NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Elosulfase alfa for treating mucopolysaccharidosis type 4A (review of HST2)

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

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

The evaluation committee is interested in receiving comments on the following:

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

Issue date: November 2021

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

After consultation:

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

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: 3 December 2021

Second evaluation committee meeting: 13 January 2022

Details of membership of the evaluation committee are given in section 5

1 Recommendations

1.1 Elosulfase alfa is not recommended, within its marketing authorisation, for treating mucopolysaccharidosis type 4A (MPS 4A) in people of any age.

1.2 This recommendation is not intended to affect treatment with elosulfase alfa that was started in the NHS before this guidance was published.

Why the committee made these recommendations

This guidance reviews the evidence for elosulfase alfa for treating MPS 4A, including new evidence collected as part of the managed access agreement (NICE highly specialised technology guidance HST2).

MPS 4A is rare and progressive, and has a significant effect on the quality of life of people with the condition, and their families and carers. It causes abnormalities in the joints and bones, respiratory symptoms, pain, fatigue and increasing dependence on a wheelchair. Current treatment options are limited.

Clinical trial evidence and data collected as part of the managed access agreement suggest that MPS 4A becomes stable in the long term with elosulfase alfa.

However, the company used the same limited economic model structure for the review that it had used for the original guidance. Also, its assumptions in model are not robust or plausible, particularly around:

- using a model that relies on wheelchair use because it does not represent well enough how the condition progresses
- making assumptions about treatment benefit rather than using the observed data
- body weight because this is likely to change over time.

The long-term benefits of elosulfase alfa are not appropriately captured in the model. The extra health and quality-of-life benefits of elosulfase alfa

are considered to be substantial. But the cost-effectiveness estimates are much higher than what NICE considers acceptable for highly specialised technologies. So, elosulfase alfa is not considered an appropriate use of NHS resources within the context of a highly specialised service, and cannot be recommended.

2 Information about elosulfase alfa

Marketing authorisation indication

2.1 Elosulfase alfa (Vimizim, Biomarin) is licensed to treat 'mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The price for elosulfase alfa is £750 per 5 mg vial (excluding VAT; BNF online accessed October 2021). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by BioMarin, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Inherited lysosomal storage disease

3.1 Mucopolysaccharidosis type 4A (MPS 4A; also known as Morquio A syndrome) is an inherited lysosomal storage disease caused by a lack of the enzyme N-acetylgalactosamine-6-sulfatase. Deficiency of this enzyme leads to glycosaminoglycans (also known as mucopolysaccharides) such as keratan sulphate accumulating in the cells of several tissues and organs. This causes progressive tissue damage.

Effect of the condition on people with MPS 4A and their families

3.2 MPS 4A causes a wide spectrum of symptoms that worsen over time, including respiratory symptoms, joint and skeletal abnormalities, hearing loss, corneal clouding and heart valve abnormalities. The condition 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. The joint and skeletal abnormalities play a role in respiratory symptoms developing. 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. The patient and clinical experts emphasised that MPS 4A affects the quality of life of people with the condition, and their families and carer (see sections 3.17 and 3.18). The clinical experts explained that the severity of the condition varies. In some people, it is particularly severe and their life expectancy is short. Other people have a form that progresses more slowly, and they may live longer. The committee concluded that MPS 4A is a complex, progressive and highly heterogeneous condition that affects the body across multiple organ systems.

Clinical management

Managed access agreement

3.3 Elosulfase alfa has been available as a treatment option as part of a managed access agreement since the original NICE highly specialised technology guidance for elosulfase alfa was published in 2015. The managed access agreement required data collection from people having treatment and their families. Before this, the only treatment option was standard care, which aims to relieve symptoms. Standard care includes several treatments such as corticosteroids and bronchodilators to improve pulmonary function, cervical fusion, decompression surgery and orthopaedic surgery. The clinical experts explained that these treatments do not affect disease progression but elosulfase alfa does. The committee was aware that the data collection period for the managed access agreement was set out to last until a review of the original guidance had been published or after 5 years (whichever was earlier). This period has been extended twice to allow the company more time for its submission. Despite this, there were still issues with the company's analysis and modelling (see sections 3.5, 3.6, 3.8, 3.12 and 3.13). The committee also noted that this review would only focus on people newly diagnosed with MPS 4A. This was because continued access to elosulfase alfa for people with MPS 4A already having treatment will be discussed separately by the company and NHS England. The committee concluded that it would consider the newly diagnosed population who had not had treatment under its previous recommendations.

