NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease) type AB and type B

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using olipudase alfa in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders 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 clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: October 2023

Note that this document is not NICE's final guidance on olipudase alfa. 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 stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using olipudase alfa in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 16/11/23
- Second evaluation committee meeting: 7/12/23
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Olipudase alfa is not recommended, within its marketing authorisation, for treating acid sphingomyelinase deficiency (ASMD; Niemann-Pick disease) in people with type AB or type B.

1.2 This recommendation is not intended to affect treatment with olipudase 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 or young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

ASMD (type AB and B) is a genetic disorder that severely affects the quality of life of people with the condition, their families and carers. It also increases the risk of death. There is no licensed treatment for the underlying causes of ASMD. Best supportive care aims to manage the symptoms, such as improving nutrition and breathing, and treating infection.

Clinical trial evidence shows that olipudase alfa improves lung function and reduces the size of the spleen in both adults and children with ASMD at 1 year follow up. The treatment effect may continue in the longer term, but this is uncertain.

There are also uncertainties in the economic model, so it is not clear what the most likely cost-effectiveness estimates are. The available estimates are higher than what NICE usually considers acceptable for highly specialised technologies. So, olipudase alfa is not considered an appropriate use of NHS resources within the context of a highly specialised service and cannot be recommended.

2 Information about olipudase alfa

Marketing authorisation indication

2.1 Olipudase alfa (Xenpozyme, Sanofi) is indicated 'as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B'.

Dosage in the marketing authorisation

2.2 The dosage schedule available in the summary of product characteristics for olipudase alfa.

Price

2.3 The cost for olipudase alfa is £3,612.00 per 20 mg vial (excluding VAT, BNF online accessed October 2023).

2.4 The company has a commercial arrangement, which would have applied if olipudase alfa had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Sanofi, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Niemann-Pick type AB and B

3.1 Niemann-Pick disease is caused by a genetic mutation that means certain cells in the body do not metabolise a substance called sphingomyelin (a type of fat) correctly, leading to a build-up of this in cells. The clinical manifestations of the disease depend on the location of the affected cells but, over time, the accumulation of this fat cause cells to die, resulting in damage to multiple organs. There are about 40 to 50 people diagnosed in

England in total with type A, B or AB. Both type AB and type B involve primary symptoms that include an enlarged spleen, low platelets, an enlarged liver and liver disease, delayed growth and puberty, and a blood lipid profile that increases the likelihood of atherosclerosis (hardening of the arteries). Type AB can also include slowly progressive neurodegeneration, which is not present in type B. The disease is associated with increased risk of death, with the leading cause being respiratory or liver failure. Type AB and B, together with type A which is not included in this evaluation, are also known collectively as acid sphingomyelinase deficiency (ASMD). Other forms of Niemann-Pick disease include type C and D, but these are not classified as ASMD nor covered in this evaluation.

Burden of the condition

3.2 ASMD is an inherited metabolic disorder caused by enzyme deficiencies within lysosome, known as lysosomal storage disease (LSD). Both type AB and type B of ASMD have a considerable impact on quality of life, not just for the person with the condition but also for their carers, family and wider social network. The patient experts explained that symptoms of the disease are multifaceted. Build-up of sphingomyelin can restrict lung capacity, which often causes tiredness and limits the ability to exercise. An enlarged spleen can cause anaemia, limit the ability to eat usual size meals, and cause nausea and vomiting. The potential for contracting infections (which can be difficult to shake off) and the risk of physical injury from contact with enlarged organs can make people afraid of normal activities such as using public transport and engaging in social activities. In children, symptoms such as delayed growth or puberty, and abdominal swelling from enlarged organs, can have a profound psychological impact (particularly in people aged 10 to 16) and can lead to bullying and social isolation. These clinical manifestations considerably impair the ability to perform daily tasks. Children with ASMD in particular often need a carer to support activities of daily living. There is also a significant impact on the quality of life of carers and siblings of people with ASMD. Caring duties

can be very time consuming and can inhibit the carer's ability to maintain employment and considerably impact their personal relationships and social lives. Psychological strain in the form of anxiety, depression and stress are common, along with fatigue resulting from the level of care needed and from the child's poor sleep. Also, when a carer is the biological parent of the person with ASMD, there may be feelings of guilt and responsibility for passing on the genetic disease. Siblings of children with ASMD may also be affected, for example, through limited attention from parents because of their caring responsibilities. This may lead to feelings of exclusion, resentment, embarrassment and anxiety. When people die from ASMD it is usually a result of respiratory or liver failure. The committee understood that ASMD is a debilitating and life-limiting disease, which has a substantial impact on quality of life for both the person and their carers.

