 4.29 The ERG considered that the assumptions used to model clinical effectiveness are uncertain. It stated that the assumptions were not fully consistent with the evidence and overestimated the benefits associated with elosulfase alfa. The ERG noted that the model assumed that elosulfase alfa would delay the onset of symptoms by 5 years and stabilise established disease (that is, prevent any progression) in 'multi-domain responders'. However, it considered these assumptions to have been optimistic and based on limited evidence, and to have predicted an implausible increase in clinical benefits during the model. The ERG explored these assumptions in scenario analyses. The ERG also noted that progression between health states was based on evidence from MOR-005 and so was limited by the non-randomised nature of the study and small population sizes.
- 4.30 The ERG noted that the model included a mortality benefit associated with elosulfase alfa both through delaying disease progression and through the relative risk of death. It considered that this double-counted the mortality benefit associated with treatment.
- 4.31 The ERG considered that the modelling of quality of life was mostly reasonable, but noted some concerns. It highlighted that elosulfase alfa was assumed to improve quality of life in each health state, and also to delay progression of disease. The ERG considered that this double-counted the utility benefit associated with elosulfase alfa treatment. The ERG also noted that the utility value for the 'paraplegic' health state was the same as that for the 'wheelchair-dependent' health state, despite feedback from experts that quality of life may be worse in patients with paraplegia. The ERG also commented on the marked decline in utility between occasional and constant wheelchair use, and highlighted some uncertainty around the value set used for the utility analysis. It highlighted

that quality of life evidence from MOR-004 and -005 does not appear to have been used in the model.

- 4.32 The ERG considered the resource use and costs included in the model to be generally appropriate. However, it noted that the company included a reduction in drug costs of 20% associated with home administration, to reflect the VAT waiver for home care. It considered that VAT should have been excluded from all analyses, so this reduction was inappropriate.
- 4.33 The ERG presented exploratory analyses to explore the effects of key assumptions on the company's cost-consequence analysis and budget impact estimates. It noted that these scenarios substantially affected the model results. In the scenario in which elosulfase alfa was assumed to slow disease progression in 'multi-domain responders' by 50% compared with established clinical management, elosulfase alfa was associated with a total of 19.79 QALYs, equating to 10.03 additional QALYs compared with conventional management. The ERG presented a combined scenario analysis in which elosulfase alfa slowed disease progression by 50% in 'multi-domain responders' but had no effect on progression in 'single-domain responders', the VAT waiver for home care was omitted, and the utility increment and mortality benefit associated with elosulfase alfa were removed. In this analysis, elosulfase alfa was associated with a total of 15.04 QALYs, equating to 5.04 additional QALYs compared with conventional management. For the budget impact analysis, the ERG presented a scenario based on the number of people that NHS England anticipates would be treated. In this analysis, it assumed that 38.5 people currently living with MPS IVa would be treated in the first year (that is, 50% of people who have the condition and wish to have treatment would get it in the first year); this was assumed to rise to 77 people from the prevalent population in the second and subsequent years, as well as 2.6 additional people diagnosed with MPS IVa each year. The results of this analysis were provided as commercial in confidence and so cannot be reported here.

- 4.34 Full details of all the evidence are in the submissions received for this evaluation, and in the ERG report, which are all available in the [Committee papers](#).

5 Consideration of the evidence

The Evaluation Committee reviewed the data available on the benefits and costs of elosulfase alfa, having considered evidence on the nature of mucopolysaccharidosis type IVa (MPS IVa) and the value placed on the benefits of elosulfase alfa by people with the condition, those who represent them, and clinical experts. It heard from the company, clinical experts and patient experts (including people with the condition, a parent of children with the condition, and the patient group). It also took into account the value for money that elosulfase alfa represents and the effective use of resources for specialised commissioning.

Nature of the condition

- 5.1 The Committee understood that mucopolysaccharidosis type IVa (MPS IVa) is a serious condition that severely affects life expectancy and quality of life. It understood the dramatic effects on the lives of people with the condition and their families and carers. The Committee also noted that MPS IVa is a highly heterogeneous condition. The Committee heard that some people have particularly severe disease with a short life expectancy, whereas others have a more mild form; it heard from the company and patient experts that even though people with a comparatively mild form of MPS IVa live longer, it is a very serious condition with severe manifestations and significant effects on quality of life.
- 5.2 The Committee heard from the clinical specialist that one of the important determinants of clinical outcomes in people with MPS IVa is cervical spinal cord damage. The Committee understood that people with MPS IVa are at a particularly high risk of damage, and all will need spinal surgery at some point in their lives. The Committee understood that spinal cord damage has a significant impact on mobility, quality of life and life

expectancy, and that preventing progression of spinal disease may be a key factor in determining long-term clinical outcomes.