Clinical effectiveness

Data sources

3.4 The committee considered the various sources of clinical-effectiveness data. This included qualitative evidence from the Rare Disease Research Partners and the MPS Society. The evidence describes how people with

MPS 4A and their families have benefited from treatment with elosulfase alfa and the outcomes that they value. The company submitted the following data for elosulfase alfa and standard care:

- MOR-004 was a 24-week randomised controlled trial comparing elosulfase alfa with placebo in 173 people 5 years and over with a 6-minute walk test (6MWT) of between 30 m and 325 m. MOR-005 was an open-label extension study including 169 people from MOR-004. In the original guidance, interim 72-week data was available from MOR-005. Since 2015, further follow-up data has become available.
- Data was collected from 69 people as part of the managed access agreement for over 5 years. This included 43 people who had not had elosulfase alfa and 26 people who had elosulfase alfa as part of the MOR clinical trials.
- MOR-001 was a natural history study including 353 people having standard care. The company included a posthoc analysis of the subgroup MorCAP-1, This applied the inclusion criteria of MOR-005 (that is, people over 5 years and baseline 6MWT between 30 m and 325 m).

After technical engagement, the company used clinical-effectiveness data from the full population in the managed access data for elosulfase alfa and the MorCAP-1 subgroup for standard care. The ERG explained that the full population in the managed access data included some people who had previously been in a MOR clinical trial and had not had the licensed weekly dose of elosulfase alfa. Also, it was not appropriate to use MorCAP-1 when comparing against the data in the managed access agreement. This was because it placed restrictions on age and baseline 6MWT that were not present in the managed access agreement. The ERG preferred to use the treatment-naive subgroup in the managed access data for elosulfase alfa and the full MOR-001 population for standard care. At the committee meeting, the company clarified that

people in the clinical trials switched to the licensed weekly dose shortly after elosulfase alfa gained its full marketing authorisation. The committee understood that some people in the clinical trial may have had elosulfase alfa every other week, and that this may have underestimated the treatment benefit. It was concerned that, by excluding people who had had treatment, some valuable long-term data was disregarded. The committee concluded that both the company's and ERG's preferred data sources were relevant for decision making.

Data analysis issues

3.5 The ERG had substantial concerns around the data the company had used in its submission provided at the start of this review. This included:

- using inconsistent timepoints, for example, data collected up to 3 years to calculate baseline to year 1 values
- high levels of missing data
- no analyses using imputation methods for missing data
- the lack of a robust propensity score-matching analysis.

The ERG recognised the large amount of work the company had done as part of technical engagement to address these issues. But some irregularities, for example, missing patient-level details for some people, could not be resolved. The clinical and patient experts described the burden of regular data collection for people with MPS 4A and their families as part of the managed access agreement. The committee was disappointed that the company did not provide more robust analyses in its submission, given the burden put on healthcare staff, people with MPS 4A and their families. This was particularly so given the additional time afforded to the company to try to address the data issues. The committee concluded that a predefined statistical analysis plan is important for all treatments that are recommended as part of a managed access agreement.

Complete case analysis

3.6 Given the issues relating to data analysis (see section 3.5), the ERG explained that a complete case analysis of all the data sources would ensure consistent cohorts are followed up. This was considered appropriate given the level of missing data and the known clinical heterogeneity of MPS 4A. After technical engagement, the company provided complete case analyses of 2-year data from its preferred data sources (that is, the full population in the managed access agreement and MorCAP-1). The company explained that it used an outcome-based approach instead of restricting analyses to people with data for all outcomes. The ERG broadly agreed with the company's approach because it maximised the available data. But, instead of using the start of treatment as a baseline, the company used the date of entry to the managed access agreement. This meant that long-term data from people having elosulfase alfa as part of the MOR clinical trials was not included in the analysis. The committee was concerned that the company had not appropriately analysed valuable long-term data from people who started elosulfase alfa as part of a clinical trial. Also, the company used 2-year data to inform the first year of the economic model, which the ERG suggested was not appropriate. The ERG preferred to use 1-year complete case analysis of its preferred data sources (that is, the treatment-naive subgroup in the managed access data and the full population from MOR-001). The committee understood that both the company's and ERG's complete case analyses relied on a naive indirect comparison that did not match baseline characteristics of people from the 2 studies. So, there was still substantial uncertainty and clinical heterogeneity. It also noted that the company had not provided a complete case analysis of MOR-005, despite this being requested at technical engagement. The committee reiterated that it wanted to use as much clinical data as possible. It was aware of the limitations of the complete case analyses because it did not include people for whom some

outcome data was missing. It recalled that the company had not provided any alternatives using statistical methods to impute missing data (see section 3.5). Therefore, the committee concluded that both the company's and ERG's complete case analyses could be considered for decision making. Also, it noted that it had not seen cost-effectiveness analyses using complete case analysis of data from MOR-005.

