Elosulfase alfa for treating mucopolysaccharidosis type IVa

Highly specialised technologies guidance
Published: 16 December 2015
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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
Contents

1 Guidance ............................................................................................................................................................................ 4
2 The condition.................................................................................................................................................................... 5
3 The technology ................................................................................................................................................................ 6
4 Evidence submissions ................................................................................................................................................... 7
   Nature of the condition .................................................................................................................................................. 7
   Clinical evidence ............................................................................................................................................................ 8
   Economic evidence ........................................................................................................................................................ 12
   Impact of the technology beyond direct health benefits and on delivery of the specialised service .......... 15
   Evidence Review Group review ........................................................................................................................................ 16
   Company’s response to the first evaluation consultation document ................................................................. 19
   Response to the second evaluation consultation document: managed access agreement ............................. 21
5 Consideration of the evidence .................................................................................................................................. 23
   Nature of the condition .................................................................................................................................................. 23
   Impact of the new technology .................................................................................................................................... 24
   Cost to the NHS and Personal Social Services ........................................................................................................ 28
   Value for money ............................................................................................................................................................ 30
   Impact of the technology beyond direct health benefits and on delivery of the specialised service .......... 36
   Conclusion .................................................................................................................................................................... 37
   Summary of Evaluation Committee’s key conclusions .......................................................................................... 38
6 Implementation ............................................................................................................................................................... 45
7 Review of guidance ......................................................................................................................................................... 46
8 Evaluation Committee members, guideline representatives and NICE project team ..................................... 47
   Evaluation Committee members .................................................................................................................................... 47
   NICE project team ........................................................................................................................................................ 48
9 Sources of evidence considered by the Committee ............................................................................................... 49
About this guidance ............................................................................................................................................................. 52
1 Guidance

1.1 Elosulfase alfa, within its marketing authorisation, is recommended for funding for treating mucopolysaccharidosis type IVa (MPS IVa) according to the conditions in the managed access agreement for elosulfase alfa.
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 respiratory disease, joint and skeletal abnormalities, hearing loss, corneal clouding and heart valve disease. MPS IVa also causes pain, fatigue, progressive loss of endurance and increasing dependence on a wheelchair. It leads to reduced life expectancy, primarily through respiratory failure and heart problems (63% and 15% of deaths respectively). The joint and skeletal abnormalities play a role in the development of respiratory symptoms but other factors, including upper and lower airway obstruction and reduced muscle strength from glycosaminoglycan deposition, can also have a significant effect on respiratory function. 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 74–77 of these people 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 has developed 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 adult 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 treatment is anticipated to continue for life.

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/week and an average body weight of 25.3 kg). The company has proposed a patient access scheme, in which elosulfase alfa would be provided at a discounted cost; the discount is commercial in confidence and so cannot be reported here. The managed access agreement includes further commercial arrangements between the company and NHS England for the duration of the agreement.
4 Evidence submissions

The Evaluation Committee (section 8) considered evidence submitted by the company of elosulfase alfa, a review of this submission by the Evidence Review Group (ERG; section 9), evidence submitted by clinical experts, patient experts and NHS England, and the responses to consultation on the first and second evaluation consultation documents from all consultees and commentators and members of the public. The Evaluation Committee also considered the managed access agreement.

Nature of the condition

4.1 It was estimated at the time of the evaluation that 88 people were living with mucopolysaccharidosis type IVa (MPS IVa) in England, with about 3 new diagnoses expected per year. About 74–77 people were anticipated to be eligible for enzyme replacement therapy and may want treatment with elosulfase alfa. Patient experts and patient groups highlighted the substantial impacts of 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 some children who had elosulfase alfa continued to grow, experienced less physical deterioration, avoided surgery and did not become dependent on a wheelchair. 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 the testimonies are subjective and 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
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 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 (uKS), 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 and 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 showed no clear trends in the change from baseline to week 24. However, this study included
patients with slowly progressive disease (attenuated) who have less obstructive
sleep apnoea than classical patients. 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 MPS 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 (PSS), 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 scheme; 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 MPS 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.
In the company's 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.

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'.

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.

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 are expected to want 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. These figures do not take into account the arrangements included in the managed access agreement.
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 worldwide, including England. 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 reasonable quality clinical studies. It noted some challenges in interpreting the clinical trial data (which are not uncommon in clinical research for rare diseases), 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
- 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. It also noted that the observed benefit was clinically meaningful (although there is no empirical evidence to support 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 results should be interpreted with caution because of the possible placebo effect. 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 to be treated in the NHS.

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 in particular 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 their 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, in the context of the NICE guide to the methods of technology appraisal 2013 (which it considered to be relevant to the highly specialised technologies programme), but explored this in a scenario analysis.

4.29 The ERG considered that the assumptions used to model clinical effectiveness were 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.
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.

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. It also commented on the marked decline in utility between occasional and constant wheelchair use. The study from which the health state utility scores were obtained reported utility values for both children and adults (although only the values for adults were used in the model). The ERG noted that the 2 sets of utility values were different, and the reasons for this were largely unknown. The ERG highlighted that quality-of-life evidence from MOR-004 and -005 does not appear to have been used in the model.