Impact of the new technology

- 5.3 The Committee considered the clinical-effectiveness evidence presented by the company. The Committee acknowledged the challenges in developing a clinical trial programme for such a rare condition, and heard from the company that the clinical trial programme included about 10% of the worldwide population of people with MPS IVa. The Committee was pleased to see that a detailed study of the natural history of MPS IVa involving many people was presented (MOR-001). The Committee heard that the clinical trials included a wide range of people with different clinical manifestations of MPS IVa, including a large cohort from the UK and, in general, reflected the spectrum of people who would be expected to have treatment in England.
- 5.4 The Committee considered whether the endpoints assessed in the clinical trials had captured the most important aspects of the condition and the benefits associated with elosulfase alfa. The Committee understood that important determinants of clinical outcomes for people with MPS IVa include cervical spinal cord damage (see section 5.2), bone health and the need for orthopaedic surgery. It noted that spinal cord damage had not been assessed in clinical trials, and heard from a clinical expert that elosulfase alfa is not anticipated to affect this aspect of MPS IVa. It heard from a clinical expert that attempts had been made in early clinical trials to measure bone health (such as bone length and bone mineral density) in people with MPS IVa, but there were difficulties in using these measures. The Committee heard from the clinical expert that bone defects are often present from birth in people with MPS IVa, and that elosulfase alfa is unlikely to affect existing damage. However, it heard that people with existing skeletal problems still get substantial benefits from treatment through improvements in other aspects of their condition, such as energy levels and fatigue, lung function and ability to complete everyday

activities. The Committee understood that people with MPS IVa often need orthopaedic surgery, including hip and knee surgery. It noted that MOR-005 included an assessment of the time to orthopaedic surgery (see section 4.8), although comparisons with the incidence of surgery in the natural history of MPS IVa (that is, from MOR-001) were not presented. It heard from a clinical expert that, in their opinion, elosulfase alfa is not anticipated to significantly reduce or delay the need for orthopaedic surgery, although it was expected to make people healthier at the time of surgery and allow a quicker recovery. The Committee noted that the European Public Assessment Report for elosulfase alfa states that there appears to be a benefit in the incidence of orthopaedic surgery in people treated with elosulfase alfa. Given the significant effect of surgery on patients, the Committee considered that it would have been helpful if the clinical trials had explored surgical outcomes in more detail. The Committee concluded that some of the key determinants of long-term outcomes in people with MPS IVa, including spinal cord damage, bone health and orthopaedic surgery, had not been fully captured in the clinical trials, and understood that elosulfase alfa was not anticipated to substantially improve these aspects of the condition.

- 5.5 The Committee heard that that cardiovascular and respiratory function may also influence life expectancy in people with MPS IVa. It heard from the clinical expert that it is plausible that enzyme replacement therapy with elosulfase alfa could affect these outcomes. The Committee understood that the primary outcome in the randomised clinical trials, the 6-minute walk test (6MWT), provides a broad measure of overall functioning, including musculoskeletal health, cardiovascular and respiratory aspects, pain and fatigue. It heard that the 6MWT has been used successfully in other MPS disorders, and is used in clinical practice to monitor progress in people with MPS IVa. Patient experts noted that improvements in 6MWT scores during clinical trials reflected improvements in other aspects of their condition and their quality of life, and emphasised that the ability to move around (for example, at school) is an important part of everyday life.

The Committee noted the effect of treatment on wheelchair use was assessed in the clinical trials (see section 4.8). However, it heard from the clinical and patient experts that the categories of wheelchair use in the clinical trials could have been subjective. They emphasised that patients use wheelchairs in different ways, to manage endurance and daily activities according to their individual needs, so the effect of treatment is not necessarily well represented by this measure. The Committee considered that this evidence was informative but was mindful of putting too much emphasis on it. The Committee considered that, although the 6MWT was not a perfect measure, there were few alternatives. The Committee concluded that, as a proxy outcome that provides a broad measure of overall functioning, the 6MWT was broadly appropriate.