Treatment benefit

3.7 The company's submission included results from MOR-005 (without complete case analysis) and the managed access agreement for 6MWT, wheelchair use, lung function measures (forced vital capacity [FVC] and forced expiratory volume1) and health-related quality of life. Longer-term data from the managed access agreement and MOR-005 generally showed broadly stable results for all outcomes over time. The clinical experts described the progressive course of untreated MPS 4A. However, they noted that, in people having elosulfase alfa, the condition is likely to be stable in the long term. They also described benefits in skeletal outcomes, which have not previously been seen in clinical practice. They postulated that this is partly because the managed access agreement has allowed younger people to have treatment. Starting treatment at 2 or 3 years, may improve skeletal disease through better surgical outcomes. The clinical experts described greater and faster correction of skeletal disease with guided growth surgery. The committee noted that skeletal outcomes were not reported in the trials or the managed access agreement. Because of this, the treatment benefit of elosulfase alfa could have been underestimated in the clinical-effectiveness evidence. The committee understood that there was some direct evidence comparing elosulfase alfa with standard care but that there is no long-term follow up. It was aware of the limitations of a naive indirect comparison using different data sources that did not match baseline characteristics. Nevertheless, the committee concluded elosulfase alfa is clinically effective compared with standard care, and the size of the benefit could

have been underestimated. It further concluded that the company had not captured the benefits of elosulfase alfa well in its analyses or model structure, despite extensions to the managed access agreement.

The company's economic model

Wheelchair-based model

3.8 The company's Markov model measured disease progression through wheelchair use. It included 7 health states (no symptoms, no wheelchair use, wheelchair use sometimes, wheelchair dependent, has paraplegia, end stage of condition and death). The company's model assumed that it takes 3 years for people having standard care and 8 years for people having elosulfase alfa to develop symptoms. The estimate for elosulfase alfa was based on clinical advice to the company. The committee was aware that the available clinical data was only used in the first year of the model. It noted that long-term predictions were based on assumptions (see sections 3.10, 3.11 and 3.13). The committee reiterated its concerns that long-term data from MOR-005 and the managed access agreement had not been used more in the economic model. It was also disappointed that the company had not done more to explore a revision to its model structure since the original guidance. This was particularly so given the amount of valuable data submitted from patient organisations on the outcomes that matter to people with MPS 4A and the benefits of elosulfase alfa. The patient experts explained that people often choose to use wheelchairs to allow independent living rather than simply for mobility issues. Because people have short stature, wheelchairs make everyday activities such as pressing buttons and using public transport easier. The clinical experts suggested that the 6MWT would be a better measure of disease progression, However, they noted that this measure is limited in young children because walking times naturally increase as children grow. At technical engagement, the ERG asked the company to consider changing its model structure to use 6MWT and lung function measures

such as FVC to measure disease progression. The company did not provide any alternative models, arguing that evidence from the managed access agreement did not show a correlation between FVC and health-related quality of life. The ERG did not agree with the company's correlation analysis because it had pooled 3 different timepoints. A positive trend showing increased health-related quality of life with increased FVC was seen when the analysis was separated by timepoint. The committee was reluctant to accept the company's wheelchair model because it did not model disease progression well, and long-term benefits relied solely on assumptions rather than clinical data. It had expected the company to address the limitations of the model structure that it had set out in the original guidance. Without any alternatives, the committee concluded that the company's model could be used for decision making. However, it noted that the model added considerable uncertainty because it did not model disease progression well.