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.

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.

Company's response to the first evaluation consultation document

4.35 Following the conclusion of the first Committee meeting, the Committee requested the company to provide 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)
- budget impact of administering elosulfase alfa at people's homes.

4.36 The company maintained that, based on evidence from MOR-005 at week 72 (see section 4.9) and the experience from using enzyme replacement therapy for other MPS disorders, elosulfase alfa would be expected to stop disease progression in 'multi-domain responders' and reduce it by 50% in 'single-domain responders'. It also presented results at week 120 from MOR-005, which were
not available at the time of the company’s original submission. These showed that the benefits seen at week 72 were sustained up to week 120. To address the Committee’s request, the company presented 2 additional analyses in which it varied the rates of disease progression across health states for multi-domain and single-domain ‘responders’ (rates were constant across health states in the base case). It stated that both analyses resulted in small changes to the base-case incremental costs and QALYs.

4.37 The company explored an alternative approach to modelling the utility benefit associated with elosulfase alfa. It obtained from the literature a utility estimate for each additional benefit reported by patients but not captured by the 6MWT or FVC; namely, pain, visual acuity, sleep, wrist function and hearing. It used those estimates in 4 analyses:

- ‘Optimistic scenario’: the utility values for each benefit were added up to estimate the total utility benefit patients would receive (constant utility value across health states of 0.147).

- ‘Conservative scenario’: the utility benefit was estimated as a proportion (20–40%) of the total possible utility benefit (constant utility value across health states of 0.074).

- The utility benefit increased as the patient moved to a worse health state (variable utility values for each health state ranging from 0.074 to 0.147).

- The utility benefit decreased as the patient moved to a worse health state (variable utility values for each health state ranging from 0.147 to 0.074).

The incremental QALYs from the above analyses ranged from 17.11 to 19.96 compared with 18.18 in the base case (that is, the incremental QALYs changed between −1.07 and +1.78 compared with the base case).

4.38 The company presented an analysis showing the effect of excluding the VAT waiver for home care. The incremental costs increased by 20.7% compared with the base case.

4.39 The company modelled 2 alternative scenarios excluding the mortality benefit of elosulfase alfa. Firstly, it applied a constant mortality rate across all health states, equal to the mortality rate seen in the general population. Secondly, it applied a mortality rate that increased as patients moved through worsening health states; this was estimated based on clinical opinion. The incremental
QALYs were 17.93 in the first scenario (decrease of 0.25 [−1.4%] compared with the base case) and 17.42 in the second scenario (decrease of 0.76 [−4.2%] compared with the base case). Incremental costs decreased by 0.2% and 3.6% respectively compared with the base case.

To assess the combined effect of the additional analyses (that is, the alternative modelling of disease progression, the utility benefit associated with elosulfase alfa, the VAT waiver for home care and mortality), the company presented a 'best case scenario' and a 'worst case scenario'. In these, it used the scenario that produced the best or worst QALYs respectively from each additional analysis. Compared with the base case, the incremental QALYs increased by 2.63 in the best case scenario and decreased by 3.23 in the worst case scenario. The incremental costs increased by 10.8% and 3.5% compared with the base case in the best and worst case scenarios respectively.

The company provided an analysis of the budget impact for the NHS and PSS of administering elosulfase alfa in people’s homes. The base case assumed that 90% of patients would have infusions at home after an initial 3 months of having infusions in hospital. The company considered this to be conservative because all MPS VI patients who receive galsulfase receive it at home. It expected that all patients with MPS IVa will also have home care. The costs used in the analysis were actual costs incurred by patients currently receiving elosulfase alfa at home. The costs of providing elosulfase alfa at home were significantly greater than the tariff costs of providing it in hospital, but these differences were overwhelmed by the VAT that would be payable if the drug was supplied via the hospital, such that the difference in cost for all patients treated would be £3,069,111 less for home care in the first year increasing to £5,941,015 less for home care in the fifth year.

Response to the second evaluation consultation document: managed access agreement

In response to the second evaluation consultation document, and facilitated by NICE, a managed access agreement was developed and submitted by a group of stakeholders comprising the company, NHS England, the MPS Society and a group of clinical experts.