- 5.6 The Committee discussed the clinical benefits associated with elosulfase alfa. It heard from clinical experts that most people treated with elosulfase alfa experienced clinical improvements beyond what could be attributed to a placebo effect. It understood that, in clinical trials, elosulfase alfa provided improvements in several outcomes, including endurance, pulmonary function, anthropometrics, wheelchair dependency and quality of life, and that the improvement in 6MWT was statistically significant compared with placebo (see sections 4.6 to 4.8). The patient experts described several important benefits associated with elosulfase alfa, including effects on endurance, fatigue, pain and recovery after exertion, education, work and social life. The Committee also heard from the patient experts that people who stopped treatment experienced substantial deterioration, leading to loss of independence and decreased quality of life. A clinical expert stated that it was likely that elosulfase alfa would slow progression of the disease, but that it was unlikely to stop disease progression completely. Based on the clinical evidence and patient testimonies, the Committee concluded that elosulfase alfa was likely to be associated with important improvements in some aspects of the condition. However, it was aware that elosulfase alfa was not expected to improve some of the key determinants of long-term health

(including spinal cord damage, bone health and orthopaedic surgery). The Committee considered that it was challenging to establish a precise picture of the clinical benefits associated with elosulfase alfa based on the available evidence, and was mindful of the substantial heterogeneity in both the condition and the treatment response.

- 5.7 The Committee heard from a clinical expert that, although a high proportion of people treated with elosulfase alfa experienced adverse events during the trials, clinicians had substantial experience in managing infusion-associated reactions and that established protocols were in place. Although some people had slowed infusions or pauses in treatment, no-one stopped treatment because of adverse events. Patient experts reported experiencing some adverse reactions but emphasised that these were quickly controlled and were vastly outweighed by the benefits of treatment.

Cost to the NHS and Personal Social Services

- 5.8 The Committee considered the budget impact analyses submitted by the company. It noted that the company's analysis suggested that the net budget impact for elosulfase alfa would rise from £17.3 million in year 1 to £28.8 million in year 5.
- 5.9 The Committee explored the number of people who would get elosulfase alfa if it were recommended. It heard from a patient expert that 77 people currently have the condition and are thought to be eligible for treatment. The Committee heard that this excludes people with paraplegia or in the end stages of the disease and those who had expressed a clear preference not to have treatment. The clinical expert anticipated that most people with MPS IVa may be eligible for treatment based on clinical criteria, but the patient expert stated that, of the 77 known patients, some might not choose to have treatment. The Committee understood that about 3 new diagnoses of MPS IVa are made per year. However, the patient expert noted that, as well as new diagnoses, some people would die during the 5 years of the budget impact analysis, and so the total

number of people being treated was unlikely to rise as much as the company had estimated. The Committee concluded that it is difficult to determine the specific groups of people who would not have elosulfase alfa treatment and, so, how many people would have treatment with elosulfase alfa in England if it were recommended.

- 5.10 The Committee discussed the assumptions in the company's budget impact analysis. It noted that the company's model assumed that 50% of the total care time was provided by professional carers (with the remainder provided by family members). It heard from a patient expert that only 5 people with MPS IVa currently have professional care, and so considered that the company had over-estimated the cost to the NHS of professional carers. The Committee noted that the company's cost analyses included a reduction in the cost of elosulfase alfa when given at home, to reflect the fact that VAT is currently waived for treatments given via home care. The Committee noted that VAT had not been included in the cost of elosulfase alfa in the economic model or budget impact analysis, stating that reducing the cost of VAT in a model from which VAT was already excluded was inappropriate. The Committee therefore agreed with the ERG that including the VAT waiver was not appropriate. The Committee concluded that the company should submit a revised budget impact analysis excluding the VAT waiver for home care.
- 5.11 The Committee noted that the company did not present an analysis of the costs associated with delivering elosulfase alfa at people's homes. It highlighted that such costs would be borne by the NHS, and therefore asked the company for further explanation of these costs. It heard that, in practice, hospital trusts would be likely to fund home care services using tax savings associated with community prescribing. The company also noted that further savings could be made by reducing the hospital costs for infusion appointments. The Committee concluded that the cost implications of home administration of elosulfase alfa had not been fully considered. The Committee concluded that the company should submit a

revised budget impact analysis exploring the impact of giving elosulfase alfa at people's homes.

- 5.12 The Committee considered the cost of elosulfase alfa in the context of the costs incurred by the company for research, development and manufacturing, and asked the company for an explanation for the cost of the drug. It heard that developing drugs to treat rare conditions was expensive and that manufacturing this drug is complex. It heard that the company has spent more than \$350 million on the clinical development programme and has also built a new manufacturing facility. The Committee understood from the company that there are about 3000 people with MPS IVa across the world, of whom an estimated 1000 to 2000 may be able to access the drug. The manufacturing and development costs of the drug combined with the rarity of the condition lead to a high cost per patient. The Committee highlighted that the acquisition cost per kilogram body weight is substantially higher than that of 1 of the company's other enzyme replacement therapies, galsulfase (a treatment for MPS VI, a disorder with which the company draws parallels in its model). Galsulfase costs £196/kg/week (British national formulary online, accessed March 2015) compared with £300/kg/week for elosulfase alfa. This difference could not be explained by the rarity of the condition because the Committee understood that MPS VI is even rarer than MPS IVa. The Committee concluded that the company had not provided an adequate explanation of the cost of elosulfase alfa in the context of providing treatment for a rare condition.