6MWT criteria used to define movement between health states

3.9 The ERG explained that the proportion of people assigned to the 7 health states at the end of the first year had a large impact on the cost-effectiveness results. This was because of the way the company had structured its model and the long-term assumptions for disease progression (see section 3.10). In its base case, the company used complete case analysis of its preferred data sources to estimate the proportion of people moving from 1 health state to another from baseline to the first year of the model. The ERG explained that this approach led to implausible results because mean 6MWT increased when people in the model moved from no wheelchair use to some wheelchair use. The ERG used 6MWT and FVC data from its preferred complete case analysis to calculate the transition probabilities from year 1 to year 2 in the model. The ERG considered that its preferred 6MWT thresholds to define movement from 1 health state to another offered better face validity than the company's model. This was because lower 6MWT values were

associated with increased wheelchair use. The patient experts explained that people with improved or stable MPS 4A are able to take part in more activities and may choose to use a wheelchair more often. The committee considered that the company's approach appeared counterintuitive because wheelchair use did not appear to adequately capture disease progression. It reiterated its disappointment that the company had not used more objective measures of disease progression such as 6MWT and FVC to define the model structure. The ERG had used some observed 6MWT and FVC data to estimate mean 6MWT and FVC for both standard care and elosulfase alfa arms at the end of the first year in the model. The committee agreed this approach was plausible. It concluded that the ERG's 6MWT criteria to define movement between health states were acceptable for decision making.

Long-term benefits

Disease progression

3.10 In the company's model, people having elosulfase alfa were assumed to have very little disease progression after the first year. People in the standard care arm were assumed to lose 6.8 m in 6MWT (in the 'no wheelchair use' and 'sometimes wheelchair use' health states) and 0.1 litre in FVC (in the 'wheelchair dependent' and 'paraplegic' health states) every year. The ERG suggested that the assumption for elosulfase alfa was not based on robust long-term data. Also, after the second year in the model, the ERG preferred to apply losses of 4.86 m for 6MWT and 0.1 litre in FVC for the standard care arm. The loss of 4.86 m for 6MWT was from the same data source as the company (Harmatz et al. 2013), but used the intention-to-treat population instead of a subgroup that was matched to the trial population from MOR-005. The clinical experts explained that MPS 4A is likely to progress more slowly with elosulfase alfa than with standard care. The committee recalled longer-term clinical evidence that suggested the condition remained broadly stable over time

(see section 3.7). It considered that the company's approach may more closely capture a stabilisation of disease. But, this is uncertain because it is based on assumptions after the first year of treatment in the model. It noted that the company's assumption of very little disease progression for people having elosulfase alfa was more optimistic than the longer-term managed access data, which generally showed stable MPS 4A. The committee also accepted the company's assumptions that it takes 3 years for people having standard care and 8 years for people having elosulfase alfa to develop symptoms. It concluded that the company's assumption of very little disease progression after the first year for people having elosulfase alfa was an acceptable proxy for stable MPS 4A. It further concluded that the ERG's preferred loss of 4.86 m for 6MWT was acceptable to model disease progression in the standard care arm.

Overall survival

3.11 After technical engagement, the company assumed that people having elosulfase alfa had the same survival as the general population of the same age and gender. Survival in the standard care arm was assumed to be 2.4 times lower than that in the elosulfase alfa arm. Clinical advice to the ERG suggested that this was not clinically plausible. This was because elosulfase alfa does not affect complications of MPS 4A such as cervical spinal compromise, chest deformities and tracheal obstruction. The clinical experts agreed it this was not clinically plausible because people with MPS 4A generally have more comorbidities than the general population. The ERG preferred a company scenario that linked mortality to lung function. In its preferred analyses, the ERG used data from its preferred data source to calculate an improvement in FVC for the elosulfase alfa arm. (The company considers the exact data to be confidential so it cannot be reported here.) The analyses also applied a 15% increase in mortality for every 10% decrement in FVC. The committee noted that elosulfase alfa is not curative and agreed that survival is unlikely to be similar to that in the general population. It

concluded that the ERG's approach linking survival to lung function was more appropriate than the company's assumption that survival with elosulfase alfa would be similar to that in the general population.

Utility values

EQ-5D-5L from the managed access agreement

3.12 EQ-5D-5L values were collected as part of the managed access agreement. The committee noted NICE's position statement on the use of EQ-5D-5L. It understood that this data had not been mapped to the EQ-5D-3L value set and agreed to take this into account. The company used baseline EQ-5D-5L data from the treatment-naive subgroup to inform utility values for each health state. After technical engagement, these were assumed to be the same for people having elosulfase alfa or standard care. The company also applied separate utility gains of 0.002 for every metre gained in the 6MWT and 0.02 for every 0.1 litre of FVC for people having elosulfase alfa. The ERG did not consider the company's values to correspond to the data seen in the managed access agreement. It explained that the company's methods for estimating the utility gain were also unclear. So, the ERG preferred to use the utility values that had been accepted in the original guidance and utility gains based on its preferred data sources. The committee preferred to make use of the data collected as part of the managed access agreement. After the committee meeting, the company submitted further information on how it analysed the data from the managed access agreement. The ERG reviewed this and noted that the company had used average utility values from the treatment-naive subgroup at baseline, 12 months and 24 months after starting elosulfase alfa. The ERG did not think it was appropriate to use utility values that included a treatment benefit from elosulfase alfa to model the standard care arm. So, it preferred to use baseline values only. The committee recognised that the ERG's values were similar to those accepted in the original guidance. It concluded that the ERG's utility

values from the treatment-naive subgroup from the managed access agreement were appropriate.