The managed access agreement takes effect with publication of this guidance.
and will remain in force until a review of the guidance has been published or after 5 years (whichever is earlier). The company has agreed to provide the relevant data to inform the review of the guidance during the fourth year of the agreement. The managed access agreement states that, if NICE does not recommend elosulfase alfa for NHS funding when the guidance is reviewed, NHS England funding for elosulfase alfa will no longer be available for any patient. Those involved in the managed access agreement will ensure that any patient receiving elosulfase alfa whose treatment is funded by NHS England under this managed access agreement is made aware of these funding limitations and accepts them upon signing the patient agreement on the terms set out in the managed access agreement.
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 also considered all comments received during consultation on the first and second evaluation consultation documents. 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) at the first, second and third meetings. 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 discussed the nature of MPS IVa. It understood that MPS IVa is a serious condition that severely affects life expectancy and quality of life, leading to dramatic effects on the lives of people with the condition, and their families and carers. The Committee heard that the severity of the disease varies among people; some people have particularly severe disease with a short life expectancy, others have a form that progresses more slowly and they may live longer. The Committee understood that MPS IVa is a complex and highly heterogeneous disorder, and evidence on the natural history of the condition is still evolving. It heard that, at the outset of the clinical trials for elosulfase alfa, the clinical community believed that MPS IVa was purely a skeletal disorder, and this was also supported by the literature. The general belief at the time was that enzyme replacement therapy would not treat musculoskeletal symptoms. However, the clinical experience during the trials was unexpectedly positive, and remarkable improvement was seen in some patients, including those who had established skeletal disease for many years. It became apparent that the skeletal features, although important, were only part of a multi-system disorder, and that non-skeletal features, including cardiac and respiratory complications, contribute heavily to the burden of illness. The Committee heard from the clinical experts that emerging evidence suggests the disease has wide systemic involvement because glycosaminoglycan deposits have been found in various organs including the lungs, heart and connective tissues. The Committee concluded that, although the disease process is not yet fully understood, MPS IVa is a debilitating condition that affects the body across multiple organ systems.
The Committee discussed the long-term clinical outcomes of MPS IVa. It noted that it is a multi-system disorder leading to respiratory, cardiac and musculoskeletal symptoms, which can all cause variable long-term clinical outcomes. The Committee understood that the respiratory and cardiac complications are the key drivers of mortality in patients with MPS IVa, accounting for 63% and 15% of all deaths respectively. It noted comments from experts that pain and fatigue are the main burdens of MPS IVa, with loss of endurance being the greatest single problem associated with the disease. The Committee heard from the clinical experts that, traditionally, cervical spinal cord damage was considered an important determinant of clinical outcomes in people with MPS IVa. However, most patients are now treated before damage occurs, with spinal surgery (cervical spine fusion and spinal decompression) currently being used prophylactically to reduce the risk of spinal cord damage. This, in turn, has significantly reduced the number of patients dying from this complication. The Committee understood that people with MPS IVa can be at risk of damage, and some will need spinal surgery at some point in their lives, particularly if they have disease with relatively rapid progression. Spinal cord damage can have an impact on mobility and quality of life, but the Committee agreed with the patient experts' view that its overall contribution to morbidity is generally small. The Committee concluded that the key determinants of mortality are the respiratory and cardiac complications, and that what matters the most to people with the condition is the ability to carry out normal everyday activities with sufficient endurance and without pain or fatigue.

**Impact of the new technology**

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.

The Committee considered whether the endpoints assessed in the clinical trials
had captured the 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 cardiac and respiratory function, cervical spinal cord damage, bone health and the need for orthopaedic surgery.

- Cardiac and respiratory function: the Committee heard that the clinical trials were not designed to explicitly study these, although they are the main causes of mortality (see section 5.2). In addition, long-term follow up is needed to assess these outcomes, but the trials were relatively short. However, the Committee heard from the clinical expert that it is plausible that elosulfase alfa could affect these outcomes. It also noted comments suggesting treatment led to reduced chest infections and improved general lung function.

- Cervical spinal cord damage and bone health: the Committee noted that spinal cord damage from spinal stenosis had not been assessed in clinical trials because the perception had always been that enzyme replacement therapy would not affect bones. The clinical experts indicated, however, that growth had been seen beyond the usual time of growth failure in people receiving enzyme replacement therapy, suggesting a potential of growth in the vertebrae, which widens the spinal canal and reduces skeletal complications. The Committee 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 noted comments from consultation stating that the true skeletal impact of elosulfase alfa will take years to be fully understood.

- Orthopaedic surgery: the Committee understood that some people with MPS IVa may need orthopaedic surgery, including hip and knee surgery. It noted that MOR-005 included an assessment of the time to orthopaedic surgery, but comparisons with the incidence of surgery in the natural history of MPS IVa (that is, from MOR-001) were not available. The Committee noted that the European Public Assessment Report for elosulfase alfa states that it appears to reduce the incidence of orthopaedic surgery. The Committee did not consider there to be sufficient evidence from clinical trials on surgical outcomes.

The Committee concluded that several benefits of elosulfase alfa treatment may have not been adequately captured in the clinical trials, so some of the true long term outcomes in people with MPS IVa remained uncertain.
The Committee discussed the endpoints assessed in the clinical trials. It understood that the primary outcome in the randomised clinical trials, the 6-minute walk test (6MWT), is a surrogate outcome that provides a broad measure of overall functioning, including musculoskeletal health, cardiovascular and respiratory aspects, pain and fatigue. The Committee noted that the improvement in 6MWT with elosulfase alfa was statistically significant compared with placebo (see sections 4.6 to 4.8). 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 also 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. Furthermore, patients do not judge their quality of life by how much they are using the wheelchair. The Committee considered that this evidence was informative but was mindful of putting too much emphasis on it. The Committee agreed 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 and useful in giving some indication of the real-life benefits of treatment experienced by patients.