Value for money

- 5.13 The Committee discussed the results of the company's cost-consequence model and the assumptions on which they were based. It noted that total costs associated with elosulfase alfa, and therefore the incremental costs, were deemed commercial in confidence by the company and so cannot be reported. The Committee noted that the company assumed that people whose disease responded to elosulfase

alfa across both endurance and pulmonary outcomes ('multi-domain responders'; see section 4.9) would not have any further progression of disease. The Committee noted that the company's assumption had been based on a 10-year study of people with MPS VI, although it heard from a clinical expert that MPS VI affects different organs to MPS IVa and so extrapolation between these conditions is difficult. The Committee accepted that elosulfase alfa was likely to slow disease progression, but would be unlikely to stop progression entirely (see section 5.6). The Committee saw that the ERG presented a scenario analysis in which elosulfase alfa slowed disease progression in 'multi-domain responders' by 50% compared with established clinical management; the clinical expert stated that this seemed broadly plausible. The Committee noted that, in this scenario, elosulfase alfa was associated with a much smaller gain in quality-adjusted life years (QALYs) compared with established clinical management than in the base case. In the base case, elosulfase alfa was associated with 18.18 additional QALYs compared with established clinical management, whereas in the ERG's scenario analysis, it was associated with 10.03 additional QALYs compared with established clinical management (see sections 4.15 and 4.33). The Committee also considered that it is plausible that 'single-domain responders' may have less benefit in disease progression than had been modelled by the company. The Committee concluded that the company's assumption that elosulfase alfa would completely stop disease progression in 'multi-domain responders' was not plausible and had overestimated the clinical benefits associated with elosulfase alfa. The Committee acknowledged that elosulfase alfa was likely to provide valuable clinical benefits for certain aspects of the condition, but considered that the gain in QALYs with treatment would be substantially lower than that estimated in the company's base case. It considered that the company should explore plausible rates of disease progression in 'single- and multi-domain responders' in more detail.

- 5.14 The Committee noted that the company's utility estimates included a substantial decline between people using wheelchairs some of the time and those who are dependent on a wheelchair. It heard from the company that this was consistent with a substantial jump in caregiving time between these states seen in the survey of the families of people with MPS IVa (see section 4.2), and with similar declines in utility seen in people with other conditions that are associated with increasing wheelchair use, such as multiple sclerosis. The Committee noted that the patient group submission highlighted that there are additional challenges in caring for people who are dependent on a wheelchair, compared with those who retain even a small amount of mobility, and that family life becomes more constrained as wheelchair use progresses. Patient expert submissions highlighted that a small improvement in mobility can make the difference between needing to adapt their whole house for a wheelchair and being able to walk around the home independently, or allow visits to shops or friends' houses that are not wheelchair accessible. The Committee concluded that the change in utility between the model's health states was acceptable.
- 5.15 The Committee also noted that the company had applied a utility increment to the elosulfase alfa group, and understood that the ERG considered that this double counted the benefits associated with elosulfase alfa. It queried the utility increment with the company, and heard that the increment was intended to reflect the assumption that elosulfase alfa is associated with several benefits in quality of life beyond the slowing of disease progression and improvements in endurance. The Committee noted that the company had calculated this utility increment using 6MWT results from the clinical trials. The Committee noted that the effect of the condition on quality of life had been assessed using the EuroQol (EQ-5D-5L) questionnaire in the natural history study (MOR-001). However, it also noted that the clinical trials for elosulfase alfa collected only limited evidence on quality of life, and did not collect EQ-5D data. The Committee understood that the evidence that was available

from the clinical trials suggested that elosulfase alfa may be associated with several improvements in quality of life. It also heard the testimonies from patient experts highlighting improvements in several aspects of quality of life, including effects on endurance and fatigue, pain, education, work and social life (see section 5.6). The Committee therefore concluded that it was reasonable to include a utility increment associated with elosulfase alfa in the economic model. However, the Committee was uncertain whether the company's estimate accurately reflected the quality-of-life benefits associated with elosulfase alfa beyond its effect on 6MWT and disease progression, and considered that the company should explore this in more detail.

