NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Velmanase alfa for treating alpha-mannosidosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using velmanase 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 velmanase 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, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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 velmanase 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: 16 August 2022

Details of membership of the evaluation committee are given in section 6.

1 Recommendations

1.1 Velmanase alfa is not recommended, within its marketing authorisation, for treating the non-neurological signs and symptoms of mild to moderate alpha-mannosidosis.

1.2 This recommendation is not intended to affect treatment with velmanase alfa that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by them, their clinician, and their parents or carers.

Why the committee made these recommendations

Alpha-mannosidosis is a rare and serious condition that severely affects the quality of life of people with the condition, and their families and carers.

Clinical trial evidence suggests that velmanase alfa is a potentially promising treatment. But, because of important limitations in the available evidence, the exact size and nature of the clinical benefits (both in the short- and longer-term) are highly uncertain.

There are also uncertainties in the economic modelling. In particular, there is very little observed evidence to inform the model, and most of the data used in the model is based on expert opinion rather than clinical trial evidence. Also, the assumed benefits of velmanase alfa treatment in the model are very uncertain.

Overall, although velmanase alfa is a promising treatment, the benefits it provides are highly uncertain. The cost-effectiveness estimates for velmanase alfa are higher than those considered value for money in the context of a highly specialised service. Taking into account all the evidence and the factors affecting the decision, including the extremely rare and disabling nature of alpha-mannosidosis, velmanase alfa is not recommended for use in the NHS.

2 The condition

2.1 Alpha-mannosidosis is an ultra-rare lysosomal storage disorder caused by inheriting a faulty copy of the MAN2B1 gene from both parents. This impairs production of the enzyme alpha-mannosidase, leading to systemic accumulation of mannose-rich oligosaccharides in various tissues, especially in the central nervous system, liver and bone marrow.

2.2 The clinical presentation is associated with a very wide range of impairments with varying degrees of severity. Signs and symptoms of alpha-mannosidosis can occur at a very young age. The most severe forms occur during infancy (before 5 years) and are associated with rapid progression, leading to early death. More moderate forms are characterised by slower disease progression with people surviving into adulthood. These more moderate forms are associated with a very wide range of impairments, complications and comorbidities that increase with time. The impairments include:

- facial and skeletal deformities (especially scoliosis and deformed hips and feet)
- speech and language deficiencies
- mental health difficulties
- bone deterioration, and joints and muscle weakness (leading to pain)
- reduced lung function because of an enlarged liver and spleen, and spinal abnormalities
- immunodeficiency with recurring infections (mainly respiratory and ear).

2.3 The overall prevalence of alpha-mannosidosis is estimated to be between 1 in 500,000 and 1 in 1,000,000. At the time of the evidence submission, the Society for Mucopolysaccharide Diseases (MPS Society) estimated that there were 25 people with alpha-mannosidosis in England.

2.4 There are currently no pharmacological treatments for alpha-mannosidosis that alter the disease course. Treatments aim to manage symptoms and improve quality of life. They include walking aids,

physiotherapy, infection management, ventilation support, general treatment of comorbidities, supportive measures at home and major surgical interventions (for example, ventriculoperitoneal shunts, cervical spine decompression, joint replacement). An allogeneic haematopoietic stem cell transplant from a matched sibling or matched umbilical cord donor is an option for some people when clinically indicated, but is associated with significant risks.

2.5 Alpha-mannosidosis is managed in UK lysosomal storage disorder specialist centres. These centres have experience of administering enzyme replacement therapies by infusion for other related conditions.

3 The technology

3.1 Velmanase alfa (Lamzede, Chiesi) is an enzyme replacement therapy produced using recombinant DNA technology. It is intended to replace natural alpha-mannosidase enzyme outside the central nervous system to help with the degradation of mannose-rich oligosaccharides. Velmanase alfa is administered once a week by intravenous infusion at a dose of 1 mg/kg. It has a marketing authorisation in the UK for treating 'non-neurological manifestations in patients with mild to moderate alpha-mannosidosis'.

3.2 The most common adverse reactions listed in the summary of product characteristics for velmanase alfa include weight gain, immune-related responses, diarrhoea, headache, arthralgia (joint pain), increased appetite and pain in the extremities. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 The list price of velmanase alfa is £886.61 per 10 mg vial (excluding VAT; company's evidence submission). The company has a commercial

arrangement, which would have applied if the technology had been recommended.

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Chiesi, 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). After its original submission in 2018, the company resubmitted further data in March 2022. To date, there have been 4 committee meetings to review the evidence for velmanase alfa. 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

Effect of alpha-mannosidosis on people with the condition, and their families and carers

4.1 The patient experts explained that alpha-mannosidosis affects all aspects of life for people with the condition, and their families and carers. They also emphasised the all-consuming nature of the condition. The clinical and patient experts also explained that the clinical manifestations of alpha-mannosidosis can be associated with a very wide range and level of impairments. The patient experts highlighted the effects of physical symptoms, and psychological and behavioural complications, and the need for a high level of care, including repeated hospital appointments, surgical procedures and medical interventions. Social and professional life can also be compromised for people with alpha-mannosidosis, and their families and carers. A patient testimony received during consultation emphasised the extent of the burden of the condition. This included difficulty in finding a job and the demoralising effect of being perceived as less capable. One patient expert explained that alpha-mannosidosis has negatively affected their education and social interactions at school. They

explained that cognitive impairments associated with the condition may also affect a person's ability to learn to drive, which affects their independence. The committee recognised that alpha-mannosidosis is an exceptionally rare condition, and the patient experts highlighted that this could mean diagnosis is delayed because it is not immediately recognised. It also recognised that many people with alpha-mannosidosis are children and young people, and that this influences the effects of the condition. The committee concluded that alpha-mannosidosis is a rare, serious and debilitating condition that severely affects the lives of people with the condition, and their families and carers.

