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, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: May 2018

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

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation determination.
- 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: 13 June 2018

Second evaluation committee meeting: 28 June 2018

Details of membership of the evaluation committee are given in section 7.

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

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 the clinician and the child or young person, or the child's or young person's 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. However, 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 model is based on expert opinions rather than clinical trial evidence. The assumed benefits of velmanase alfa treatment that are included in the model are very uncertain. The cost-effectiveness estimates for velmanase

alfa in children, young people and adults are all much higher than the range that NICE considers acceptable for highly specialised technologies.

Overall, although velmanase alfa is a promising and innovative treatment, the benefits it provides are highly uncertain and it does not appear to provide value for money in the context of a highly specialised service. Velmanase alfa is therefore not recommended for routine funding in the NHS.

2 The condition

2.1 Alpha-mannosidosis is an ultra-rare lysosomal storage disorder (LSD) 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 highly heterogeneous and 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 and there is survival 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; and 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, and 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). 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 LSD specialist centres that are already in place in the UK. These centres have experience of administering enzyme replacement therapies via 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, increased appetite and pain

in the extremities. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 The price of velmanase alfa is £886.61 per 10-mg vial (excluding VAT; company's evidence submission). The company has agreed a patient access scheme with the Department of Health and Social Care. If velmanase alfa had been recommended, this scheme would have provided a simple discount to the list price of the drug, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health and Social Care considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

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). 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 the condition on patients, and their families and carers

4.1 The patient experts explained that alpha-mannosidosis affects all aspects of life for patients, and their families and carers, and they emphasised the all-consuming nature of the condition. The clinical and patient experts also explained that the clinical manifestations of alpha-mannosidosis are highly heterogeneous, and 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 patients, and their families and carers. The committee recognised that alpha-mannosidosis is an exceptionally rare condition, and the patient experts highlighted that this can 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 patients, 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). Although the marketing authorisation of velmanase alfa is not restricted by age, the company presented clinical and economic evidence only for people 6 years and older, who it considered would have mild-to-moderate forms of alpha-mannosidosis. This was consistent with the scope for the evaluation. The clinical experts explained that age is accepted as a marker of severity in alpha-mannosidosis, and heard that the severe form tends to be diagnosed before 5 years. The committee therefore understood that considering velmanase alfa only for people 6 years and older would be consistent with mild-to-moderate alpha-mannosidosis as specified in the marketing authorisation. The clinical and economic evidence available for velmanase alfa did not include people with advanced disease, such as those dependent on a wheelchair, so the committee was uncertain whether velmanase alfa would be considered for this group. It stated that more clarity on how velmanase alfa treatment would be considered for more advanced forms of mild-to-moderate alpha-mannosidosis in clinical practice would be welcome. 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 transplant (HSCT)

4.3 Allogeneic HSCT was listed as comparator for velmanase alfa in the scope for the evaluation, but was not presented by the company. The clinical experts explained that allogeneic HSCT can be an option for some people but is associated with significant morbidity and mortality. They also explained that, in children, the decision about whether to offer allogeneic HSCT is based on a risk–benefit assessment involving the clinician, the patient, and their parents or carers, but that people 6 years and older are unlikely to have allogeneic HSCT because of the increased mortality risk. The ERG explained that they had received advice suggesting that some people 6 years and older might have allogeneic HSCT. The committee recognised that it would not be able to make recommendations on velmanase alfa for people for whom allogeneic HSCT would be considered because of a lack of evidence. However, it concluded that allogeneic HSCT was unlikely to be a relevant comparator for people 6 years and older with alpha-mannosidosis.

Impact of the new technology

Clinical evidence

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

- rhLAMAN-05 (n=25) was a double-blind randomised placebo-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 (younger than 18 years compared with 18 years and older) as part of the post-hoc analysis.
- rhLAMAN-10 (n=33) was a single-arm open-label study that provided data on patients treated with velmanase alfa for up to 48 months. It

captured data about patients 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 pre-planned analysis (younger than 18 years compared with 18 years and older) and in a post-hoc analysis (6 to 11 years, 12 to 17 years, 18 years and older).