- 5.16 The Committee considered whether the benefits in mortality associated with elosulfase alfa may have been double counted, by including a mortality benefit both through delaying disease progression and through the relative risk of death. It heard from the ERG that the 10-year death rate in the company's model was about 6 times higher in the elosulfase alfa group than in the established management group, but would be expected to be about 3 times higher given the hazard ratio between these groups. The Committee heard that this discrepancy provided evidence for the double counting. The Committee noted that the hazard ratio was based on limited evidence from MPS VI, and recalled that extrapolation between MPS VI and MPS IVa was difficult (see section 5.13). It was uncertain whether the company's modelling of survival accurately reflected the mortality risks associated with MPS IVa, such as the risks of cervical complications, trauma and heart failure. The Committee concluded that the mortality benefit associated with elosulfase alfa had been overestimated and considered that the company should explore this in more detail.

- 5.16.1 The Committee considered the overall value for money provided by elosulfase alfa. It noted comments from NHS England that there is a single budget for specialised services of £13 billion, of which only a small portion is available for commissioning technologies such as this. The

Committee considered it would be helpful to have further details of the budget available for highly specialised technologies, and requests that NHS England provides more information. The Committee also heard that about 80 technologies were being considered for commissioning at the time of the evaluation, and that some of these may be displaced if elosulfase alfa is recommended. The clinical and patient experts recognised the limited resources available and stated that it would be possible in clinical practice to limit treatment to patients who would benefit most. A clinical expert stated that starting and stopping criteria for enzyme replacement therapy were constantly being reviewed by the National Advisory Group for Lysosomal Storage Disorders and that, when combined with clinical flexibility, such criteria would help target treatment toward people who would benefit most. The Committee noted that starting and stopping criteria could improve the value for money provided by elosulfase alfa and considered that it would have been helpful if the company had explored this in a scenario analysis. However, it acknowledged that such a scenario analysis may include several important uncertainties (including the most appropriate starting and stopping criteria) and so might not be appropriate for decision-making. A clinical expert noted that, in general, people who start treatment with elosulfase alfa early in life may benefit more than those who start later. The clinical expert also noted that people with established spinal cord damage or severe forms of the condition are unlikely to benefit from treatment, although the Committee heard from patient experts that people with severe skeletal deformities experience benefits from treatment in other aspects of the condition (see section 5.5). The Committee acknowledged that treatment would be targeted towards people who would benefit the most. It reiterated that both the condition and the response to treatment were highly heterogeneous, and so considered that the effect of this approach on the value for money offered by the treatment was uncertain. The Committee considered that it needed more information about the criteria for starting and stopping treatment with elosulfase alfa in clinical practice, and requested that the company and NHS England

provide further details on this. The Committee noted that, although it understood the evidence of clinical benefits from clinical trials and the patient testimonies, the magnitude of overall benefit offered by elosulfase alfa was uncertain. Because of this and the cost of the drug, the Committee expressed concerns about the value for money provided by this treatment.

Impact of the technology beyond direct health benefits and on delivery of the specialised service

5.17 The Committee understood that elosulfase alfa may provide important benefits to patients and their families in addition to the direct health benefits of treatment. It heard from patient experts that improving endurance and reducing fatigue allows people with MPS IVa to continue working, and understood that this had important financial implications. As well as the direct benefits on physical aspects of the condition, elosulfase alfa may provide important indirect mental health benefits. Patient experts emphasised that treatment with elosulfase alfa can provide additional predictability in the condition and therefore introduce normality and control in people's lives. The Committee heard that people can maintain independence, participate in social activities, develop longer-term plans and have fewer unplanned hospital visits. The Committee heard that, for children with MPS IVa, improved management of the condition has important benefits for education, particularly if elosulfase alfa can be given at school to minimise disruption. The Committee noted in particular that MPS IVa does not affect cognitive function, and was aware that this makes it distinct from other lysosomal storage disorders. The Committee concluded that elosulfase alfa is likely to have a significant impact on people's lives beyond its direct health benefits.

5.18 The Committee noted that treatment with elosulfase alfa needs weekly infusions, and heard from the patient experts that travelling to a specialist centre can be a significant burden. The Committee also understood that elosulfase alfa may be given in people's homes, and that this would

dramatically reduce this burden. The Committee noted comments from patient experts that some people had already begun to have treatment at home or in school (through programmes offered by the company and some hospitals) with great success. The patient experts noted that this has had positive effects both on people with the condition and their families, who may be able to return to work and avoid the financial costs of travelling to hospital. The Committee understood that people with MPS IVa have complex needs in emergency situations, but was reassured that robust safeguards were in place.