The Committee discussed the clinical benefits associated with elosulfase alfa as experienced by patients. It heard from the patient experts that, with treatment, patients can expect the disease to stabilise and also to get better. The clinical experts stated that most people treated with elosulfase alfa experienced clinical improvements beyond what could be attributed to a placebo effect, including improved endurance, pulmonary function, anthropometrics, wheelchair dependency and quality of life. The patient experts also described positive effects on sleep, pain, energy levels and fatigue, dexterity and ability to complete everyday activities. However, these benefits were not known at the onset of the clinical trials for elosulfase alfa, so the trials were not designed to capture them. In general, the patient experts considered that treatment offered
substantial benefits to people with the condition, with some going from being non-ambulant, unable to speak and having a short life expectancy to being in stable health, able to speak again and resume university studies. The Committee heard that young people who started treatment maintained their ability to walk and continued to grow. In addition, treatment improved pulmonary function, so reducing the frequency and severity of chest infections and allowing a normal recovery from common respiratory illnesses. The patient experts also highlighted the quicker recovery from physical exertion with elosulfase alfa, which saved energy for other day-to-day activities. Based on the patient testimonies, the Committee concluded that elosulfase alfa improved various abilities and aspects of health compromised by the disease, and that the patients’ experience with treatment had been largely positive, with health and quality of life improving significantly in some patients. However, it was aware that anecdotal, patient-reported outcomes are likely to vary between patients, so ought to be considered with some degree of caution.

The Committee discussed whether the evidence from clinical trials and the patient testimonies can be reconciled. It noted from the clinical experts that elosulfase alfa conferred substantial benefits that patients valued greatly and significantly improved several dimensions of quality of life. However, the Committee was aware that the clinical trials measured primarily proxy outcomes (for example, the 6MWT), and did not substantiate most of the direct health benefits described by patients. The Committee was aware that the patient experts’ opinion, although useful, was subjective and may be at risk of bias because it may represent the experience of only a selected group of patients. The Committee acknowledged that real-world data on the proportion of patients receiving and stopping treatment with elosulfase alfa, the doses used, adverse effects of treatment and clinically meaningful benefits of treatment realised by patients would be very useful to mitigate some of the existing uncertainties in the clinical evidence base. The Committee considered that the assessments described in the managed access agreement would generate evidence for MPS IVa that was directly relevant to patients in the UK through research and collection of ‘real-world’ data. The Committee concluded that the data collected via the registry within the context of the managed access agreement would be likely to provide ‘real-world’ data that would help to reconcile the differences between the patient testimonies and clinical trial data when this guidance is reviewed.
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**

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 at its list price would rise from £17.3 million in year 1 to £28.8 million in year 5 (the budget impact analyses incorporating the patient access scheme are commercial in confidence and so cannot be reported here).

The Committee explored the number of people who would receive elosulfase alfa if it were recommended. It heard from a patient expert that 77 people in England are thought to be eligible for treatment. The Committee heard that this excludes people with paraplegia or who are 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, the precise number of people who would have treatment with elosulfase alfa in England if it were recommended is uncertain.

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 original 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 that including the VAT waiver was not appropriate. In its addendum, the Evidence Review Group (ERG) presented a budget impact analysis incorporating the patient access scheme that excluded the VAT waiver for home care. The Committee concluded that the ERG’s analysis excluding the VAT waiver should be used in its decision-making.

5.12 The Committee noted that the company did not present an analysis of the costs associated with delivering elosulfase alfa at people's homes in its original submission. 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. In response to consultation, the company provided an analysis of the budget impact of administering elosulfase alfa at people's homes. The differences between hospital costs and home costs were estimated at £3,069,111 in the first year, increasing over the years to £5,941,015 in the fifth year. The Committee was aware that treating people with MPS IVa costs the NHS around £10,000/patient/year exclusive of enzyme replacement therapy.

5.13 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. The company stated that, because elosulfase alfa is a treatment that can only be used by a small number of patients, the high cost is largely driven by the need to recoup the investment in research and development, and manufacturing. The Committee heard that there are only about 3000 people with MPS IVa across the world, of whom an estimated 1000 to 2000 may be able to access the drug. Furthermore, it heard that developing drugs to treat rare conditions is expensive and that the manufacture of this drug is complex. The company
estimated that the cost of the clinical trial programme for elosulfase alfa had been about $350 million over 10 years, with the company risking failure at each step because the level of scientific knowledge was low for MPS IVa. In addition, the company noted that it had invested more than $130 million in England through developing elosulfase alfa, and had built a new manufacturing facility. It cited 1 paper suggesting that the return on equity for manufacturers of treatments for rare diseases is only 28% of that of other pharmaceutical companies because the investment in research is higher, and argued that treatments for rare diseases need to have a high cost to be commercially viable. The Committee highlighted that the acquisition cost per kilogram body weight is substantially higher than that of galsulfase, one of the company's other enzyme replacement therapies used to treat MPS VI (£196/kg/week for galsulfase compared with £300/kg/week for elosulfase alfa). The Committee heard from the company that comparing the cost of elosulfase alfa and galsulfase using the acquisition cost per kilogram of body weight is inaccurate because it does not reflect the annual cost of treatment per patient. Although the vial acquisition costs for the 2 treatments differ, the actual annual treatment costs are similar because the average weights of patients differ; patients with MPS IVa weigh less than those with MPS VI in the UK. The Committee acknowledged the company's efforts to address its concerns about the cost of elosulfase alfa, but was not satisfied that its high cost was fully justified.