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 trials were generally well conducted and of reasonable quality. The ERG highlighted that there were uncertainties associated with both trials. In particular, it noted that, in rhLAMAN-05, patients in the velmanase alfa arm were more compromised than patients in the placebo arm; this could have affected some outcomes but the ERG was uncertain about whether it would favour velmanase alfa or placebo. The ERG also noted the lack of a control arm in rhLAMAN-10, which could have affected the interpretation of the results. 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. However, it recognised that this was influenced by the extreme rarity of the condition. The committee concluded that the clinical-effectiveness evidence was associated with several uncertainties.

Generalisability of the evidence to clinical practice in England

4.5 Patients included in the rhLAMAN trials were likely to have been younger (between 5 years and 35 years) than patients seen in clinical practice in England. Alpha-mannosidosis progresses faster in younger patients and so it is easier to detect clinically significant differences in younger patients. The committee therefore queried whether the benefits seen in the trials

reflected what might be seen in clinical practice in England. Also, patients with IgE levels above 800 IU/ml were excluded from the trials and the committee considered that this might have affected the generalisability of the safety findings. However, the clinical experts stated that the patients included in the rhLAMAN trials were representative of patients 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 improvement in serum oligosaccharide levels compared with placebo in rhLAMAN-05 (adjusted mean difference in relative change between velmanase alfa and placebo group: −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. 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 (LSDs), the principle of substrate reduction through enzyme replacement therapy has been established as a way to produce important clinical benefits. However, 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 some outcomes in rhLAMAN-10, but these were all considered negligible

or marginal. Similar assessment was not reported for rhLAMAN-05. The committee considered that the knowledge around serum oligosaccharides 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 was not able to infer the nature or magnitude 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 [3-MSCT], 6-minute walk test [6-MWT], forced vital capacity [FVC]) or quality of life (Childhood Health Assessment Questionnaire [CHAQ], 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-MSCT: 13.8%, p=0.004; FVC % predicted: 10.5%, p=0.011; EQ-5D-5L: 11.2%, p=0.036) but not in 6-MWT (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, particularly noting 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, and was unclear whether the benefits would translate into substantially meaningful improvements for patients. It heard from the clinical experts that small improvements would be important to patients. 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 magnitude of the benefits. The committee concluded that the evidence suggested that velmanase alfa is a potentially promising

treatment but there was insufficient evidence to establish the extent of the clinical benefits.

Long-term benefits of velmanase alfa

4.8 The committee was aware of the relatively short duration of the rhLAMAN trials. It heard from clinical experts and NHS England that the experience of other enzyme replacement therapies in other LSDs has shown that long-term treatment (over 5 to 15 years) has been associated with important reductions in complications that were otherwise hallmarks of the conditions, but these benefits only manifest after a long period of treatment. The committee therefore inferred that some of the benefits of velmanase alfa might only be seen after long-term treatment. It concluded that the long-term benefits of velmanase alfa were uncertain.

Infections

4.9 Infection rates were not collected from the trials as an efficacy outcome. The company acknowledged that infections are an important outcome which have a significant effect on patients' lives. It explained that understanding of alpha-mannosidosis has grown over time and infection rates are being collected in future trials. 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 serum IgG (adjusted mean difference compared with placebo: 3.47 g/litre, $p<0.0001$). They also showed that, of patients in rhLAMAN-05 with low baseline serum IgG (n=9/25), 60% (n=3/5) in the velmanase alfa arm had normal IgG levels and 40% (n=2/5) improved, while no patients in the placebo arm had improved IgG 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 patients in the velmanase alfa arm used fewer antibiotics than patients in the placebo arm, and an analysis of

carers' reports of infection rates supported a reduction in infections associated with velmanase alfa in rhLAMAN-10. The committee was aware that these data were interpreted by the company as indicating likely improvements in infection rates. The committee also noted comments from the patient experts and testimonies from patients treated with velmanase alfa, which 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.