- 5.19 The Committee understood that it was not anticipated that substantial changes to the delivery of specialised services would be needed to use elosulfase alfa. It noted that, in this respect, elosulfase alfa was not significantly different to other enzyme replacement therapies. The Committee concluded that the impact of elosulfase alfa on the delivery of specialised services was likely to be relatively negligible.

Conclusion

- 5.20 The Committee concluded that MPS IVa is a serious condition with severe effects on the lives of people with the condition and their families and carers. It considered that elosulfase alfa was likely to provide valuable clinical benefits for certain aspects of the condition, including quality of life. The Committee also considered that elosulfase alfa would provide distinctive benefits beyond the direct health benefits. However, it noted that elosulfase alfa would not affect spinal cord or skeletal damage, and would not entirely stop disease progression, and highlighted that both spinal cord damage and disease progression significantly affect quality and length of life in people with MPS IVa. Reviewing the company's economic model, the Committee emphasised that the assumption that elosulfase alfa would stop disease progression was not plausible. In light of this, and noting that the effect of elosulfase alfa on mortality had also been overestimated, the Committee considered that the benefits of elosulfase alfa treatment in the company's model had been

overestimated. The Committee highlighted the cost of elosulfase alfa in the context of the costs of developing and manufacturing this drug and the costs of enzyme replacement therapies for other rare conditions (such as galsulfase for MPS VI). It considered that the cost of elosulfase alfa had not been adequately explained by the company. Because of the cost and the fact that the clinical benefits had been overestimated in the company's economic model, the Committee expressed concerns about the value for money provided by elosulfase alfa treatment. The Committee understood that treatment with elosulfase alfa would be targeted towards people who would benefit the most, and considered that it needed more information about the criteria for starting and stopping treatment in clinical practice. The Committee was therefore minded not to recommend elosulfase alfa, within its marketing authorisation, for treating MPS IVa.

5.21 The Committee requests that the company provides a further explanation of the cost of elosulfase alfa, in the context of development and manufacturing costs, the benefits it provides to people with the condition, and the budget impact on the NHS and Personal Social Services. The Committee also requests that the company provides additional economic analyses exploring:

- plausible rates of disease progression in 'single- and multi-domain responders', with appropriate sensitivity analyses
- alternative estimates for the utility benefit (increment) associated with elosulfase alfa in each health state
- exclusion of the VAT waiver for home care
- alternative modelling of mortality to accurately reflect the mortality risks associated with mucopolysaccharidosis type IVa (excluding the double-counting of the mortality benefit associated with elosulfase alfa).

In addition, the Committee requests an analysis of the budget impact for the NHS and personal social services of giving elosulfase alfa at people's homes. It also requests that the company and NHS England provide

further details of the criteria for starting and stopping elosulfase alfa treatment in clinical practice.

Summary of Evaluation Committee’s key conclusions

Evaluation title: Elosulfase alfa for treating mucopolysaccharidosis type IVa		Section
Key conclusion		
<p>The Committee was minded not to recommend elosulfase alfa, within its marketing authorisation, for treating mucopolysaccharidosis type IVa (MPS IVa).</p> <ul style="list-style-type: none"> • The Committee concluded that MPS IVa is a serious condition with severe effects on the lives of people with the condition, and their families and carers. • The Committee considered that elosulfase alfa was likely to provide valuable clinical benefits for certain aspects of the condition, including quality of life, and would provide distinctive benefits beyond the direct health benefits. • However, the Committee noted that elosulfase alfa would not affect spinal cord or skeletal damage, and would not entirely stop disease progression. • The Committee considered that the benefits of elosulfase alfa treatment in the company’s model had been overestimated. • The Committee considered that the cost of elosulfase alfa had not been adequately explained by the company and expressed concerns about the value for money provided by elosulfase alfa treatment. • The Committee understood that treatment with elosulfase alfa would be targeted towards people who would benefit the most, and considered that it needed more information about the criteria for starting and stopping treatment in clinical practice. 		1.1 5.21
Current practice		
Nature of the condition, including availability of other treatment options	<p>The Committee understood that MPS IVa is a serious condition that severely affects life expectancy and quality of life for people with the condition, and has dramatic effects on their families and carers. The Committee also noted that MPS IVa is a highly heterogeneous condition. Managing MPS IVa involves a multi-disciplinary approach to treat the symptoms and address the complications.</p>	5.1 2.3

