NICE National Institute for Health and Care Excellence

NICE guidance

Elosulfase alfa for treating mucopolysaccharidosis type 4A

Highly specialised technologies guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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

This guidance replaces HST2.

1 Recommendations

1.1 Elosulfase alfa is recommended, within its marketing authorisation, as an option for treating mucopolysaccharidosis type 4A (MPS 4A) for people of all ages. It is only recommended if the company provides elosulfase alfa according to the commercial arrangement.

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 technologies guidance 2).

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.

The company used the same limited economic model structure for the review as for the original guidance. This was despite encouragement to improve the structure to better reflect the characteristics of MPS 4A, target population and treatment benefits of elosulfase alfa. There is uncertainty around the model because it:

- relies on wheelchair use, which does not represent well enough how the condition progresses
- uses several uncertain assumptions to capture the long-term benefit of elosulfase alfa
- includes some analyses of the managed access data with missing information
- uses utility values based on managed access data that includes only a small number of people.

Clinical trial evidence, data from the managed access agreement, and feedback from patient and carer experience were collected. These suggest that MPS 4A is likely to

progress more slowly when treated with elosulfase alfa compared with standard care. The health and quality-of-life benefits of elosulfase alfa are considered to be substantial. Also, data from younger people who may benefit more from elosulfase alfa is not specifically included, and additional skeletal benefits may not be fully captured.

Taking these factors into account, the cost-effectiveness estimates are within the range that NICE considers acceptable for highly specialised technologies. So, elosulfase alfa is recommended for people with MPS 4A.

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 for elosulfase alfa.

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. This makes elosulfase alfa available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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 section 3.18 and section 3.19). 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 technologies 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 was 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 3.6, 3.7, 3.9, 3.13 and 3.14). The committee focused on the evidence for people newly diagnosed with MPS 4A. This was because continued access to elosulfase alfa for people with MPS 4A already having treatment was discussed separately by the company and NHS England. The committee concluded that it would consider the newly diagnosed population for its decision making. However, it noted that the recommendation would apply to everyone, that is, people who have been newly diagnosed and people already having treatment.

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 a baseline 6MWT of between 30 m and 325 m).

  After consultation, the company used clinical-effectiveness data from the newly diagnosed population in the managed access dataset for elosulfase alfa and from MOR-001 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 the data from the newly diagnosed population in the managed access agreement and from MOR-001 were relevant for decision making.

People newly diagnosed with MPS 4A

3.5 At consultation, stakeholders commented that the newly diagnosed population were likely to be younger, healthier and more likely to benefit from elosulfase alfa compared with people currently having treatment. Data submitted from Great Ormond Street Hospital suggested that, for classical MPS 4A, the median age for starting treatment was around 3.1 years. After consultation, the company amended the proportion of people assigned to each health state at the start of the model and the baseline age. These changes were made to reflect a newly diagnosed population who were younger and healthier when starting elosulfase alfa. The company's changes were based on the baseline characteristics of people 6 years and younger in the managed access data. The ERG agreed that a younger and healthier baseline population may be relevant. It noted that the company had used the ERG's preferred body weights in its analyses. The ERG explained that, for each health state in the model, the company had changed the starting proportion and baseline age but not the mean body weight. This led to clinically implausible combinations of age and body weight. For example, people with a mean age of 4 years in the 'no wheelchair use' health state weighed 19.8 kg but in the 'sometimes use wheelchair' state weighed 27.0 kg. At the start of the model, the ERG preferred to assume that 5% of people were 'asymptomatic' and weighed 3.6 kg, and 95% were in the 'no wheelchair use' health state and weighed 13.5 kg. The committee noted that the ERG's approach resulted in a healthier starting population compared with the company's. The committee recognised that the clinical-effectiveness data used in the model did not fully reflect a younger population who may benefit more from elosulfase alfa. It concluded that the ERG's approach to modelling a younger and healthier baseline population was appropriate to reflect the newly diagnosed population.

Data analysis issues

3.6 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

3.7 Given the issues relating to data analysis (see section 3.6), 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 consultation, the company provided complete case analyses of 2-year data from the newly diagnosed population in the managed access agreement and MOR-001. In its revised base case after consultation, the company used its 2-year complete case analysis to inform transition probabilities and the long-term benefit of elosulfase alfa. 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 some 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 its 1-year complete case analysis because it considered that to be more reliable in assessing changes over time in a clinically heterogenous population. The committee understood that both the company's and ERG's complete case analyses relied on a naive indirect comparison that did not match for 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 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 3.6). It understood that the ERG preferred to use its: 1-year complete case analysis to inform transition probabilities (see section 3.10); the annual loss in 6MWT in the standard care arm; and the long-term benefit for elosulfase alfa (see section 3.11). The committee concluded that the ERG's complete case analysis could be considered for decision making even though it included less data. This was because it was more robust than the company's analysis.