Multi-domain responder analysis (MDRA)

4.10 The company also submitted a post-hoc MDRA for rhLAMAN-05 and -10. It explained that the analysis was conducted at the request of the European Medicines Agency to help understand the clinical relevance of the data and the variability between patients for some outcomes. The aim of the MDRA was to combine multiple clinically important endpoints into 3 domains (pharmacodynamics, functional and quality of life), to establish how many patients had a clinically meaningful improvement. A patient was classified as a 'responder' to treatment if the response criteria were reached in at least 2 domains. The MDRA showed that more patients were 'responders' in the velmanase alfa arm of rhLAMAN-05 than the placebo arm (87% compared with 30% respectively), and more patients younger than 18 years were 'responders' than patients 18 years and older in rhLAMAN-10 (100% compared with 71%). The ERG explained that there were several concerns with the MDRA, in particular: the assumption that the domains were of equal importance; the omission of infection rates; and the post-hoc nature of the analysis. The committee also highlighted that the relevance of the comparison between velmanase alfa and placebo was unclear because the response to the pharmacodynamic domain (reduction in oligosaccharides) had already been established from rhLAMAN-05 (that is, that patients taking velmanase alfa would have a

pharmacodynamic response whereas those having placebo would not). The company recognised this limitation and explained that the MDRA captured several layers, including the variation in treatment response between domains as well as in the individual domains. The committee concluded that the MDRA had several limitations and the relevance of the results was uncertain.

Adverse events

4.11 The proportion of patients 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 patients 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

4.12 The company presented an economic analysis based on a Markov model, in which patients could move through 4 primary health states according to their mobility: walking unassisted (WU), walking with assistance (WWA), wheelchair dependent (WC), severe immobility (SI) and dead. Patients 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 years and older). 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 patients, but that there were other measures of disease progression; lung function might also have been a good surrogate. The

committee concluded that the overall model structure was adequate for decision-making.

Sources of data in the model

4.13 Most of the parameters used to inform the model were from either an expert elicitation panel (EEP) or interviews with key opinion leaders (KOLs). This was because clinically important aspects (such as severe infections and need for surgical intervention) were not captured in the rhLAMAN trials and could not be derived from observed data. 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 EEP was based on a formal elicitation process using well-respected methods, although it heard from the ERG that the KOL interviews had greater limitations. The committee was reassured that experts and KOLs from the UK were enrolled in these studies, so their experiences were likely to be representative of UK clinical practice. 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, and the magnitude and direction of any errors or bias were unknown.

Benefits of velmanase alfa in the model

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

- delay disease progression compared with best supportive care (BSC), based on the EEP
- improve patients' mobility from baseline (that is, patients in the WWA and WC states could move to better heath states in the model), whereas BSC did not

- reduce the mortality, complications and recovery time associated with severe infections and major operations by 50% compared with BSC.

The committee recognised that the benefits of velmanase alfa in the model were based on assumptions and expert opinions, rather than evidence. It was also aware that the assumed improvements from baseline contradicted what was seen in rhLAMAN-05, in which the same proportion of patients improved from WWA to WU in the velmanase alfa and placebo groups. It considered that the magnitude of the benefits in the model appeared large in the context of the benefits seen in the trials and was unclear whether there was sufficient evidence to support benefits of this size. In the absence of evidence, the committee was unable to conclude that the benefits assumed in the model were inappropriate but emphasised the high level of uncertainty associated with the results.

Quality-of-life benefit of velmanase alfa

4.15 The company assumed that velmanase alfa improved quality of life throughout treatment, over and above its effects on mobility and response to infection and surgery as described in section 4.14. It therefore attributed a utility gain of 0.1 to any patient treated with velmanase alfa. 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; reducing rates of psychiatric problems; reducing ventilation dependency; providing improvements within the ambulatory heath states (WU, WWA); providing structured homecare visit; and the possibility that some further benefits of velmanase alfa will appear after several years of treatment. The value of 0.1 was chosen with reference to the improvements seen in EQ-5D in rhLAMAN-10 (0.05 in WU and 0.058 in WWA). The ERG explained that the utility gain with velmanase alfa was unclear and the company's approach had limitations. Because of this, the ERG presented scenario analyses in which the utility gain was decreased to 0.05 or 0. The committee highlighted that several benefits of velmanase alfa were

captured elsewhere in the modelling, and was not convinced that there were sufficient benefits not otherwise captured to justify a utility gain of 0.1. However, it considered that it was plausible that velmanase alfa could provide some additional benefits (for example, reduction in pain) so assuming a utility gain of 0 was not appropriate. The committee concluded that the ERG's exploratory analysis that used a utility gain of 0.05 was reasonable.