Place in the treatment pathway

4.2 Velmanase alfa has a marketing authorisation for treating non-neurological manifestations in people with mild to moderate alpha-mannosidosis (see section 3.1). The clinical experts explained that severe disease is easily distinguished by central nervous system involvement and loss of skills in the first year of life, which rapidly progresses. The velmanase alfa marketing authorisation is not restricted by age, but the company initially presented clinical and economic evidence only for people 6 and over, who it considered would have mild to moderate forms of alpha-mannosidosis. At the fourth committee meeting, the company supplied new evidence for children under 6 with mild to moderate forms of alpha-mannosidosis. The committee noted that the NICE scope had been amended to include this population in keeping with the updated marketing authorisation. One clinical expert explained that there are 3 routes to diagnosis in younger children. These include:

- diagnosis on clinical grounds when there is a high burden of clinical symptoms and rapid progression suggestive of severe disease, the person would not be eligible for treatment with for velmanase alfa
- detection in children under 6 when there is clinical suspicion, but diagnosis needs confirmation by genetic and biochemical testing.

- diagnosis in children who are asymptomatic and have siblings with alpha-mannosidosis, which can only be done by laboratory investigation.

The NHS England representative confirmed that these were the appropriate routes of diagnosis and genetic screening at birth is not routine nor proposed in the NHS. The committee agreed that the population in the marketing authorisation for velmanase alfa might include some children under 6, but that this number was likely to be small. It was also aware that the clinical and economic evidence available for velmanase alfa did not include people with advanced disease, for example, people dependent on a wheelchair. So, the committee was uncertain whether velmanase alfa would be considered for this group. It stated that it would be helpful to clearly define how velmanase alfa treatment would be considered for more advanced forms of mild to moderate alpha-mannosidosis in clinical practice. The committee concluded that the evidence presented was consistent with the marketing authorisation for velmanase alfa and its expected use in practice.

Allogeneic haematopoietic stem cell transplants (HSCTs)

4.3 An allogeneic HSCT was listed as a comparator for velmanase alfa in the scope for the evaluation. But it was not presented as a comparator by the company in either its original submission or resubmission. The clinical experts explained that an allogeneic HSCT is associated with significant morbidity and mortality, which increases with age. Because of this, an allogeneic HSCT is not normally used in children over 5. The patient and clinical experts explained that the decision about whether to offer an allogeneic HSCT is based on a risk–benefit assessment involving the clinician, the person with alpha-mannosidosis, and their parents or carers. They further explained that the decision considers the identified mutation, the symptoms of the condition and donor availability. The committee recalled that some people with mild to moderate alpha-mannosidosis would be diagnosed when under 6. It understood that there was an overlap between people under 6 with mild to moderate disease who would

be suitable for a transplant and suitable to have velmanase alfa. The clinical experts explained that, for children who have central nervous system involvement that is likely to be reversible, an allogeneic HSCT would be the preferred treatment option. They further explained that people usually wait around 6 months for a transplant. The committee considered whether velmanase alfa could be used during this period or as a bridge to a transplant. The clinical experts explained that enzyme replacement therapies, such as velmanase alfa could improve cardiac function and immune response, and reduce infections before surgery. This was based on their experience using enzyme replacement therapies in mucopolysaccharidosis 1 disease, a similar condition to alpha-mannosidosis. The committee noted that the company had positioned velmanase alfa treatment only for people in whom an allogeneic HSCT is unsuitable. It recognised that there was no data to compare velmanase alfa with an allogeneic HSCT, or for people who may use velmanase alfa as a bridge to a transplant. It concluded that it would not be able to make recommendations in people for whom an allogeneic HSCT would be considered as a possible treatment.

Impact of the new technology

Clinical evidence

4.4 The committee discussed in detail the clinical evidence most relevant to the decision problem submitted by the company:

- rhLAMAN-05 (n=25) was a double-blind randomised controlled trial that assessed the efficacy and safety of velmanase alfa (n=15) compared with placebo (n=10) over 12 months. Results were reported by age group (under 18 compared with 18 and over) as part of the post-hoc analysis.
- rhLAMAN-10 (n=33) was a single-arm open-label study that provided data on people who had treatment with velmanase alfa for up to 48 months. It captured data about people who enrolled in either the compassionate-use programme or 1 of the 2 open-label studies

(rhLAMAN-07 or -09) and combined these with all available data from across the rhLAMAN clinical trial programme (including rhLAMAN-02, -03, -04 and -05) as part of an integrated analysis. Results were reported by age group in a preplanned analysis (under 18 compared with 18 and over) and in a post-hoc analysis (6 to 11 years, 12 to 17 years, 18 and over). The company presented an updated analysis as part of its resubmission.

The outcomes measured in the clinical trials covered serum oligosaccharide levels, mobility and functional capacity, lung function, quality of life, cognition and hearing. Other neurological outcomes were not presented and were not expected to be affected by velmanase alfa because it does not cross the blood–brain barrier. The committee acknowledged that the trials were generally well conducted and of reasonable quality. The ERG highlighted that there were uncertainties associated with the trials. It noted the lack of a control arm in rhLAMAN-10. This could have affected the interpretation of the results, especially in children because it did not consider the natural history of the disease over time. The committee considered the amount of evidence to be fairly small, and that it would have been better if the trials had run for longer. But it recognised that this was influenced by the extreme rarity of the condition. The committee concluded that the clinical-effectiveness evidence from the rhLAMAN trials was associated with several uncertainties.

Generalisability of the evidence to clinical practice in England

4.5 People included in the rhLAMAN trials were likely to have been younger (between 5 years and 35 years) than people seen in clinical practice in England. Alpha-mannosidosis progresses faster in younger people, so it is easier to detect clinically significant differences in younger people. The committee therefore queried whether the benefits seen in the trials reflected what might be seen in clinical practice in England. The ERG noted that, in rhLAMAN-05, people in the velmanase alfa arm were more compromised at baseline than people in the placebo arm. This could have

affected some outcomes, but the ERG was uncertain about whether it would favour velmanase alfa or placebo. People who were at high risk of developing reactions to velmanase alfa (those with IgE levels above 800 IU/ml) were excluded from the trials. The committee considered that this might have affected the generalisability of the safety findings. But the clinical experts stated that the people included in these trials were representative of people who would be seen in clinical practice in England. The committee concluded that the generalisability of the rhLAMAN clinical evidence was acceptable.