Clinical management

Existing treatment

3.3 The clinical experts explained that there is no licensed treatment addressing the underlying causes of ASMD. Best supportive care involves supportive or palliative treatment to support nutritional needs (with or without feeding tubes), respiration (including supplemental oxygen and treatment of infections), liver disease (including consideration of a liver transplant), blood products and treatment for low bone mineral density. The patient experts explained that the current treatments do not bring the disease under control to a sufficient degree, and many people still need carers. Day-to-day care for people with ASMD is done at home with the help of carers, but the complex and wide-ranging nature of ASMD means that frequent hospital visits and visits to specialist centres throughout the country are needed to manage the condition. The committee understood that there is an unmet need for treatments that improve outcomes and quality of life for people with ASMD.

3.4 Both the clinical and patient experts noted that olipudase alfa represents a transformative addition to ASMD treatments. The patient experts explained that the treatment can greatly reduce the burden of the disease by addressing the key clinical manifestations. Importantly it reduces the size of the spleen and liver, and increases lung capacity. They explained that this could have a life-changing impact on quality of life for people with ASMD, because they may regain the ability to perform everyday tasks and this would reduce the time needed for carers to attend to their caring responsibilities. This may allow the carer to potentially return to work and improve their quality of life. It may also reduce the number of people who die from ASMD. The clinical experts agreed and noted that the side effects are relatively minor, especially compared with the symptoms of ASMD. They also noted that the neurological manifestations of ASMD would not be addressed by olipudase alfa. The committee understood that olipudase alfa represents a potential new treatment option for people with ASMD type AB and B.

Clinical effectiveness

Data sources and representativeness of the trial populations

3.5 Clinical-effectiveness data for olipudase alfa came from several clinical trials. ASCEND (n=36) is a phase 2/3, double-blind randomised controlled trial comparing olipudase alfa with placebo in adults with ASMD. After having the randomised treatment for 52 weeks, everyone had olipudase alfa in the extension period of the trial, which is ongoing and reported data for an additional year at the time of submission. ASCEND-Peds is an open-label single-arm trial in which 20 children and young people aged under 18 had olipudase alfa with 52 weeks follow up. DFI13412 is an open-label trial in which 5 adults had olipudase alfa with a 26-week follow up. Finally, LTS13632 is an open-label extension study including people from the ASCEND-Peds and DFI13412 trials. This extension study is also ongoing and reported data for 7 children and 5 adults at a follow up of 4 years and 6.5 years, respectively. The EAG noted that the inclusion and

exclusion criteria of the trials were stringent and was concerned that those with a milder condition or higher severity may have been excluded. The clinical experts explained that those with the most severe condition and a group of adults with a mild condition, for example those with mild lung capacity condition, were excluded from the trials. Each of these exclusions accounted for about 20% of the ASMD population in practice. But the clinical experts explained that usually people with the most severe disease are children, and data from the early access programme suggested that they could also benefit from the treatment. The EAG noted that the baseline weight in these trials was lower than what would be expected in the UK. Also, although the marketing authorisation for olipudase alfa was for people with either type AB or type B disease, it is unclear how many had type AB or B in the trials. The EAG explained that people with type AB disease sometimes present with neurological symptoms that are unaffected by olipudase alfa. This means that the level of representation of type AB in the overall cohort is potentially important, because olipudase alfa may have differential effects on key outcomes and quality of life in people with type AB compared with type B. Baseline characteristics show that roughly 25% of people in ASCEND and 40% of people in ASCEND-Peds had neurological symptoms consistent with type AB disease. But the clinical experts explained that these may be because of developmental delay resulting from non-neurological manifestations of the disease (such as poor nutrition), and not necessarily indicate type AB disease. The clinical and patient experts explained that it is common that some people with ASMD have reduced height and weight. Some people with ASMD may be smaller but it is unlikely there will be a big difference across the population. After some time on the treatment, people could catch up to the general population in both height and weight. They also noted that it is challenging to differentiate between type AB and B in practice, particularly when people are young. Also, although the proportion of people with type AB disease is unknown, the high proportion of people with neurological symptoms in trials suggests that people with

type AB may be over-represented. This may result in a conservative estimate of the efficacy of olipudase alfa. The committee noted the variable clinical manifestations associated with ASMD and the spectrum of the disease. It concluded that the populations in trials may be representative of those seen in the NHS, but there are uncertainties about whether the trials included the range of people who would have olipudase alfa in clinical practice.