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Before elosulfase alfa became available, there were no treatments that address the underlying disease.	2.3
	The Committee understood that elosulfase alfa may provide important benefits to patients and their families in addition to the direct health benefits of treatment.	5.18
Adverse reactions	<p>The Committee noted that:</p> <ul style="list-style-type: none"> although a high proportion of people treated with elosulfase alfa experienced adverse events during the trials, clinicians had substantial experience in managing infusion-associated reactions and established protocols were in place adverse events were quickly controlled and were vastly outweighed by the benefits of treatment. 	5.7
Clinical evidence		
Availability, nature and quality of evidence	<p>The Committee heard that the clinical trials included a wide range of people with different clinical manifestations of MPS IVa and, in general, reflected the spectrum of people who would be expected to have treatment in England.</p> <p>The Committee was pleased to see that a detailed study of the natural history of MPS IVa involving many people was presented.</p>	5.3
Uncertainties generated by the evidence	<p>The Committee understood that cervical spinal cord damage is an important determinant of clinical outcomes for people with MPS IVa, but was not assessed in clinical trials.</p> <p>The Committee considered that it would have been helpful if the clinical trials had explored surgical outcomes in more detail.</p>	5.4
	<p>The Committee considered that it was challenging to establish a precise picture of the clinical benefits associated with elosulfase alfa based on the available evidence, and was mindful of the substantial heterogeneity in both the condition and the treatment response.</p>	5.6

Impact of the technology	<p>The Committee concluded that elosulfase alfa was likely to be associated with important improvements in some aspects of MPS IVa, although it was aware that elosulfase alfa was not expected to improve some of the key determinants of long-term health (including spinal cord damage, bone health and orthopaedic surgery).</p> <p>The Committee considered that it was challenging to establish a precise picture of the clinical benefits associated with elosulfase alfa based on the available evidence.</p>	5.6
Cost evidence		
Availability and nature of evidence	<p>The company presented a cost–consequence analysis comparing elosulfase alfa 2 mg/kg/week with established clinical management. The analysis was based on a Markov model with a lifetime time horizon and a 1-year cycle length. The analysis was conducted from the perspective of the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 1.5% per year.</p> <p>The company presented a budget impact analysis to predict the costs of elosulfase alfa in the NHS and personal social services.</p>	<p>4.11</p> <p>4.18</p>
Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis	<p>In the economic analysis:</p> <ul style="list-style-type: none"> • The Committee concluded that the assumption that elosulfase alfa would completely stop disease progression in ‘multi-domain responders’ was not plausible and had overestimated the clinical benefits associated with elosulfase alfa. • The Committee concluded that it was reasonable to include a utility increment associated with elosulfase alfa in the economic model, but was uncertain whether the company’s estimate was appropriate. • The Committee concluded that the mortality benefit associated with elosulfase alfa had been overestimated. <p>In the budget impact analysis:</p> <ul style="list-style-type: none"> • The Committee concluded that there was uncertainty how many people would have treatment with elosulfase alfa in England if it were recommended. • The company’s model assumed that 50% of the total care time was provided by professional carers. The Committee heard from a patient expert that only 5 people with MPS IVa currently have professional care, and 	<p>5.13</p> <p>5.15</p> <p>5.16</p> <p>5.9, 5.10 and 5.11</p>

	<p>so the company had over-estimated the cost to the NHS of professional carers.</p> <ul style="list-style-type: none"> • The Committee noted that the analyses included a reduction in the cost of elosulfase alfa when given at home, to reflect the fact that VAT is currently waived for treatments given via home care. It considered that this VAT waiver was not appropriate. • The Committee considered that the cost implications of home administration of elosulfase alfa had not been fully considered. 	
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee noted that the company's utility estimates included a substantial decline between people using wheelchairs some of the time and those who are dependent on a wheelchair. It heard that this was consistent with a substantial jump in caregiving time between these states for people with MPS IVa and other conditions, and heard that there are additional challenges in caring for people who are dependent on a wheelchair.</p> <p>The Committee also noted that the company had applied a utility increment to the elosulfase alfa group. The Committee concluded that it was reasonable to include a utility increment, but was uncertain whether the company's estimate was appropriate.</p>	<p>5.14</p> <p>5.15</p>
<p>Cost to the NHS and PSS</p>	<p>The Committee noted that the company's analysis suggested that the net budget impact for elosulfase alfa would rise from £17.3 million in year 1 to £28.8 million in year 5.</p> <p>The Committee concluded that the company had not provided an adequate explanation of the cost of elosulfase alfa.</p>	<p>5.8</p> <p>5.12</p>
<p>Value for money</p>	<p>The Committee noted that the magnitude of overall benefit offered by elosulfase alfa was uncertain and had been overestimated in the company's model. Because of this and the cost of the drug, the Committee expressed concerns about the value for money provided by this treatment.</p>	<p>5.17</p>