Serum oligosaccharide levels as a surrogate endpoint

4.6 Velmanase alfa was associated with a statistically significant reduction in serum oligosaccharide levels compared with placebo in rhLAMAN-05 (adjusted mean difference in relative change between velmanase alfa and placebo arms: −70.47%, $p<0.001$) and compared with baseline in rhLAMAN-10 (−62.8%, $p<0.001$). The committee was aware that serum oligosaccharide levels are a surrogate outcome. It recalled that, in alpha-mannosidosis, impaired production of the alpha-mannosidase enzyme leads to increases in oligosaccharide levels, which cause the impairments seen in this condition. The company explained that serum oligosaccharide levels are an important biomarker that show the effect of velmanase alfa at a cellular level and are a marker of potential clinical complications of alpha-mannosidosis. The clinical experts explained that serum oligosaccharide levels are used in clinical practice to diagnose alpha-mannosidosis but, because of the lack of treatments, have not been used to assess treatment effects. The clinical experts explained that serum oligosaccharide levels could be prognostic of disease severity. They highlighted that, in other lysosomal storage disorders, the principle of substrate reduction through enzyme replacement therapy has been established as a way to produce important clinical benefits. But benefits vary between conditions and depend on the nature and reversibility of established damage. The ERG explained that there appeared to be only a limited relationship between serum oligosaccharide levels and clinical

outcomes in the rhLAMAN trials. Also, the company did not submit any formal assessment of the surrogacy relationship using standard criteria. It did assess correlations between serum oligosaccharide levels and some outcomes in rhLAMAN-10, but these were all considered negligible or marginal. Similar assessments were not reported for rhLAMAN-05. The committee considered that the knowledge around serum oligosaccharide levels was limited, and recognised that it is an evolving area of research. It concluded that the results provided biochemical evidence that velmanase alfa has an effect, but it was not able to infer the nature or size of the clinical benefits from these results.

Mobility, functional capacity and quality of life

4.7 There were no statistically significant differences between velmanase alfa and placebo in:

- mobility and functional capacity (3-minute stair climb test, 6-minute walk test, forced vital capacity)
- quality of life (Childhood Health Assessment Questionnaire, EuroQol five-dimension-five-levels [EQ-5D-5L]) in rhLAMAN-05.

The ERG explained that it was unclear whether the trial met its objective of showing clinical efficacy. In rhLAMAN-10, there were statistically significant differences compared with baseline in most outcomes at the last observation (3-minute stair climb test: 13.8%, p=0.004; forced vital capacity % predicted: 10.5%, p=0.011; EQ-5D-5L: 11.2%, p=0.036) but not in the 6-minute walk test (7.1%, p=0.071). The committee highlighted that, without a comparison with placebo, it was unclear how much of the changes could be attributed to velmanase alfa. It particularly noted that some of the changes may be explained by expected physiological changes with age. The committee discussed how to interpret the clinical-effectiveness results. It noted, in particular, that the size of the observed benefits was small. It also noted that it was unclear whether the benefits would translate into substantially meaningful improvements for people with alpha-mannosidosis. The clinical experts explained that small

improvements would be important to people with the condition. The committee recognised that the small population size may have influenced the uncertainty of the evidence (for example, statistical significance), but would not necessarily be expected to have affected the size of the benefits. The committee concluded that the evidence suggested that velmanase alfa is a potentially promising treatment but that there was insufficient evidence to establish the extent of the clinical benefits.

Clinical evidence for children under 6

4.8 In its resubmission, the company presented clinical evidence to support the broader population from rhLAMAN-08. This was a single-arm open-label phase 2 study in 5 children under 6 with mild to moderate alpha-mannosidosis. The results suggested a reduction in serum oligosaccharide levels and improvement in mobility parameters from baseline after 24 months of treatment with velmanase alfa (the results are academic in confidence and cannot be reported here). The clinical experts explained that, although there was limited evidence in this age group, there was no biological reason to expect results to differ from those for people over 6. The committee concluded that the clinical evidence was likely to be generalisable across the population.

Long-term benefits of velmanase alfa

4.9 The committee was aware of the relatively short duration of the rhLAMAN trials. In its resubmission, the company submitted evidence to address the long-term effects of velmanase alfa from Etoile-Alpha, an ongoing retrospective registry study. This included 16 people having velmanase alfa off label in France until June 2020 or already enrolled in rhLAMAN-07 or -08. The company also presented individual case series for 6 people from across Europe, including 1 person from the UK. The ERG highlighted that there were limitations and uncertainties associated with the real-world registry data, including that:

- the population in the study was likely more severe than that expected in clinical practice

- it was a single-arm study that compared results with baseline rather than best supportive care
- there were many missing data points, which may not have been missing at random
- there was a lack of adjustment for age for outcomes in which childhood growth could lead to improvement
- data was not collected on all outcomes used to assess response to velmanase alfa in the company's proposed starting and stopping criteria

The results of the Etoile-Alpha study showed improvements or stabilisation in serum oligosaccharides, mobility and forced vital capacity measures (exact results and follow-up times are academic in confidence and cannot be reported here). The ERG highlighted that these results suggested velmanase alfa's treatment effect was larger in children than adults. It considered that some of this difference in children may be explained by expected physiological changes with age, but noted the lack of natural history data on alpha-mannosidosis to confirm this. The clinical experts stressed the heterogeneity of the condition and challenges in data collection in people with mobility and cognitive symptoms. But, at least in younger people, their experience suggests that improvement in physiological measurements would be expected with best supportive care. The committee acknowledged the limited sample size and uncertainties associated with the evidence, but recognised that this was influenced by the extreme rarity of the condition. It agreed to consider the long-term follow-up data for velmanase alfa in its decision making