Clinical effectiveness

3.6 Evidence from the clinical trials shows that olipudase alfa improves various key outcomes. Evidence from ASCEND showed that olipudase alfa was associated with a greater improvement from baseline in mean percentage predicted diffusing capacity of the lungs for carbon monoxide (DLco) compared with placebo at both 26-week (14.14; 95% confidence interval [CI] 5.85 to 22.44) and 52-week follow up (19.01%; 95% CI 9.32 to 28.70). The differences were statistically significant. In ASCEND-Peds, evidence showed that percentage predicted DLco increase by a mean of 33% (95% CI 13.4 to 52.5) from baseline for olipudase alfa. A responders analysis done by the company also showed that 5 out of 18 adults on olipudase alfa in ASCEND had a clinically significant improvement (defined by the company as an improvement of 15% or higher) in lung diffusion capacity at week 52. The EAG noted that there could be further improvements after 52 weeks but there is uncertainty because no further responder analyses were done. It also noted the high rates of missing outcome assessments at 2-year follow up (50% for DLco). Spleen volume reduced for people taking olipudase alfa. In the ASCEND trial, 94% of people taking olipudase alfa had a reduction of 30% or more in spleen volume at 12 months, whereas no change was seen in the placebo arm. The EAG noted that there were again a high amount of missing outcome assessments at 2 years for this outcome (30% and above). But, clinical advice to the EAG suggested that it is plausible that the reduction would maintain at this level at least in the months after the trial. Data from the extension study LTS13632 also showed that at 78 months there was a

mean reduction in spleen volume for both adults (59.5%, n=5) and children (the data is considered confidential so is not reported here). Liver volume also showed a large decrease at both 6-month and 78-month follow up (the exact result cannot be reported here as it is considered confidential). A treatment effect largely in the same direction was also seen for other clinical outcomes, including platelet counts and liver function. The committee noted the improvement in clinical outcomes associated with olipudase alfa, but also noted the relatively short follow ups in trials. It questioned the treatment effect of olipudase alfa in the longer term. The clinical experts explained that olipudase alfa was associated with significant improvement in the first 6 to 12 months, and the improvement could continue after 2 years. The patient experts also explained that having the treatment allows them to exercise better, which can further improve their wellbeing. The EAG noted that although there were improvements in clinical outcomes, some symptoms, for example, spleen volume, remained several times larger than usual. The clinical experts also explained that in ASMD there may be improvement in people with milder degrees of organ damage. But this would not be seen in most people with more severe damage, such as those with lung or liver fibrosis. The committee concluded that olipudase alfa improves clinical outcomes associated with ASMD, but there are uncertainties in its longer-term treatment effect.

Treatment effect on HRQoL

3.7 The ASCEND and ASCEND-Peds trials collected health-related quality of life (HRQoL) data using the EQ-5D and the SF-36. Results showed that there was no difference between arms in ASCEND. Both the company and EAG agreed that these results are inconsistent with the key outcome data from the trials and testimony from experts that suggests the improvements in key clinical outcomes have direct effects on quality of life. The EAG noted that it is likely that standard instruments such as EQ-5D or SF-36 are not sufficiently sensitive to improvement in clinical outcomes in ASMD. Also, given the relatively short follow up of the

ASCEND trial and the small sample size, it was unlikely to see statistically significant differences in quality of life measured by EQ-5D or SF-36. The company suggested that because ASMD is a chronic condition, people may have adapted to it over time, which the instruments may not be sensitive enough to pick up. A positive benefit was shown in children in ASCEND-Peds, with 8 to 18 year olds having mean improvements in HRQoL that were above the threshold for minimally important differences (MIDs) at 6 months and had increased further by 12 months. Children aged 5 to 7 had an increase near the threshold for MIDs by 12 months. The EAG explained that ASCEND-Peds was open-label and this poses a risk of bias for the interpretation of the evidence. But it noted that other studies not included in the submission seem to also show a benefit, meaning the improvement in quality of life from baseline in children may be genuine. The committee understood that the evidence on olipudase alfa's treatment effect on HRQoL was mixed. But there are limitations in the evidence given the different study designs, the small sample sizes, and the relatively short duration of follow up in trials.