Treatment benefit

3.8 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 volume in 1 second [FEV1]) and health-related quality of life. Longer-term data from the managed access agreement and MOR-005 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 progress more slowly in the long term compared with standard care. 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 outcomes of surgery. 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- and cost-effectiveness evidence. The committee recalled that a younger and healthier baseline population was appropriate to reflect people newly diagnosed with MPS 4A in clinical practice (see section 3.5). The clinical experts explained that the future population would include mostly young children and that only around 5% would be adults with milder symptoms. The committee understood that the analyses provided by both the company and the ERG only changed the baseline population age. The clinical-effectiveness data for elosulfase alfa was from people of all ages in the newly diagnosed subgroup of the managed access data. 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 for baseline characteristics. Nevertheless, the committee concluded that elosulfase alfa is clinically effective compared with standard care and that the size of the benefit could have been underestimated. This was because the benefits could be higher in a younger population and because some skeletal outcomes may not have been fully captured in the model. It further concluded that the company had not captured the benefits of elosulfase alfa well in its analyses or model structure. This was despite the weakness of these being noted in the original NICE evaluation of elosulfase alfa in 2015 and extensions allowed to the managed access agreement.

The company's economic model

Wheelchair-based model

3.9 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 9 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 3.11, 3.12 and 3.14). 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. The patient experts explained that people often choose to use wheelchairs to allow independent living rather than simply for mobility issues. Because people with MPS 4A 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 would be 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 attempt to address the limitations of the model structure that it had set out in the original guidance. In the absence of 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.

Transition probabilities and 6MWT criteria to define movement between health states

3.10 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 3.11). In its base case, the company used its 2-year complete case analysis 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 score 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 the standard care and elosulfase alfa arms at the end of the first year in the model. The committee agreed that this approach was plausible. After consultation, the company amended its transition probabilities for both treatment arms. The transition probabilities for standard care were based on its 2-year complete case analysis of MOR-001. For elosulfase alfa, the company assumed that, from baseline to year 1 of the model, people would stay in the same health state. At the second committee meeting, the company stated that the transition probabilities were based on a linear regression analysis of people in the managed access agreement who were 6 years and younger. The company explained that there was no disease progression in this subgroup at 2 years. But the committee noted a discrepancy in the data showing that, in 1 patient, there was disease progression. The company agreed that this was the case but explained that this was a rare event and could have been related to surgical outcomes rather than natural disease progression. The committee recalled that it preferred the modelling approach of starting with a younger population that did not include any people who were wheelchair dependent at baseline. The clinical experts emphasised that, in the current model structure, the 'wheelchair-

Long-term benefits

Disease progression

3.11 In the company's model, people having elosulfase alfa were assumed to have almost no disease progression after the first year. People in the standard care arm were assumed to lose 6.80 m in the 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 annual 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 considered that the company's approach reflected almost no disease progression with elosulfase alfa. But this was uncertain because it was based on assumptions after the first year of treatment in the model. After consultation, the committee reconsidered this issue because the effect was much larger when applied to a younger starting population who were in better health states at baseline. Because of the way the company had structured its model, no people having elosulfase alfa would become wheelchair dependent in their lifetime. One clinical expert described positive outcomes when people as young as 18 months have had treatment. One clinical expert agreed that enzyme replacement treatments such as elosulfase alfa are likely to slow disease progression but are unlikely to be curative. The committee noted that the company's assumption of almost no disease progression for people having elosulfase alfa was more optimistic than the longer-term managed access data. It understood that the ERG had done a scenario analysis that used an alternative long-term benefit for elosulfase alfa. The ERG used 6MWT and FVC data from the 1-year complete case analysis of the managed access data. This data showed a benefit for elosulfase alfa compared with standard care. This was applied each year in the model (the company consider this data to be confidential so it cannot be reported here). The committee also accepted the company's assumptions that it takes 3 years for people having standard care and 9 years for people having elosulfase alfa to develop symptoms. It concluded that the company's assumption of almost no disease progression after the first year for people having elosulfase alfa was not acceptable for this younger population. Instead, the committee preferred the ERG's scenario analysis that made use of the observed data from the managed access agreement. The committee concluded that the ERG's scenario analysis with an

Overall survival

3.12 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 survival with elosulfase alfa 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 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

3.13 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 newly diagnosed 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 accepted in the original guidance and the utility gains linked to changes in 6MWT and FVC in the managed access data. The committee accepted the greater rigour of the values used in the original guidance. But it 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 newly diagnosed 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. After consultation, the company updated its preferred values for both treatment groups. For standard care, it used baseline values from its 2-year complete case analysis of people 6 years and older who had not had elosulfase alfa in the managed access agreement. For elosulfase alfa, it used data at 2-year follow up from the same population. The ERG found inconsistencies in the company's analysis. The ERG explained that using data from the 2-year timepoint for elosulfase alfa meant that very few people were included in the analysis. This was particularly so in the 'wheelchair-dependent' health state. This health state included 1 patient who sometimes used a wheelchair at baseline and had improved health-related quality of life. This was not consistent with the company's assumption that increased reliance on a wheelchair was associated with lower health-related quality of life. The ERG also noted that it was unable to replicate some values used by the company. The committee recognised the limitations of the company's approach. However, it noted that it was based on the managed access data and that some inconsistent data was expected. It also noted that the company used a higher