Infections

4.10 Infection rates were not collected as an efficacy outcome in the trials. The company acknowledged that infection rates are an important outcome that have a significant effect on the lives of people with the condition lives. It explained that understanding of alpha-mannosidosis has grown over time, and that infection rates are an outcome in future trials of alpha-

mannosidosis. It also provided post-hoc analyses of immunological outcomes from rhLAMAN-05 and -10 in response to clarification. The results showed that velmanase alfa was associated with a statistically significant improvement in the levels of 1 component of the immune system (serum IgG; adjusted mean difference compared with placebo: 3.47 g/litre, $p<0.0001$). They also showed that, of people in rhLAMAN-05 with low levels of IgG at baseline (n=9/25, of which 5 were in the velmanase alfa arm), 60% (n=3/5) in the velmanase alfa arm had normal IgG levels after 12 months and 40% (n=2/5) had improved levels, but no people in the placebo arm had improved levels. The clinical experts stated that these results were striking, and that IgG might be a relevant surrogate marker for immune function because of the nature of the immune problems associated with alpha-mannosidosis. A post-hoc analysis of antibiotic use in the low-serum IgG group showed that people in the velmanase alfa arm used fewer antibiotics than people in the placebo arm. Also, an analysis of carers' reports of infection rates supported a reduced number of infections associated with velmanase alfa in rhLAMAN-10. The committee was aware that this data was interpreted by the company as showing likely improvements in infection rates. The committee also noted comments from the patient experts and testimonies from people who had treatment with velmanase alfa. These highlighted the effect of recurrent infections associated with alpha-mannosidosis, and reported that there were fewer infections with velmanase alfa treatment. The committee concluded that velmanase alfa appears to have immunological benefits, but that the evidence on this is limited and uncertain.

Multidomain responder analysis

4.11 The company also submitted a post-hoc multidomain responder analysis for rhLAMAN-05 and -10. It explained that the analysis was done at the request of the European Medicines Agency to help understand the clinical relevance of the data and variability between people for some outcomes. The aim of the analysis was to combine multiple clinically important

endpoints into 3 domains (pharmacodynamics, functional and quality of life), to establish how many people had a clinically meaningful improvement. Someone was classified as a 'responder' to treatment if the response criteria were reached in at least 2 domains. The multidomain responder analysis showed that more people were 'responders' in the velmanase alfa arm of rhLAMAN-05 than in the placebo arm (87% compared with 30% respectively). Also, more people under 18 were 'responders' than people 18 and over in rhLAMAN-10 (100% compared with 71% respectively). The ERG explained that there were several concerns with the analysis, in particular:

- the assumption that the domains were of equal importance
- the omission of infection rates
- the post-hoc nature of the analysis.

The committee also highlighted that the relevance of the comparison between velmanase alfa and placebo was unclear. This was because the response to the pharmacodynamic domain (reduction in serum oligosaccharide levels) had already been established from rhLAMAN-05 (that is, that people taking velmanase alfa would have a reduction in serum oligosaccharide levels whereas those having placebo would not). The company recognised this limitation and explained that the multidomain responder analysis captured several layers, including the variation in treatment response between domains as well as in the individual domains. In response to consultation, and following expert opinion, the company submitted an additional responder analysis based on the functional domain only. In this analysis, 60% of people were classed as 'responders' in the velmanase alfa arm and 30% in the placebo arm. The ERG noted that the additional analysis only potentially addressed the committee's concern that the domains were considered of equal importance. But it did not address the other concerns (omission of infection rates and the post-hoc nature of the analysis). The committee also considered an analysis submitted by the company in its resubmission, in which only people who showed a clinically meaningful

response in all 3 domains were classed as 'responders' to velmanase alfa ('super-responder' analysis). But it concluded that the multidomain responder analysis had several limitations, and the relevance of the results was difficult to interpret.

Adverse events

4.12 The proportion of people having velmanase alfa who had any adverse event in rhLAMAN-05 and -10 was high (88% to 100%), but most events were reported as being mild or moderate. The most frequent adverse events with velmanase alfa were infection and infestation (86.7% of people in rhLAMAN-05 and 72.7% in rhLAMAN-10). The ERG explained that the safety of treatment over a lifetime is unknown. The committee concluded that the tolerability profile of velmanase alfa was likely to be acceptable.

Cost to the NHS and value for money

Company's economic model

4.13 The company presented an economic analysis based on a Markov model, in which people could move through 4 primary health states according to their mobility: walking unassisted, walking with assistance, wheelchair dependent, severe immobility and dead. People could also have severe infections or need surgery. The model was based on 3 cohorts according to age at the start of treatment: a paediatric cohort (6 to 11 years), a young person cohort (12 to 17 years) and an adult cohort (18 and over). The committee questioned the appropriateness of the model structure. It recognised that mobility would be expected to capture many of the most important aspects of alpha-mannosidosis for people, but that there were other measures of disease progression. For example, it suggested that lung function might also have been considered as an option for defining the model structure. The committee concluded that the overall model structure was adequate for decision making.

Sources of data in the model

4.14 Most of the parameters used to inform the model were assumptions based on evidence from Etoile-Alpha or drawn from an expert elicitation panel or from interviews with key opinion leaders. This was because clinically important aspects (such as severe infections and need for surgical intervention) were not captured in the rhLAMAN trials. The parameters derived from the clinical trial observations were limited to the starting health state of the population and the rate of stopping treatment because of lack of efficacy. The committee was concerned that so few parameters were informed by data from the clinical trials. It recognised that the expert elicitation panel was based on a formal elicitation process using well-established methods, although the ERG explained that the key opinion leader interviews had greater limitations. The committee was reassured that experts and key opinion leaders from the UK were enrolled in these studies, so their experiences were likely to represent UK clinical practice. But the company did not repeat the expert elicitation panel to consider the longer-term evidence available from Etoile-Alpha as part of the resubmission. Instead, it validated the previous estimates of extended time in health states for 'responders' to treatment with a single clinical expert. The committee understood this increased the uncertainty in the model assumptions. The committee understood the reason for the lack of clinical data. But it concluded that the extensive use of elicited data and expert opinion, and the lack of observed evidence to inform the model, were significant limitations in the economic analysis. It also concluded that the size and direction of any errors or bias were unknown.