Health-state utilities

4.16 The company used the utilities collected from a survey conducted by UK Society for Mucopolysaccharide Diseases (UK MPS Society). The survey provided utilities for WU (0.906), WC (0.100) and SI (-0.011) using the model's definition of health states. The utility for WWA was extracted from unpublished UK KOL audit data (this cannot be reported because it is academic in confidence) because no patient was in this health state using the model's definitions. The ERG acknowledged that these utilities 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 utilities collected from the rhLAMAN trials (using CHAQ and EQ-5D) because they were generated from a larger sample (n=24) compared with the utilities from the survey and the other source (n=5). The committee considered that both sets of utilities had important limitations. It thought that the utility value for WU from the survey (used in the company's base case) seemed implausibly high, and recognised that the larger sample size for the trial data was preferable. The committee concluded that, although both sets of utility values were highly uncertain, on balance, the values from the rhLAMAN trials (as used in the ERG's scenario analyses) were preferable for decision-making.

Ventilation costs

4.17 The company assumed that patients initially treated with velmanase alfa who stopped treatment (and switched to BSC) would need 50% less ventilation assistance than patients treated with BSC throughout. The

committee considered that this assumption was not realistic and that patients would be unlikely to benefit from velmanase alfa to this extent after stopping treatment. The ERG amended this assumption in their base case by removing the continuing benefit of velmanase alfa after stopping treatment. The committee concluded that the ERG's approach was preferable for decision-making.

Stopping rules

4.18 The company proposed draft stopping rules for treatment with velmanase alfa (subject to consultation with UK experts), which it included in the model. The stopping rules would allow treatment to stop for patients who gain no benefit (defined as failing to meet 2 of the 3 response criteria in the MDRA at 12 months), patients with life-limiting conditions, and patients who cannot tolerate the treatment or cannot comply with monitoring (either for practical reasons or because of worsening disease). These rules were included in the model as: 'non-response' (based on multi-domain 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 KOL interviews); and an annual risk of withdrawal (based on KOL interviews; 10%). The committee accepted that it was reasonable to consider the proposed stopping rules and acknowledged that they had been incorporated into the model.

Discounting rate for costs and health effects

4.19 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 discounting rate is 3.5%. However, it also states that a non-reference-case 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; if it is highly likely that there will be long-term benefits; and if the treatment does not commit the NHS to significant

irrecoverable costs. The committee acknowledged that treatment was not expected to commit the NHS to irrecoverable costs. However, given that velmanase alfa does not affect the neurological consequences of alpha-mannosidosis, it could not return patients to full or near-full health. In addition, although it may be expected that velmanase alfa provides long-term benefits, there was not sufficient clear evidence to consider that it was highly likely that long-term health benefits would be achieved. The committee therefore concluded that velmanase alfa does not meet the NICE's criteria for applying a discounting rate of 1.5%. It concluded that a discounting rate of 3.5% should be applied for cost and health effects.

Other assumptions

4.20 The ERG flagged up several additional assumptions and parameters that were uncertain but which could not be addressed. In particular, the benefit of velmanase alfa in delaying disease progression might have been double counted, leading to overestimated modelled life expectancy. The ERG noted that assuming patients treated with BSC cannot improve their health state was likely to change the incremental cost-effectiveness ratio (ICER), although the direction was not known. It also noted that the use of fixed weights (when calculating the dosage of the treatment) rather than a distribution of weights may not have reflected the true uncertainty. However, whether this was favourable or not to velmanase alfa is unknown. The committee acknowledged that the effects of these assumptions were unknown, but considered that they contributed to the uncertainties in the economic model results.

Application of quality-adjusted life year (QALY) weighting

4.21 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 magnitude 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 QALY gains associated with velmanase alfa, and highlighted that these were substantially below 10 (between 1 and 3.3) in the company's base case, the ERG's base case and all of the ERG's exploratory analyses. The committee concluded that there was no evidence to suggest that velmanase alfa would meet the criteria for applying a QALY weight.