5.14 The Committee considered that further assurances were needed to ensure that the cost of elosulfase alfa to the NHS is appropriately contained before elosulfase alfa is routinely used for patients with MPS IVa. The Committee concluded that it was satisfied that the company and NHS England had included commercial arrangements in the managed access agreement to limit the total costs of elosulfase alfa during data collection.

Value for money

5.15 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, in the original model, 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. This was based on a 10-year study of people with MPS VI. 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; this resulted in a much smaller gain in quality-adjusted life years (QALYs) compared with established clinical management than in the company's original base case. The Committee agreed that elosulfase alfa was likely to slow disease progression, but would be unlikely to stop it entirely. The Committee noted that the company presented 2 additional analyses in response to consultation. In these, the company varied the rates of disease progression across health states for multi-domain and single-domain 'responders', with the rates used based on clinical advice to the company. The Committee understood that these analyses explored the possibility that the impact of elosulfase alfa on disease progression depended to some extent on how much irreversible damage was present when treatment started. The Committee heard from clinical experts that disease progression varies widely among people depending on factors such as age and disease pathology, and that it would be difficult to model this with reasonable accuracy. However, the clinical experts agreed that it would be more clinically plausible to assume a variable, rather than a constant, rate of disease progression depending on the burden of the disease at the point at which treatment is received. Therefore, they considered the company's additional analyses to be more realistic than the original base case. The Committee noted the patient perspective that people consider the disease to be stable when the benefit gained from treatment is maintained over time, and the patient is able to get on with their life without symptomatic progression. The Committee acknowledged that elosulfase alfa was likely to provide valuable clinical benefits to people with the condition. However, it considered that assuming that elosulfase alfa would completely stop disease progression in 'multi-domain responders' is not plausible and would overestimate the benefit of treatment. The Committee concluded that varying the rate of disease progression across health states would better reflect the natural history of the disease instead of using constant rates.

5.16 The Committee noted that the company's utility estimates in their original submission included a substantial decline between people using a wheelchair 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.

5.17 The Committee also noted that the company had applied a utility increment to the elosulfase alfa group to reflect the benefits beyond the slowing of disease progression and improving endurance. The ERG considered that this double counted the treatment benefits. This utility increment was estimated 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), but that the clinical trials for elosulfase alfa collected only limited evidence on quality of life, and did not collect EQ-5D data. The Committee considered the additional analyses presented by the company in response to consultation, in which the company modelled the utility benefit associated with elosulfase alfa based on utility estimates obtained from the literature. It noted that this had a modest impact on incremental QALYs. The Committee understood that measures of quality of life had not been extensively used in clinical trials for this condition. It heard from the company that the MPS Childhood Health Assessment Questionnaire was initially thought to be the best available measure of quality of life in children, but it later became apparent that it did not adequately capture all the dimensions of health that matter to patients. The Committee heard from the patient experts that it can be very difficult to fill in quality-of-life questionnaires, particularly for children who usually do not recollect their quality of life before treatment to compare it with how they feel after treatment. One patient expert felt that the questionnaires did not ask the right questions because they elicited information on the patient’s ability to do day-to-day activities, whereas the ability might be similar before and after treatment but the critical difference is in how the patient feels after doing the activity; that is, in their recovery. The
Committee noted that, as the determinants of quality of life have become better understood, alternative measures are being studied and new creative ways to capture quality of life are being considered (for example, using smartphones). Having considered the evidence from clinical trials and the testimonies of the patient experts, the Committee acknowledged that elosulfase alfa improves several dimensions of quality of life, including endurance and fatigue, pain, education, work and social life (see section 5.6). The Committee therefore agreed that it was reasonable to include a utility increment associated with elosulfase alfa in the economic model. However, it appreciated that the evidence on quality of life was limited, and that what evidence there was had been synthesised using methods that had not been fully developed or validated. The Committee concluded that the existing evidence did not allow the utility benefit associated with elosulfase alfa to be robustly modelled.

5.18 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 original 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. 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. In response to consultation, the company modelled 2 alternative scenarios excluding the mortality benefit of elosulfase alfa (see section 4.39). The Committee concluded that these scenarios were more clinically plausible.

5.19 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 and no separate budget for highly specialised technologies. NHS England stated that only a small portion of the overall budget for specialised services is available for commissioning technologies such as this, and that about 80 technologies were being considered for commissioning at the time of the evaluation. 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. On the basis of the available evidence on overall benefit, the Committee considered that the cost of elosulfase alfa incorporating the patient access scheme was too high for it to be recommended outside the context of a managed access agreement. It noted that, in addition to the patient access scheme, the managed access agreement included other commercial arrangements that reduced the total costs to the NHS. The Committee concluded that including these other commercial arrangements in the managed access agreement as well as the patient access scheme would offer a more acceptable value for money in the context of the uncertainty of the clinical benefits.