Benefits of velmanase alfa in the model

4.15 The committee noted that the model captured different aspects of the expected benefits of velmanase alfa using several assumptions. Velmanase alfa was assumed to:

- have a period of complete stability followed by delayed disease progression compared with best supportive care, based on Etoile-Alpha results and expert elicitation panel
- improve some peoples' mobility from baseline (that is, people in the walking-with-assistance and wheelchair-dependent health states could move to better health states in the model)
- reduce the mortality, complications and recovery time associated with severe infections and major operations by 50% compared with best supportive care.

The committee recognised that the benefits of velmanase alfa in the model were based on assumptions and expert opinions, rather than directly informed by evidence. The committee was aware that the assumed improvements from baseline (that is, that people having velmanase alfa could improve their health state whereas those having best supportive care could not) contradicted what was seen in rhLAMAN-05. In this trial, the same proportion of people improved from walking with assistance to walking unassisted in the velmanase alfa and placebo arms. The ERG noted that assuming people having best supportive care could not move to an improved health state was likely to substantially change the incremental cost-effectiveness ratio (ICER). The company explained that this assumption reflected clinical experts' views because it was not plausible that people having best supportive care would improve. The committee recalled that improvement in physiological measurements would be expected with best supportive care in younger people (see section 4.9). The company presented a scenario analysis in which people having best supportive care and those having velmanase alfa could improve health state (with a higher rate of improvement with

velmanase alfa). This slightly increased the ICER. This assumption was included in the ERG's base case for the fourth committee meeting. The committee recognised the uncertainty in the improvements modelled in the company's scenario. But it thought that the likelihood of improving mobility in the model should have been consistent with the observed trial data. It concluded that the model should have allowed for improvements in mobility for people having both velmanase alfa and best supportive care.

Progression through the model for people having velmanase alfa

4.16 The committee recalled that the company defined 'responders' as people who met the minimum clinically important difference in 1 or more endpoint in at least 2 domains in the responder analysis. At the fourth committee meeting, the ERG noted that using the company's definition, 'responders' could show no response (or deterioration) in all the other endpoints within a domain. It also explained that it was not possible to identify people who met the criteria of 'responder' (who remain on treatment in clinical practice) in the evidence. This was because not all the outcomes in the company's criteria for stopping treatment had been collected in the trials. The committee understood that aligning treatment benefit and clinical trial outcomes with the rate of progression through the model was challenging. It agreed that there were 2 levels of assumptions built into the model after resubmission, that:

- people whose condition responded to velmanase alfa did not progress for 5 years
- after 5 years, people whose condition responded to velmanase alfa had extended time in health states compared with best supportive care as estimated by the expert elicitation exercise.

The company stated that these assumptions aligned with longer-term data available from Etoile-Alpha and case studies. The committee considered that the evidence from Etoile-Alpha supporting a halt in disease progression for 5 years was uncertain. It agreed that the evidence

suggested that velmanase alfa is a potentially promising treatment. But it thought that there was insufficient evidence to establish the extent of the clinical benefits. It concluded that assuming 3 years of delayed disease progression followed by an extended time in health states based on the original expert elicitation was acceptable for decision making while accounting for uncertainty in the evidence. Overall, the committee considered that the size of velmanase alfa's benefits suggested by the model appeared large in the context of the benefits seen in the trials and it was unclear whether there was sufficient evidence to support benefits of this size. It emphasised the high level of uncertainty associated with the modelled treatment benefits, which could have had a substantial effect on the ICER.

Quality of life and additional utility gain associated with velmanase alfa

4.17 The company assumed that velmanase alfa improved quality of life throughout treatment, beyond its effects on mobility and response to major infection and surgery. So, it applied an additional gain in utility to anyone in the velmanase alfa arm of the model whilst they were on treatment. The company explained that this value aimed to capture many aspects of alpha-mannosidosis that were not completely accounted for in the model. These included:

- reducing rates of minor infections and minor surgery
- reducing rates of psychiatric problems, and improving cognition and mental health
- improving hearing, upper extremity and fine motor deficits
- reducing pain and fatigue
- reducing ventilation dependency
- providing improvements in the ambulatory health states (walking unassisted, walking with assistance)
- the possibility that some further benefits of velmanase alfa would appear after several years of treatment.

The committee recognised that, beyond the modelled health states for mobility and infection, there may be additional benefits from velmanase alfa not captured in the model. But it agreed that the exact utility gain was uncertain. At the third meeting, the company applied an additional utility gain of 0.1 to all age groups based on the improvements seen in EQ-5D in rhLAMAN-10 (0.05 in walking unassisted and 0.058 in walking with assistance). In its resubmission, the company updated the utility benefit for children and young people to 0.254. This was based on EQ-5D values mapped from functional capacity tests in Etoile-Alpha. It used assumptions from NICEs technology appraisal guidance on elosulfase alfa for treating mucopolysaccharidosis type 4A. In this, a utility gain had been accepted linked to improvements in forced vital capacity (0.2 utility per 1 litre gain) and 6-minute walk test (0.02 utility per additional 10 m walked). This was to account for the association between improvements in these parameters and increased quality of life and survival. The clinical experts explained that mucopolysaccharidosis 4A is a similar condition to alpha-mannosidosis in that it is a heterogeneous lysosomal storage disease that has a large effect on people's quality of life. The company preferred the mapped values because there was missing direct EQ-5D data (only complete for 24 of 33 people) from rhLAMAN-10. But everyone in Etoile-Alpha had results for forced vital capacity and 6-minute walk tests. The committee considered the differences between the mapped utility values and directly observed EQ-5D data in rhLAMAN-10, noting that more data was available using EQ-5D. The committee understood that the results were relatively aligned for adults, but that there was a large difference for children. The company explained that the missing EQ-5D was because of challenges in collecting data from children and people with cognitive difficulties. The ERG explained that it was plausible that these data may not have been missing at random. The potential to select people with better or worse outcomes may have biased the results. The committee recalled that the 6-minute walk test results had not been adjusted for age in the Etoile-Alpha data (see section 4.9). One clinical expert explained that children with alpha-mannosidosis would be