Cost-effectiveness results

4.22 The company presented a base case in which velmanase alfa was associated with QALY gains of 2.53 for the paediatric cohort, 2.66 for the young person cohort and 2.67 for the adult cohort. The ICERs for all 3 cohorts were substantially higher than £100,000 per QALY gained. The ERG presented an alternative base case in which it amended: the utility gain associated with velmanase alfa (to 0); the utilities for WU and WWA (based on the trial results); the discount rate (to 3.5%); and the ventilation cost (equivalent to BSC after stopping velmanase alfa). It also amended an error in the transition probabilities. The committee noted that ERG's base-case ICERs were more than double those of the company's for all 3 cohorts. The company and the ERG presented scenario analyses that explored uncertainties around key assumptions. They highlighted that the ICERs were sensitive to the acquisition cost of velmanase alfa and the discount rate (in the company's analyses), and to the utility gain associated with velmanase alfa, the costs of ventilation and the utility for WU and WWA (in the ERG's analyses). Taking into account its conclusions on the key assumptions, the committee considered that the most plausible scenario was the ERG's scenario analysis with a utility gain of 0.05 (see section 4.15), utilities for WU and WWA taken from the clinical trial (see section 4.14), discounting at 3.5% (see section 4.19), the

amended ventilation cost (see section 4.17), and the corrected transition probabilities. The most plausible ICER was confidential and cannot be reported here, but was substantially higher than the range that can be considered an effective use of NHS resources for highly specialised technologies.

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

4.23 The committee discussed the effect of velmanase alfa beyond its direct health benefits. It understood from patient and clinical experts that all aspects of life for the patients, families and carers are affected by the condition. The committee noted that patients need a high level of care, and that professional life could be compromised for patients, families and carers.

4.24 The committee noted that alpha-mannosidosis is managed in established LSD specialist centres, so no additional infrastructure or staff training will be needed to manage use of velmanase alfa in England.

Other factors

4.25 The committee discussed the innovative nature of velmanase alfa, noting that it is the first pharmacological disease-modifying therapy for alpha-mannosidosis. The company considers that velmanase alfa is a step-change in managing alpha-mannosidosis 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.

4.26 No equality issues were identified.

Managed access

4.27 The committee acknowledged that the substantial uncertainties associated with velmanase alfa suggest that collecting additional evidence

may be valuable. It therefore noted that a managed access arrangement (MAA) might be a possible route to address and resolve some of the uncertainties. However, the committee considered that an MAA would only be an appropriate option for velmanase alfa if it could be shown that the drug had a plausible potential to be considered a cost-effective use of resources for highly specialised technologies. It emphasised that, if an MAA were to be considered, the evidence collection should focus on the key uncertainties and, in particular, the health benefits associated with velmanase alfa, including benefits over time. The committee acknowledged that an MAA would be unlikely to resolve the uncertainties about long-term benefits. It noted that any MAA would also need to define starting and stopping criteria agreed between stakeholders. It recalled that it was uncertain how velmanase alfa treatment would be managed in people with more progressed disease (see section 4.2), but that the evidence presented already focused on people who could walk unaided or with assistance (and did not include people who depended on a wheelchair). It also recalled that the company's economic model included proposed stopping rules (see section 4.18). The committee recognised that applying stopping rules such as these, which had not been applied in the clinical trials, 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 treatment with velmanase alfa. However, it noted that the stopping rules, being applied after 12 months, would not affect the clinical benefits before this point. The committee also considered that starting and stopping rules within an MAA may be unlikely to substantially improve the cost effectiveness of velmanase alfa beyond that estimated in the most plausible scenarios, but should nevertheless be clearly defined. The committee further noted that the other elements of MAAs, as defined in the interim process and methods of the highly specialised technologies programme (2017), should also be included. The committee concluded that evidence collection through an MAA could help resolve some of the

uncertainties in this evaluation. However, it also concluded that velmanase alfa could not be recommended within an MAA because it did not currently have the potential to be considered cost effective.

Conclusion

4.28 The committee acknowledged that alpha-mannosidosis is an exceptionally rare condition that causes a wide variety of symptoms and impairments, and has a serious and substantial effect on the quality of life of patients, and their families and carers. It was aware that small increases in clinical outcomes can translate to substantial improvements for patients. The committee noted that the clinical evidence suggested that velmanase alfa may provide clinical benefits. However, 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 ICERs were above the range that can be considered an appropriate use of NHS resources for highly specialised technologies in the company's base case, the ERG's base case and exploratory analyses, and the committee's preferred analysis. It also noted that velmanase alfa did not meet the criteria for QALY weighting to be applied, and that there remained important uncertainties within the economic model. The committee therefore 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 the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
May 2018

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), a technical adviser and a project manager.

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Technical Lead

Ian Watson
Technical Adviser

Joanne Ekeledo
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