Treatment costs

Body weight in the model

3.13 The summary of product characteristics for elosulfase alfa states that the licensed weekly dose is 2 mg/kg of body weight. In its base case, the company applied a constant weight from baseline to the end of the model. For people in the asymptomatic health state, it used data from MOR-001. The ERG thought that assuming the same body weight throughout the model was clinically implausible and likely to have underestimated the treatment costs of elosulfase alfa. It favoured using alternative values based on its preferred data source and the Montano et al. (2008) study to estimate baseline body weight for each health state. The ERG also assumed that all people's body weight would reach 36.7 kg by 18 years. The clinical experts explained that children with MPS 4A generally grow in line with that seen in Montano et al. They also explained that adults with MPS 4A generally weigh less than the general population because they are much shorter. Their body weight usually reaches about 40 kg. The committee noted that assumptions about body weight had a large impact on the cost-effectiveness estimates. It agreed that the company's approach was likely to have underestimated the treatment costs. It considered that the ERG's long-term assumptions about body weight were in line with clinical practice. The committee concluded that the ERG's approach to calculating body weight was appropriate for decision making.

Discount rate

1.5% and 3.5% discount rates

3.14 The company only submitted analyses that applied a 1.5% discount rate. The committee noted that NICE's interim process and methods of the

highly specialised technologies programme (2017) states that analyses that use a non-reference-case discount rate for costs and outcomes may be considered:

- in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and
- when this is sustained over a very long period (usually at least 30 years).

The committee recalled its earlier conclusions that MPS 4A is progressive and still shortens life, and that elosulfase alfa is not curative (see section 3.11). It did not consider that elosulfase alfa restored people to full or near full health, so concluded that a 3.5% discount rate was appropriate.

Quality-adjusted life year (QALY) weighting

Criteria for applying a QALY weight

3.15 The committee understood that NICE's interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per QALY gained for a highly specialised technology is usually considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is shown by the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the QALY gains associated with elosulfase alfa. It highlighted that these were above 30 in the company's base case and below 10 in ERG's analyses. (The exact QALY gains are considered commercial in confidence by the company, so cannot be reported here.)

The committee recalled its earlier conclusion that the company's wheelchair model did not measure disease progression well. It also recalled that it thought benefits such as skeletal outcomes were likely not included in the cost-effectiveness analyses (see section 3.7). The committee concluded that elosulfase alfa met the criteria for applying a QALY weight.

Cost-effectiveness estimates

Committee's preferred assumptions

3.16 The company's base-case results after technical engagement resulted in an ICER under £300,000 per QALY gained (that is, the maximum ICER normally considered to be a cost effective use of NHS resources applying a the maximum QALY weight). The committee recalled that this did not account for its preferred assumptions of:

- both the company's and the ERG's preferred data source and analysis (see sections 3.4 and 3.6). The ERG's approach included using observed 6MWT and FVC data to estimate mean values for both arms at the end of the first year in the model (see section 3.9)
- the ERG's 6MWT criteria to define movement between the health states (see section 3.9)
- the company's approach for modelling long-term disease progression for people having elosulfase alfa because it was an acceptable proxy for stable MPS 4A (see section 3.10)
- the ERG's loss of 4.86 m for 6MWT to model disease progression in the standard care arm (see section 3.10)
- overall survival is linked to lung function (see section 3.11)
- the ERG's utility values from the managed access data (see section 3.12)
- body weight changes over time and reaches 36.7 kg by 18 years (see section 3.13)

- a discount rate of 3.5% (see section 3.14).

The committee noted that the ERG made several changes to the company's base case. The most influential changes were assuming that:

- 6MWT and FVC losses were equal in both arms
- alternative transitions thresholds were applied
- body weight changes over time.

The committee noted that it did not see ICERs that reflected all its preferred assumptions. However, it noted that all the ERG's analyses were above £300,000 per QALY gained.