expected to grow at a similar rate to the general population until they are around 9 or 10 years. So, this means that physiological measures linked to this would improve as well. The results in both Etoile-Alpha and rhLAMAN-10 were compared with baseline measures rather than a control arm. The committee noted that this may have meant measurements from people under 10 were influenced by growth. So, any gain in utility in these people may have been overestimated. This would have been in keeping with the committee's concern that the mapped utility values lacked face validity. This was because the company's updated additional utility gain from treatment with velmanase alfa (that captured effects beyond its effect on mobility) was considerably larger than the utility gain from moving between mobility-based health states. In addition, when adding a 0.254 utility gain to the existing value for the walking-with-assistance health state, people whose disease responded to velmanase alfa had a similar utility value to the general population. This did not align with clinical evidence or submissions from the patient and clinical experts. The committee recalled that it preferred a utility benefit of 0.05 from the ERG's explanatory analyses at the third meeting. This was based on the EQ-5D utility gains directly observed in rhLAMAN-10 (0.08 for children and young people and 0.03 for adults). The committee recognised that the model may not have captured:

- within health-state benefits from velmanase alfa (such as reduced fatigue and pain, and improved cognition)
- benefits from velmanase alfa not captured in EQ-5D measurements.

So, the committee agreed that a 0.1 utility gain for children and young people, and a 0.05 utility gain for adults should be used for decision making.

Health-state utility values

4.18 The company used utility values collected from a survey by the UK Society for Mucopolysaccharide Diseases (MPS Society). The committee appreciated that the survey:

- followed a structured approach using validated quality-of-life questionnaires
- was completed by people living in the UK
- showed internal consistency between people with alpha-mannosidosis and their carers.

The survey provided utility values for walking unassisted (0.906), wheelchair dependency (0.100) and severe immobility (−0.011) using the model's definition of health states. The utility value for walking with assistance was extracted from unpublished UK key opinion-leader audit data (this cannot be reported because it is academic in confidence). This was because no one was in this health state using the model's definitions. The ERG acknowledged that these utility values had the advantage of being matched to the model definitions because they were generated to match the model. In its scenario analysis, the ERG used the utility values collected from the rhLAMAN trials (using the Childhood Health Assessment Questionnaire and EQ-5D). This was because they were generated from a larger sample (n=24) than the utility values from the survey and the other source (n=5). The committee considered that both sets of utility values had important limitations. It thought that the utility value for walking unassisted from the survey (used in the company's base case) seemed implausibly high. It emphasised that, because of its small sample size, the average utility value was unlikely to accurately represent the true average utility value for all people in that health state. It recognised that the larger sample size for the trial data was preferable because it was more likely to represent people living with the condition. The committee concluded that, although both sets of utility values were

highly uncertain, on balance, the utility values from the rhLAMAN trials were preferable for decision making.

Ventilation costs

4.19 The company assumed that people who had velmanase alfa first and stopped treatment (switching to best supportive care) would need 50% less ventilation assistance than people having best supportive care throughout. The committee considered that this assumption was not realistic and that people would be unlikely to benefit from velmanase alfa to this extent after stopping treatment. The ERG amended this assumption in its exploratory analyses by removing the continuing benefit of velmanase alfa after stopping treatment. The committee concluded that analyses in which the continuing benefit of velmanase alfa on ventilation assistance was removed were preferable for decision making.

Home-infusion costs

4.20 At the fourth committee meeting, both the company and ERG introduced costs for once-weekly home infusion for people having velmanase alfa in their final base cases. One patient expert explained that, after the first few doses in hospital, home infusion is standard practice for enzyme replacement therapies. The committee concluded that including costs of home-care administration of velmanase alfa was appropriate.

Starting and stopping rules

4.21 The company explored potential stopping rules for treatment with velmanase alfa, which it included in the model. The initial proposals for stopping rules were that treatment would stop for people who do not benefit, have life-limiting conditions or cannot tolerate the treatment or comply with monitoring. Based on these, the company implemented treatment stopping in the model through:

- ‘non-response’ (based on multidomain response in the first year of treatment in rhLAMAN-05: 13.3%)

- treatment withdrawal in the most severe health states (severe immobility or severe infection leading to death; based on key opinion-leader interviews) and
- an additional annual risk of withdrawal (based on key opinion-leader interviews; 10%).

The committee accepted that it was reasonable, in principle, to consider potential stopping rules and to include them in the economic model. It acknowledged that the rules described by the company had been incorporated appropriately in the company's final base-case model.

Starting and stopping rules in proposed managed access arrangement (MAA)

4.22 At the third committee meeting, the company presented refined starting and stopping rules for velmanase alfa through its proposed MAA (see section 4.3132). It stated that formal economic analysis incorporating these refined rules was not possible, but it would be reasonable to expect that these rules would improve velmanase alfa's value for money. The company and ERG explored possible ways to illustrate how much any starting or stopping rules in the MAA could affect the ICERs at the current price. The committee considered these analyses were informative only to show:

- the potential direction of effect on the ICERs of an MAA with strict starting and stopping rules
- the lowest modelled ICER at the current price.

In response to consultation, the company had looked at the effect of other definitions of response through different stopping rates because of lack of response (40%, 30% and 20%). But the committee recalled that there were limitations in the modelling for these scenarios. It concluded that the most plausible ICER associated with velmanase alfa could be lower than the company's base case if strict starting and stopping rules were applied.

Defining response in the stopping rule

4.23 The committee noted that stopping rules such as these had not been applied in the clinical trials. It agreed that applying them would imply that people who continue treatment would gain greater long-term benefits than the averages seen in the clinical trials. This is because people getting less benefit would stop velmanase alfa treatment. But it noted that the stopping rules, being applied after 12 months, would not affect the clinical benefits before this point. To address this concern, the company submitted additional analyses during consultation. In these, more optimistic approaches were taken to model disease progression in people whose condition had responded to treatment. It explored a 50% reduction in the rate of disease progression. It also used the upper credible intervals of the estimates elicited from clinical experts for the additional time spent in each health state compared with best supportive care. The ERG highlighted limitations in both of these approaches. The committee was aware that the delay in disease progression elicited from the experts was already based on an assumption of disease response, so adjustment may not have been needed. It accepted that it was plausible that using a more stringent definition of response might have further increased the delay in disease progression. But it was aware that there was no evidence to support the size of any potential effect. Also, the company's starting and stopping rules had not been reviewed after the availability of longer-term data from Etoile-Alpha. The committee recalled the company had presented scenarios in which only 'super-responders' were modelled to remain on treatment. But the ERG highlighted that this scenario might overestimate the number of people on velmanase alfa as the definition of a 'super-responder' was less strict than the company's criteria to continue treatment. So, the committee noted that these results were associated with considerable uncertainty. The committee was not convinced the company's additional analysis captured the efficacy of velmanase alfa appropriately for people whose condition had responded to treatment. It considered that the results from this analysis illustrated the potential effect

of changing the definition of response, but were not directly informative for decision making.