Treatment costs

Body weight in the model

3.14 The summary of product characteristics for elosulfase alfa states that the licensed weekly dose is 2 mg/kg of body weight. In its original 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. After consultation, the ERG amended the baseline body weight to reflect a younger starting population (see section 3.5). 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

3.15 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 3.12). 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

3.16 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 improved skeletal outcomes were likely not captured by the cost-effectiveness analyses (see section 3.8). The committee concluded that elosulfase alfa met the criteria for applying a QALY weight.

Cost-effectiveness estimates

Committee's preferred assumptions

3.17 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:

- the ERG's approach to modelling a younger and healthier baseline population that includes changes to baseline body weight (see section 3.5 and section 3.14)
- the ERG's 1-year complete case analysis that used observed 6MWT and FVC data to estimate transition probabilities and 6MWT criteria to define movement between the health states (see section 3.7 and section 3.10)
- the ERG's scenario analysis to model long-term disease progression for people having elosulfase alfa (see section 3.11)
- the ERG's loss of 4.86 m for 6MWT to model disease progression in the standard care arm (see section 3.11)
- linking overall survival to lung function (see section 3.12)
- company utility values (see section 3.13)
- body weight changes over time, reaching 36.7 kg by 18 years (see section 3.14)
- a discount rate of 3.5% (see section 3.15).

The committee noted that taking its preferred assumptions into account, the ICER using the company's utility values was under £300,000 per QALY gained. It recognised that the ICER increased substantially when using the ERG's utility values that were also based on the data from the managed access agreement. It noted the substantial uncertainty in the company's modelling and utility values. However, it also recalled benefits with elosulfase alfa that it believed had not been fully captured in the model (see section 3.8). It concluded that the most plausible ICER for elosulfase alfa was less than £300,000 per QALY gained. It also concluded that the undiscounted QALYs lay somewhere between the ERG's and company's estimates, although the value is deemed confidential by the company and cannot be reported here (see section 3.16).

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

Indirect benefits

3.18 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

3.19 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

3.20 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

3.21 The committee considered elosulfase alfa to be innovative, noting that the company considered that 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

3.22 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 3.8). The committee noted that the company's analyses were very uncertain because:

- the model structure was based on 'wheelchair-use' health states and it did not capture disease progression adequately (see section 3.9)
- the complete case analysis of the managed access data was limited by missing data and relied on a naive indirect comparison that did not match baseline characteristics (see section 3.7)
- the model used a number of uncertain assumptions to capture the long-term benefit of elosulfase alfa (see section 3.11)
- there was substantial uncertainty around the utility values, particularly for the 'wheelchair-dependent' health state (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

3.23 The committee took into account its preferred assumptions (see section 3.17), indirect benefits of elosulfase alfa (see section 3.18) and that the long-term benefits were not appropriately captured in the model (see section 3.22). It noted that the most plausible ICER was under £300,000 per QALY gained, but recognised substantial uncertainty around the model structure, complete case analysis and utility values. The committee also recalled benefits from elosulfase alfa that may not have been fully captured in the model (see section 3.8). It also noted that elosulfase alfa met the criteria for a QALY weighting to be applied. The committee concluded that elosulfase alfa was cost effective compared with standard care. Therefore, it recommended elosulfase alfa for routine use in the NHS for treating MPS 4A in people of any age, only if the company provides elosulfase alfa according to the commercial arrangement. The committee was aware that the data collected as part of the managed access agreement was based on clinical criteria that defined when treatment could be started. To continue treatment during the managed access period, there were requirements for the treating clinician to carry out regular assessments and compare them with assessments done at the start of treatment around:

- lung function (as measured by FVC or FEV1)
- ambulation (as measured by a 6MWT or 25 ft ambulation test)
- reductions in urinary keratan sulphate
- a decline in ejection fraction compared with the start of treatment.

The committee noted that the detailed criteria included in the managed access agreement no longer apply. However, it expected that treatment should continue as long as there is continuing clinical benefit. NICE understood that healthcare providers have treatment approval and monitoring systems in place. It agreed that simpler treatment continuation criteria around clinical measures (such as cardiac function, lung function or improved mobility) were appropriate. NICE considers that clinical benefit should always be considered by healthcare professionals in the NHS when considering treatment decisions and this does not need to be specified in NICE's recommendations.

4 Implementation

4.1 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 appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has mucopolysaccharidosis type 4A 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.

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
Project manager

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Accreditation