Economic model

Company's modelling approach

3.8 The company constructed a state transition model with 9 health states to model the disease course of ASMD for olipudase alfa and best supportive care. The model has a time horizon of 100 years. Health states were categorised by both spleen volume and DLco, with 3 levels of severity for each outcome. Spleen volume groups included less than 6 multiples of normal, 6 to 15 multiples of normal, and 15 and above multiples of normal. DLco states included a mild reduction (80% and above predicted value), moderate reduction (40% to 80%) and severe reduction (40% and below). The 9 health states modelled consist of the 9 different combinations of the spleen volume and DLco health states, plus an additional health state for death. The movement between the health states was determined by transition probabilities informed by data from the clinical trials (see section

3.5), along with additional data from the SPHINGO-100 trial and a pooled chart review analysis. The committee concluded that the model structure was appropriate for decision making.

Modelling long-term treatment effect

3.9 The company modelled health-state transitions for the best supportive care arm using data from the placebo arm of ASCEND. This means that people can continue to move between health states until the end of the time horizon, or they die. But, for the olipudase alfa arm, the company assumed that everyone would transition to the least severe health state (defined by spleen volume less than 6 multiples of normal and DLco 80% and above predicted value) from year 10, and would remain there for the rest of the modelled time horizon or death. The EAG noted that there may be some long-term treatment effect associated with olipudase alfa, but it was concerned with the company's approach. It explained that the most robust data from the trails are up to 1 year, with 2-year data having limitations because of the high rates of missing outcome assessments at this time point (see section 3.6). Given the uncertainties, the EAG did 3 scenario analyses in which the treatment effect of olipudase alfa was assumed to:

- scenario 1: freeze from year 3 onwards, meaning that people stay in the same health state they are in after 2 years' treatment
- scenario 2: recycle from year 2 onwards, meaning that after year 2 people move through health states based on the transition probabilities seen in year 2 of the trials
- scenario 3: begin to wane from year 2, meaning everyone having olipudase alfa follows the transition probabilities of best supportive care from year 2 onwards.

The EAG considered that the most plausible options was to freeze the treatment effect from year 3 onwards, and included this assumption in its preferred base case. The patient experts explained that olipudase alfa

could lead to a rapid and drastic improvement in outcomes for people taking it and that this improvement increases over time. One of the clinical experts noted that evidence from the trials showed that the treatment effect lasted for about 10 years in some people without declining. The committee recalled its discussions about olipudase alfa's treatment effect on clinical outcomes and the uncertainties surrounding it in the longer term (see section 3.5 and 3.6). It considered that freezing the treatment effect after 2 years as the EAG preferred may be pessimistic, but the committee was also concerned with the lack of justification for the company's approach. It considered that it may be plausible to assume some long-term treatment effect. It noted that the EAG's scenario analysis of treatment effect continuing after year 2 might be an option, but although there were improvements in clinical outcomes, some symptoms persisted (see section 3.6). The committee concluded that there may be ongoing and gradual improvement when on treatment. But, because there was uncertainty in the evidence it would like the company to explore the scenario of a treatment effect that continues for 9 years and is then frozen from year 10.

Modelling mortality

3.10 The original company base case modelled mortality using the SPHINGO-100 trial, an observational study of 58 people with ASMD type B in North America over an 11-year period. Based on this study, the company estimated a standardised mortality risk (SMR) of 4.3 for people with ASMD compared with the general population, while for those with severe disease (defined as people with severe splenomegaly) an SMR of 43.1 was applied. The EAG commented that there were several limitations associated with this method. These included the low number of deaths occurring during follow up (8 people died) in the study, and categorising severe disease simply as whether the person had severe splenomegaly or not. After technical engagement, the company revised its analysis to use a different source of data to estimate mortality for the best supportive care arm, using a pooled analysis of a chart review of 270 people with ASMD.