Discounting rate for costs and health effects

4.24 The committee was aware that NICE's guide to the methods of technology appraisal (2013) and its interim process and methods of the highly specialised technologies programme (2017) specify that the reference case discount rate is 3.5%. But it also states that a non-reference-case discount rate of 1.5% may be used when: treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives; it is highly likely that there will be long-term benefits; and the treatment does not commit the NHS to significant irrecoverable costs. The committee acknowledged that treatment was not expected to commit the NHS to significant irrecoverable costs. But, given that velmanase alfa does not affect the neurological consequences of alpha-mannosidosis, it could not return people to full or near-full health. Also, although it may be expected that velmanase alfa provides long-term benefits, there was not sufficient clear evidence that long-term health benefits were highly likely to be achieved. So, the committee concluded that velmanase alfa does not meet NICE's criteria for applying a discount rate of 1.5%. It concluded that a discount rate of 3.5% should have been applied for costs and health effects.

Other assumptions

4.25 The company estimated the cost of each health state and of velmanase alfa in the model. In its initial base case, the velmanase alfa dose and costs were calculated from a fixed average weight of people in rhLAMAN-10. In its final base case, velmanase alfa costs in the model were calculated using a distribution of people's weights derived from data obtained by the Medical Research Council. In addition, in the final base case, health-state costs were adjusted for inflation. The committee accepted that the approaches in the final base case were appropriate. The ERG flagged an additional uncertainty in an assumption that could

not be addressed. It noted that stopping treatment because of a lack of efficacy was assumed to occur in the middle of the first year rather than at the end. This was likely to be marginally unfavourable to velmanase alfa. The committee acknowledged that the effect of this was small. At the fourth committee meeting, the ERG updated its base case to include the baseline walking health-state distribution from the final analysis of rhLAMAN-10, which had been provided by the company as a scenario. The committee acknowledged that it was appropriate to use the most recent data to inform the baseline distributions. It agreed that the ERG's approach should be used for decision making.

Cost-effectiveness results

4.26 The company's final base case showed that velmanase alfa was associated with ICERs of greater than £88,912 per quality-adjusted life year (QALY) gained in children, £126,214 per QALY gained in young people and £185,872 per QALY gained in adults. The company and the ERG presented scenario analyses that highlighted that the ICERs were sensitive to:

- the acquisition cost of velmanase alfa
- the discount rate
- the utility value gain for 'responders' to velmanase alfa
- duration of halting disease progression associated with velmanase alfa
- the costs of ventilation
- the utility values for walking unassisted and walking with assistance.

Taking into account its conclusions on the key assumptions, the committee considered that its preferred scenario was:

- delayed disease progression for 3 years for people whose condition responded to velmanase alfa, after which transitions through health states from the expert elicitation exercise applied (see section 4.16)
- a utility gain of 0.1 for children and young people and 0.05 for adults (see section 4.17)

- utilities for walking unassisted and walking with assistance taken from the clinical trial (see section 4.1818)
- a discount rate of 3.5% (see section 4.244)
- the amended ventilation cost (see section 4.1919)
- the possibility for people having best supportive care to improve health state (see section 4.15)
- the cost of home infusion included (see section 4.20)
- the baseline walking health-state distribution from the final analysis of rhLAMAN-10 (see section 4.25)
- the corrected transition probabilities.

The committee recognised that several of its other considerations would further affect the ICER. It recalled that strict starting and stopping rules such as those proposed by the company could reduce the ICER (see section 4.222). The committee further recalled the high level of uncertainty in the model because of the extensive use of elicited data and expert opinion (see section 4.14). But it agreed that the effect of this on the ICER was unclear. Given all these factors, the committee concluded that the most plausible ICERs were highly uncertain and would likely be above £159,651 per QALY gained in children, £211,717 per QALY gained in young people and £271,389 per QALY gained in adults. So, it was not considered value for money in the context of a highly specialised service could not be recommended for routine commissioning.

Application of QALY weighting

4.27 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally 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, as revealed through 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 incremental QALY gains associated with velmanase alfa and highlighted that these were substantially below 10 in the company's final base case. The committee concluded that there was no evidence to suggest that velmanase alfa would meet the criteria for applying a QALY weight.

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

4.28 The committee discussed the effect of velmanase alfa beyond its direct health benefits. It understood from the patient and clinical experts that all aspects of life for people with alpha-mannosidosis, and their families and carers are affected by the condition. It noted that people with the condition need a high level of care, and that professional life could be compromised for them, and their families and carers. It also noted that alpha-mannosidosis is managed in established lysosomal storage disorder specialist centres. So, no additional infrastructure or staff training would be needed to manage use of velmanase alfa in England.

Other factors

Innovation

4.29 The committee discussed the innovative nature of velmanase alfa, noting that it is the first pharmacological disease-modifying therapy for alpha-mannosidosis and there is significant unmet need for it. The company considered that velmanase alfa is a step-change in managing alpha-mannosidosis. This was because of its potential to change the natural course of the disease by improving mobility or delaying disease progression. The committee concluded that velmanase alfa is innovative.