5.20 The Committee supported the company's commitment to continue to strengthen the evidence base for this condition, through patient registries and research, as part of a managed access agreement with NHS England. The Committee was aware that elosulfase alfa will be made available through the managed access agreement and that people would consent when starting treatment that ongoing funding cannot be guaranteed to be provided by NHS England after 5 years if the clinical outcome data do not support continued treatment. The Committee was advised by NICE that this made it sufficiently clear to people starting treatment with elosulfase alfa in the context of the managed access agreement that the treatment period could be finite.

5.21 The Committee discussed whether applying criteria for starting and stopping treatment could improve the value for money of elosulfase alfa. It heard from the clinical experts that the National Advisory Group for Lysosomal Storage Disorders has developed such criteria for enzyme replacement therapy, which the company also cited in its response to consultation. The clinical experts indicated that these criteria were developed 2 years ago and may need to be adjusted over time, but that they can be used for the time being to target treatment to people who would benefit most. The Committee heard that the criteria for starting and stopping treatment are not based on evidence and need to be individualised for each patient, but that some general principles can guide treatment decisions in clinical practice. For example, treatment is likely to be offered to people with early stage disease because these people are thought more likely to benefit from treatment, whereas those with severe forms of the disease may not. Once started, treatment would not normally continue in people whose disease does not respond at all, or in those who are unable to
comply fully with the treatment schedule. Importantly, the clinical experts emphasised the importance of having a discussion with patients before treatment starts to manage the patient’s expectations and talk through the clinical scenarios in which treatment may be stopped. The patient experts recognised the limited resources available and supported using criteria for starting and stopping treatment, particularly the upfront discussion with clinicians to ensure that the patient had realistic expectations from treatment. The Committee heard from the company that starting and stopping criteria are estimated to reduce costs by 20% and QALYs gained by 10%. The clinical experts pointed out that treatment can appear to offer benefit after being stopped, sometimes for up to 2 years, during which time no costs would be incurred. The Committee would have liked the economic impact of starting and stopping criteria to have been explored in more detail, but it acknowledged there are significant uncertainties that would be included in the modelling (including the most appropriate starting and stopping criteria), which might result in estimates that are not appropriate for decision-making. The Committee was aware that MPS IVa is a heterogeneous condition, with a response to treatment that varies greatly among patients. Although the economic impact of using criteria for starting and stopping treatment had not been established because of the absence of robust evidence, the Committee concurred with comments from the clinical experts. It considered the criteria in the managed access agreement for starting and stopping elosulfase alfa, including the response criteria for continuing treatment. The Committee concluded that the criteria in the managed access agreement would encourage a discussion before treatment starts to manage patients' expectations of treatment, and to get agreement on the clinical scenarios for potentially stopping treatment.

5.22 The Evaluation Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when evaluating elosulfase alfa. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this evaluation of elosulfase alfa. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the value for
money offered by elosulfase alfa.

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

5.23 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 noted 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.

5.24 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.

5.25 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

5.26 The Committee discussed the appropriate recommendations for elosulfase alfa for MPS IVa. It acknowledged that MPS IVa is a serious condition that has severe effects on the lives of people with the condition, as well as their families and carers. The Committee accepted that elosulfase alfa can provide valuable clinical benefits for some aspects of the condition, including quality of life. It also considered that elosulfase alfa could provide distinctive benefits beyond those directly related to health. The Committee noted that some patients who received elosulfase alfa reported significant health and quality-of-life benefits, but that the clinical trials measured primarily proxy outcomes and the evidence from them could not be reconciled with the patient testimonies (see section 5.7). In addition, the Committee noted the high acquisition cost of elosulfase alfa and did not consider that this had been fully justified. Taken together, the Committee had concerns about the true value for money provided by elosulfase alfa, and could not ascertain whether the benefits of treatment measured in short-term clinical trials would, on average, be associated with gains in longevity and persisting benefits in those outcomes that are important to patients. On the basis of the available evidence on overall benefit, the Committee considered that the cost of elosulfase alfa, incorporating the patient access scheme, was too high for it to be recommended outside the context of a managed access agreement. However, it was satisfied that there was sufficient evidence that some patients did well on elosulfase alfa to justify further exploration of its costs and benefits in routine clinical practice, within the context of a managed access agreement, to inform a future review of this guidance. The Committee concluded that including other commercial arrangements in the managed access agreement in addition to the patient access scheme would offer more acceptable value for money in the context of the uncertainty of the clinical benefits. Because of this, the Committee concluded that elosulfase alfa could be recommended for treating MPS IVa if it is given according to the conditions in the managed access agreement.
Summary of Evaluation Committee’s key conclusions