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

Indirect benefits

3.17 The committee understood that elosulfase alfa may provide important benefits to people with MPS 4A and their families in addition to the direct health benefits of treatment. The patient experts explained that improving endurance and reducing fatigue allows people with MPS 4A to continue working. The committee understood that this has important financial implications. As well as the direct benefits on physical aspects of the condition, elosulfase alfa may provide important indirect mental health benefits. The patient experts emphasised that treatment with elosulfase alfa can provide people with MPS 4A greater predictability about how their condition will progress, giving them a greater sense of control. It also means that people can maintain independence, take part in social activities, develop longer-term plans and have fewer unplanned hospital visits. The committee heard that, for children with MPS 4A, improvement in managing the condition has important benefits for education. This is particularly so if elosulfase alfa can be given at school to minimise disruption. The committee noted in particular that MPS 4A does not affect

cognitive function, and was aware that this makes it distinct from other lysosomal storage disorders. It concluded that elosulfase alfa is likely to have a significant effect on people's lives beyond its direct health benefits.

Home infusions

3.18 The committee noted that treatment with elosulfase alfa needs weekly infusions. The patient experts explained that travelling to a specialist centre can be a significant burden. The committee understood that people may be able to have elosulfase alfa in their own homes, and that this would dramatically reduce this burden. The clinical experts estimated that around 85% of people newly diagnosed with MPS 4A will administer infusions at home. The patient experts noted that this has had positive effects on people with the condition. Also, it has benefited 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 4A have complex needs in emergency situations, but was reassured that robust safeguards are in place.

Other factors

Equality issues

3.19 No specific equality issues were raised in the original guidance. At technical engagement, patient expert submissions raised potential equality issues around:

- the significant cost of elosulfase alfa
- difficulties in showing benefit because of the very small number of people with MPS 4A.

The committee considered the factors associated with a highly specialised technology in line with NICE's methods and process guides. It did not consider the issues raised to be equality issues. This was because the

recommendation applies to all people with MPS 4A within the marketing authorisation for elosulfase alfa.

Innovation

3.20 The committee considered elosulfase alfa to be innovative, noting that the company considered the drug's mechanism of action represents a step change in managing MPS 4A. The patient experts explained that continued access to elosulfase alfa would give hope to people with the condition, and their families and carers. The committee noted that the innovative nature of elosulfase alfa would be captured in the modelling if the data was measured and analysed appropriately.

Conclusion

Long-term benefits

3.21 The committee recognised that MPS 4A is rare, serious and progressive, and can substantially affect the lives of people with the condition, and their families and carers. It understood that the only alternative to elosulfase alfa is standard care and this provides limited symptom relief. After considering all available evidence, and the opinions of the clinical and patient experts, the committee agreed that there are likely to be long-term benefits with elosulfase alfa. It also recalled that improvements in skeletal disease were not captured in the model (see section 3.7). The committee noted that the company's analyses were not robust because:

- the model structure was based on wheelchair-use health states and it did not capture disease progression adequately (see section 3.8)
- the long-term benefits of elosulfase alfa were based on assumptions rather than observed data (see section 3.10)
- body weight is likely to change over time (see section 3.13).

The committee reiterated its disappointment that the company had not changed its model structure despite extensions to the managed access

agreement. It considered that a model structure defined by lung function or endurance would capture the benefits of elosulfase alfa more appropriately. It recalled that qualitative evidence had been submitted from the patient organisations (see section 3.4). This evidence included descriptions of outcomes and benefits that are valued by people with MPS 4A. The committee considered that the company should have used this data to inform its analyses and model. It was also aware of the significant data collection burden on people with MPS 4A and their families. The committee considered that the company had not taken the opportunity to make substantial changes to its analyses while the managed access agreement was extended.

Recommendation

3.22 The committee took into account its preferred assumptions (see section 3.16), indirect benefits of elosulfase alfa (see section 3.17) and that the long-term benefits were not appropriately captured in the model (see section 3.21). It noted that the most plausible ICER was substantially higher than what is usually considered an appropriate use of NHS resources for highly specialised technologies. It also noted that elosulfase alfa met the criteria for a QALY weighting to be applied. The committee concluded that elosulfase alfa at its current price was not cost effective compared with standard care. Therefore, it did not recommend elosulfase alfa for routine use in the NHS for treating MPS 4A in people of any age.

4 Proposed date for review of guidance

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

Peter Jackson

Chair, highly specialised technologies evaluation committee

October 2021

5 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that 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.

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Abitha Senthinathan
Technical lead

Christian Griffiths
Technical adviser

Gavin Kenny
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