Equalities

4.30 The committee discussed whether any consideration should have been made to reflect the fact that the population under consideration for this

technology includes children. It was aware that alpha-mannosidosis is a serious condition that begins in infancy. It considered that the fact that children are affected by the condition was reflected in the clinical evidence and economic model, and in its understanding of the nature of the condition. It took into account the nature of the population in its decision making, including the fact that the population includes children. But it concluded that no further considerations or adjustments were needed beyond those already considered. The committee recognised that alpha-mannosidosis can have a substantial effect on people's lives, and many people with alpha-mannosidosis have a disability within the provision of the Equality Act. It discussed whether the disability might cause people to be disadvantaged within the evaluation. It considered that the effect of the disability associated with this condition and the benefits of the technology had been fully captured in the evidence, economic modelling and committee considerations. It also highlighted that it had considered patient testimony and all the available evidence, including indirect evidence and studies including small numbers of people. It considered this in the context of the nature of the condition and the uncertainty in the evidence base. It concluded that it had taken into account the disability associated with this condition when developing its recommendations. The committee recalled that alpha-mannosidosis is extremely rare, even in the context of highly specialised technologies evaluations. It recognised that people with extremely rare conditions can otherwise be disadvantaged, because of the challenges in developing medicines for these conditions and collecting appropriate evidence. It acknowledged that the small number of people who would be eligible for velmanase alfa contributed to a relatively small budget impact for the NHS. It considered that it was appropriate to take into account the very small population size, and the size of the impact on the NHS in its decision making. At the fourth committee meeting, the committee considered that people with alpha-mannosidosis may have cognitive impairments that make completion of quality-of-life questionnaires challenging. It acknowledged that this increased the uncertainty in the results and noted the small number of people in the

company's trials. But it agreed that this issue had been considered in its preferred utility benefit for velmanase alfa, which was above that recorded using EQ-5D questionnaires in rhLAMAN-10 (see section 4.17). The committee considered whether any other factors would affect its decision. It was aware of the full range of factors affecting decision making in the highly specialised technologies programme (including the nature of the condition, clinical evidence, value for money and impact of the technology beyond direct health benefits). It also considered the comments on these factors received during consultation and at resubmission. It concluded that all relevant factors had already been taken into account in its considerations, and that no specific additional considerations were needed.

Managed access

4.31 The committee concluded that velmanase alfa could not be recommended for routine commissioning. So, it discussed whether an MAA might address and resolve some of the uncertainties. It acknowledged that, because of the substantial uncertainties with velmanase alfa, collecting additional evidence may be valuable. The company proposed an MAA that would last for 3 years. It also defined starting criteria, stopping criteria, evidence collection and a data collection plan. The committee noted that, since the company's original proposal, the Innovative Medicines Fund has launched. So, any managed access agreement would be funded through this route. It acknowledged the various sources of data described by the company, including over 50 people enrolled in the SPARKLE registry, and the AllStripes study. It also noted the company's prespecified statistical analysis plans. But it was not convinced that the proposed MAA would resolve the key uncertainties in the evidence. This was because the ongoing trial and registry data would not provide more robust estimates for quality of life or long-term clinical effectiveness. Also, there are substantial challenges in collecting any robust evidence from the small number of people with alpha-mannosidosis who would be eligible to have velmanase alfa in clinical

practice. The committee noted that the company's latest submission contained several years of additional evidence that was not available when it first considered velmanase alfa. But it agreed that this had not substantially resolved the uncertainties discussed at previous evaluations. It concluded that it was highly unlikely that evidence collected within an MAA of a reasonable duration would resolve the key uncertainties enough for it to re-evaluate velmanase alfa with a greater degree of certainty at the end of the managed access period.

Starting and stopping rules in the MAA

4.32 The committee also explored the starting and stopping rules in the proposed MAA. It recognised that the company's main focus of the proposed MAA was to select people who would benefit most from treatment and ensure only those whose condition improved would continue treatment. The company expected that the proposed MAA would improve value for money and reduce uncertainty. This was because the starting rules would ensure only the people likely to benefit most from velmanase alfa would have treatment. The committee recognised that the company's approach would restrict the population eligible for treatment. This contradicts 1 Innovative Medicines Fund principles, which is that the entire eligible patient population should have the opportunity to access medicines within an MAA. It recalled that stopping rules based on non-response were included in the model. It also noted that it had taken into account the effect of starting and stopping rules on value for money (see sections 4.212 and 4.223). The committee was aware that further work would be needed to ensure that any agreement met the principles of the Innovative Medicines Fund. It considered an MAA would only be appropriate for velmanase alfa if it:

- had plausible potential to provide value for money in the context of highly specialised technologies
- aligned with the principles of the Innovative Medicines Fund.

The committee concluded that velmanase alfa does not have plausible potential to be cost effective. It also thought that a period of further data collection through an MAA would be unlikely to resolve the key uncertainties in the evaluation.

Conclusion

4.33 The committee acknowledged that alpha-mannosidosis is an exceptionally rare condition that causes a wide variety of symptoms and impairments. It also agreed that it has a serious and substantial effect on the quality of life of people with the condition, and their families and carers. It was aware that small increases in clinical outcomes can translate to substantial improvements for people with alpha-mannosidosis. The committee noted that the clinical evidence suggested that velmanase alfa may provide clinical benefits. But it considered that these clinical benefits were highly uncertain because of important limitations in the nature and extent of the evidence, and the size of the improvements seen in the clinical trials. The committee considered that the most plausible ICERs to inform decision making were greater than £150,000 per QALY gained. It also noted that velmanase alfa did not meet the criteria for QALY weighting to be applied, and that important uncertainties in the economic model remained. The committee accepted that it was appropriate to take into account the low budget impact and exceptional rarity of the condition in its decision making. It also took into account the other factors affecting its decision, including the substantial uncertainty in the clinical and economic evidence. Overall, the committee concluded that velmanase alfa would not provide value for money and could not be recommended for routine commissioning. It also concluded that velmanase alfa could not be recommended within a MAA. This was because it did not currently have plausible potential to provide value for money and, importantly, further data collection would be unlikely to resolve the key clinical uncertainties.

So, the committee did not recommend velmanase alfa as an option for treating alpha-mannosidosis.

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by NICE 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE 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
June 2022

6 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 appraisal.

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

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