Impact beyond direct health benefits and on the delivery of the specialised service	The Committee understood that elosulfase alfa may provide important benefits to patients and their families in addition to the direct health benefits of treatment.	5.18
	The Committee noted that treatment with elosulfase alfa needs weekly infusions, but understood that elosulfase alfa may be given in people's homes.	5.19
	The Committee concluded that the impact of elosulfase alfa on the delivery of specialised services was likely to be relatively negligible.	5.20
Additional factors taken into account		
Access schemes	The company has proposed a patient access agreement, in which elosulfase alfa would be provided at a discounted cost; the discount is commercial in confidence and so cannot be reported here.	3.3
Equalities considerations and social value judgements	n/a	

6 Implementation

- 6.1 If elosulfase alfa were to be recommended, section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) would require clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 6.2 NICE has not developed implementation tools. If elosulfase alfa were to be recommended, NICE would work with NHS England to ensure implementation of the recommendations is monitored.

7 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

There is no related NICE guidance for this technology.

8 Proposed date for review of guidance

- 8.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, Highly Specialised Technologies Evaluation Committee

April 2015

9 Evaluation Committee members, guideline representatives and NICE project team

Evaluation Committee members

The highly specialised technologies Evaluation Committee is a standing advisory committees of NICE. Members are appointed for a 3-year term, and a Chair and vice chair are also appointed for 3 years. A list of the Committee members who took part in the discussions for this evaluation appears below.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each Evaluation Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Peter Jackson (chair)

Consultant Physician and Honorary Reader in Clinical Pharmacology

Sotiris Antoniou

Consultant Pharmacist, Cardiovascular Medicine, Barts Health NHS Trust.

Steve Brennan

Chief Finance Officer, NHS North Kirklees Clinical Commissioning Group

Jonathan Howell

Consultant in Public Health

Jeremy Manuel

Lay Member

Francis Pang

Vice-President, Market Access, Biogen Idec

Linn Phipps

Lay Member

Mark Sheehan

Oxford BRC Ethics Fellow, The Ethox Centre, University of Oxford

Lesley Stewart

Director, Centre for Reviews and Dissemination, York

Sheela Upadhyaya

Highly Specialised Program of Care Lead (London Region), NHS England

Anthony Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, Guy's & St. Thomas' Hospitals, London

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more technical personnel, a project manager and the Associate Director for the Highly Specialised Technologies Programme.

Ian Watson

Technical Analyst

Raisa Sidhu

Technical Adviser

Leanne Wakefield

Project Manager

Josie Godfrey

Associate Director

10 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this evaluation was prepared by Southampton Health Technology Assessments Centre (SHTAC):

Cooper K, Kalita N, Harris P et al. (2015) Elosulfase alfa for the treatment of mucopolysaccharidosis type IVA: A Highly Specialised Technology Evaluation. Southampton Health Technology Assessments Centre (SHTAC)

B. The following organisations accepted the invitation to participate in this evaluation as consultees and commentators. They were invited to comment on the draft scope and the evaluation consultation document (ECD). Organisations listed in I, II and III were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final evaluation determination.

I. Company:

- BioMarin Pharma inc.

II. Professional/specialist and patient/carer groups:

- MPS Society
- Save Babies Through Screening Foundation UK
- Birmingham Children's Hospital NHS Foundation Trust
- British Inherited Metabolic Disease Group
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians
- Royal Free Lysosomal Storage Disorders Unit
- Willink Unit, Royal Manchester Children's Hospital, CMFT

III. Other consultees:

- Department of Health
- NHS England

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Welsh Government
- Cochrane Cystic Fibrosis and Genetic Disorders Group
- Society for the Study of Inborn Errors of Metabolism

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Elosulfase alfa for treating mucopolysaccharidosis type IVA by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ECD.

- Dr Fiona Jenkinson, nominated by Royal College of Pathologists– clinical expert
- Dr Suresh Vijay, nominated by British Inherited Metabolic Disease Group – clinical expert
- Angela Paton, nominated by MPS Society – patient expert
- Anna Eaton, nominated by MPS Society – patient expert
- Christine Lavery, nominated by MPS Society – patient expert
- Jibreel Arshad, nominated by MPS Society– patient expert

D. The following individuals were nominated as NHS Commissioning experts by NHS England. They gave their expert/NHS commissioning personal view on Elosulfase alfa for treating mucopolysaccharidosis type IVA by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ECD.

- Edmund Jessop and Iain Mellis selected by NHS England

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- BioMarin Pharma inc.