<table>
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<tr>
<th>HST2</th>
<th>Evaluation title: Elosulfase alfa for treating mucopolysaccharidosis type IVa</th>
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<tr>
<td></td>
<td><strong>Key conclusion</strong></td>
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<td></td>
<td>Elosulfase alfa, within its marketing authorisation, is recommended for funding for treating mucopolysaccharidosis type IVa (MPS IVa) according to the conditions in the managed access agreement for elosulfase alfa.</td>
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<td>On the basis of the available evidence on overall benefit, the Committee considered that the cost of elosulfase alfa incorporating the patient access scheme was too high for it to be recommended outside the context of a managed access agreement. However, it was satisfied that there was sufficient evidence that some patients did well on elosulfase alfa to justify further exploration of its costs and benefits in routine clinical practice, within the context of a managed access agreement, to inform a future review of this guidance.</td>
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<td><strong>Current practice</strong></td>
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<td><strong>Nature of the condition, including availability of other treatment options</strong></td>
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<td>The Committee understood that MPS IVa is a serious condition that severely affects life expectancy and quality of life and leads to dramatic effects on the lives of people with the condition and their families and carers. The Committee heard that initially, MPS IVa was believed to be purely a skeletal disorder, but it later became apparent that the skeletal features were only part of a multi-system disorder, and that non-skeletal features contribute heavily to the burden of illness. The Committee concluded that the disease process is not yet fully understood but that MPS IVa is a debilitating and highly heterogeneous condition that affects the body across multiple organ systems.</td>
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<td>The Committee concluded that the key determinants of mortality are the respiratory and cardiac complications, and that what matters the most to people with the condition is the ability to carry out normal everyday activities with sufficient endurance and without pain or fatigue. The Committee agreed that, although spinal cord damage can have an impact on mobility and quality of life, its overall contribution to morbidity is generally small.</td>
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The technology
| Proposed benefits of the technology | The clinical experts stated that most people treated with elosulfase alfa experienced improvements in endurance, pulmonary function, anthropometrics, wheelchair dependency and quality of life. The patient experts also described positive effects on sleep, pain, energy levels and fatigue, dexterity and ability to complete everyday activities. The Committee concluded that elosulfase alfa improved various abilities and aspects of health compromised by the disease, and that the health and quality of life of some patients improved significantly on treatment. | 5.6 |
| 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 |
| Adverse reactions | Patient experts reported experiencing some adverse reactions but emphasised that these were quickly controlled and were vastly outweighed by the benefits of treatment. | 5.8 |

### Clinical evidence

| Availability, nature and quality of evidence | The Committee was pleased to see that a detailed study of the natural history of MPS IVa involving many people was presented. The Committee was satisfied that the clinical trials generally reflected the spectrum of people who would be expected to have treatment in England. | 5.3 |
| | The Committee noted that various benefits experienced by patients who received elosulfase alfa were not known at the onset of the clinical trials, and so the trials were not designed to capture them. | 5.4 |
| | The Committee noted that the primary outcome in the randomised clinical trials, the 6-minute walk test (6MWT), is a surrogate outcome that provides a broad measure of overall functioning, which it concluded was broadly appropriate and useful in giving some indication on the real-life benefits of treatment experienced by patients. | 5.5 |
| | The Committee noted that much of the evidence represented anecdotal, patient-reported outcomes. | 5.6 |
The Committee concluded that some of the true long-term outcomes in people with MPS IVa, such as cardiac and respiratory function and the need for orthopaedic surgery, remained uncertain.

The Committee was aware that the patient experts' opinion was subjective and was at risk of bias because it may represent the experience of only a selected group of patients.

The Committee was aware that the clinical trials measured primarily proxy outcomes, and did not substantiate most of the direct health benefits described by patients. The Committee concluded that data collected within the context of the managed access agreement would help to reconcile the differences between the patient testimonies and clinical trial data when this guidance is reviewed.

Based on the patient testimonies, the Committee concluded that elosulfase alfa improved various abilities and aspects of health compromised by the disease, and that the patients' experience with treatment had been largely positive, with health and quality of life improving significantly in some patients. However, it was aware that patient testimonies ought to be considered with some degree of caution.

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 (PSS), and costs and benefits were discounted at a rate of 1.5% per year.

The company presented a budget impact analysis to predict the costs of elosulfase alfa in the NHS and PSS.
### Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis

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<td>The Committee heard that disease progression varies widely among people, and that it would be difficult to model this with reasonable accuracy. The Committee concluded that varying the rate of disease progression across health states would better reflect the natural history of the disease instead of using constant rates.</td>
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| 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 so considered that the company had overestimated the cost to the NHS of professional carers. The Committee concluded that the budget impact analyses used in its decision-making should exclude the VAT waiver. | 5.11 |

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<th>Incorporation of health-related quality-of-life benefits and utility values</th>
<th>The Committee noted that the company's utility estimates in their original submission included a substantial decline between people using a wheelchair 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. The Committee noted that there are additional challenges in caring for people who are dependent on a wheelchair.</th>
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<td>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?</td>
<td>The Committee agreed that it was reasonable to include a utility increment associated with elosulfase alfa in the economic model. However, it appreciated that the evidence on quality of life was limited, and that what evidence there was had been synthesised using methods that had not been fully developed or validated. The Committee concluded that the existing evidence did not allow the utility benefit associated with elosulfase alfa to be robustly modelled.</td>
<td>5.17</td>
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<td>Cost to the NHS and PSS</td>
<td>The Committee noted that the company's budget impact analysis at the list price 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. The analyses incorporating the patient access scheme are confidential and cannot be reported here. The managed access agreement includes further commercial arrangements between the company and NHS England for the duration of the agreement.</td>
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<td>The Committee was not satisfied that the high cost of elosulfase alfa was fully justified and considered that further assurances were needed to ensure that the cost of elosulfase alfa to the NHS is appropriately contained before elosulfase alfa is used routinely for patients with MPS IVa. The Committee concluded that it was satisfied that the company and NHS England had included commercial arrangements in the managed access agreement to limit the total costs of elosulfase alfa during data collection.</td>
<td>5.14</td>
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## Value for money

The Committee noted that some patients who received elosulfase alfa reported significant benefits, but that the clinical trials primarily measured proxy outcomes and the evidence from them could not be reconciled with the patient testimonies. In addition, the Committee noted that the high cost of elosulfase alfa had not been fully justified. Taken together, the Committee had concerns about the true value for money provided by elosulfase alfa, and could not ascertain whether the benefits of treatment could be generalised to the average patient. Based on the available evidence on overall benefit, the Committee considered that the cost of elosulfase alfa (incorporating the patient access scheme) was too high for it to be recommended outside the context of a managed access agreement. The Committee concluded that including other commercial arrangements in the managed access agreement in addition to the patient access scheme would offer more acceptable value for money in the context of the uncertainty of the clinical benefits.

### 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.

The Committee noted that treatment with elosulfase alfa needs weekly infusions, but understood that elosulfase alfa may be given in people's homes.

The Committee concluded that the impact of elosulfase alfa on the delivery of specialised services was likely to be relatively negligible.

## Additional factors taken into account

### Patient access schemes (PPRS)

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. The managed access agreement includes further commercial arrangements between the company and NHS England for the duration of the agreement.

The Committee concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the value for money offered by elosulfase alfa.
| Equalities considerations and social value judgements | There were no potential issues relating to equality considerations that needed to be discussed by the Committee. | - |
6 Implementation

6.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires 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 When NICE recommends a treatment the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has MPS IVa and the doctor responsible for their care thinks that elosulfase alfa is the right treatment, it should be available for use, in line with NICE's recommendations.

6.3 The Department of Health and the company have agreed that elosulfase alfa will be available to the NHS with a patient access scheme that makes elosulfase alfa available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Nigel Nicholls (Country Director UK/Ireland) at BioMarin Pharmaceuticals – NNicholls@bmrn.com.
7 Review of guidance

7.1 The guidance on this technology will be reviewed 4 years after its publication. The managed access agreement expires 5 years after guidance publication or when the review of guidance has been published (whichever is sooner).

Andrew Dillon
Chief Executive
December 2015
8 Evaluation Committee members, guideline representatives and NICE project team

Evaluation Committee members

The Highly Specialised Technologies Evaluation Committee is a standing advisory committee 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.

Dr Peter Jackson (chair)
Consultant Physician and Honorary Reader in Clinical Pharmacology

Mr Sotiris Antoniou
Consultant Pharmacist, Cardiovascular Medicine, Barts Health NHS Trust

Mr Steve Brennan
Chief Finance Officer, NHS North Kirklees Clinical Commissioning Group

Dr Trevor Cole
Geneticist/Consultant in Clinical and Cancer Genetics/Honorary Reader in Medical Genetics

Ms Sarah Davis
Senior Lecturer in Health Economics, Sheffield University

Dr Jonathan Howell
Consultant in Public Health

Dr Vincent Kirkbride
Consultant Paediatrician, Sheffield NHS Foundation Trust
Mr Jeremy Manuel
Lay Member

Mr Francis Pang
Vice-President, Market Access, Biogen Idec

Mrs Linn Phipps
Lay Member

Dr Mark Sheehan
Oxford BRC Ethics Fellow, The Ethox Centre, University of Oxford

Professor Lesley Stewart
Director, Centre for Reviews and Dissemination, York

Mrs Sheela Upadhyaya (until October 2015)
Highly Specialised Program of Care Lead (London Region), NHS England

Dr 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.

Ahmed Elsada, Ian Watson
Technical Analysts

Fiona Pearce, Raisa Sidhu, Linda Landell
Technical Advisers

Leanne Wakefield
Project Manager

Josie Godfrey, Sheela Upadhyaya (from November 2015)
Associate Directors
9 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):


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 documents (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

II. Professional/specialist and patient/carer groups:

- Birmingham Children's Hospital NHS Foundation Trust
- British Inherited Metabolic Disease Group
- MPS Society
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians
- Royal Free Lysosomal Storage Disorders Unit
- Salford Royal NHS Foundation Trust
- Save Babies Through Screening Foundation UK
- Willink Unit, Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust
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 providing oral and written evidence to the Committee.

- Prof Chris Hendriksz, nominated by Salford Royal NHS Foundation Trust
- 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 providing oral and written evidence to the Committee.

- Edmund Jessop, selected by NHS England – NHS Commissioning expert
- Iain Mellis, selected by NHS England – NHS Commissioning expert
E. Representatives from the following company attended the Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- BioMarin Pharma
About this guidance

This guidance was developed using the NICE highly specialised technologies guidance process.

We have produced information for the public explaining this guidance. Information about the evidence it is based on is also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN: 978-1-4731-1589-7