Mortality was modelled for the olipudase alfa arm by applying a hazard ratio of 0.1 to best supportive care mortality. The EAG cautioned against using this revised approach. It highlighted that it may not be suitable for decision making because there were severe limitations in the company's revised approach. This included: extensive missing data on baseline severity markers such as spleen volume, liver volume and DLco in the chart review; lack of details on the methods; the source of the hazard ratio used to model the olipudase alfa arm; and lack of analysis and reporting on the checking and suitability of chosen survival curves. For example, the Kaplan–Meier survival curve was only presented for the overall population with risk adjustment but there were no details on the adjustments made. Also, only the extrapolations for the overall survival in adults were presented, but the area under the curve (AIC) and Bayesian information criteria (BIC) statistics were provided for the overall population including both adults and children, so it was not possible to select the best fitting curve (based on AIC and BIC statistics) for each. Further, there was no checking for the visual fit of the selected curves. Given the lack of details and reporting on the analysis and methods used, the EAG preferred to maintain the company's original approach in its base case, but noted there are also uncertainties. The company explained that it used the AIC and BIC statistics for the overall population to inform the curve fitting in each group. This is because of the difficulties in binarily splitting the population into adults and children given that ASMD is a spectrum disease and dividing it by adults and children could lead to the wrong results. The committee noted that the company's revised approach was based on a natural history study in an ASMD population, which might be a more appropriate data source because the shape of the hazard would not follow that of the general population. But the committee also recognised the severe limitations in the reporting of the company's approach, as noted by the EAG. Given the lack of information and analysis presented for the company's revised approach, the committee concluded that it preferred the EAG's approach for modelling mortality. But, it would like the

company to present additional information and analysis in its revised approach for decision making.

Disease-related mortality in children

3.11 The company's original and final base case both included disease-related mortality in children, meaning some children would die as a direct consequence of the disease. The EAG considered this inappropriate, noting that in the SPHINGO-100 trial, 3 out 30 children died during the 11-year follow-up period, and the primary cause of death in all 3 children was pneumonia. The clinical experts explained that they have experience with children dying as a result of the disease for both ASMD type B and AB, and this is in line with what is suggested by the published literature. The committee concluded that it is appropriate to include disease-related mortality in children in the model.

Discounting rate

3.12 In its base case, the company presented cost-effectiveness results assuming a 1.5% discount rate for costs and benefits, rather than 3.5% as used in the NICE reference case and as preferred by the EAG. The NICE health technology evaluations manual states that a rate of 1.5% may be considered by the committee if it is satisfied that 3 criteria are met.

Criteria 1

3.13 The treatment must be for people who would otherwise die or have a very severely impaired quality of life. In its response to technical engagement, the company noted that people with ASMD have an increased risk of mortality compared with the general population and it had clinical advice that supported this. The EAG noted that although there is an increased mortality risk, the extent of this risk is unclear, and it is also unclear how it differs between people with type AB and type B disease. The committee recalled testimony from patient experts outlining the considerable impact the disease has on quality of life and agreed that ASMD likely does severely impair quality of life, but the risk of mortality is unclear.

Criteria 2

3.14 The technology is likely to restore people to full or near-full health. After technical engagement, the company presented results from an online survey and semi-structured interviews of 10 children or their carers before and after treatment with olipudase alfa. This showed that the treatment improved all non-neurological symptoms. The EAG agreed that this survey showed important improvements associated with olipudase alfa, but the small sample size of the study and unclear methodology limited the confidence in the findings. Also, the EAG highlighted that clinical evidence showed that organs are still enlarged after treatment (at around 6 multiples of normal for spleen volume) and that mean DLco at 52 weeks is around 70% of predicted value, which indicates that people are not restored to full health. The clinical experts commented that spleen volume could still be enlarged and there are still symptoms. The committee considered that the persistence of a significantly enlarged spleen cannot be considered as near normal or full-health. It also recalled its discussion about olipudase alfa's treatment effect on clinical outcomes and the clinical experts' opinion on whether all organ damage is reversible (see section 3.6). It agreed that there is some evidence that olipudase alfa improves clinical outcomes in people with ASMD, but whether the extent of the improvement is full or near-full health is uncertain.

Criteria 3

3.15 The benefits must be sustained over a long period of time. The company noted that the extension of trials provided data up to 4 years for children and up to 6.5 years for adults. It also explained that there is evidence in Gaucher disease that the effects of enzyme replacement therapy (ERT) are maintained up to 20 years after starting treatment. One of the clinical experts noted that some people in the extension of phase 1b trials have had olipudase alfa for up to 10 years without evidence of treatment effect declining. The patient experts also supported this, suggesting that their experience indicates that the effect is sustained in the long term. The EAG highlighted that the small number of people with data available at the

longer-term follow-up time points in the clinical trials meant that results were uncertain. Also, it is unclear whether evidence from Gaucher disease is generalisable to ASMD. The committee recalled its discussions on the treatment effect of olipudase alfa in the longer term (see section 3.6and section 3.10). It concluded that it is plausible the treatment effect may maintain for some time but there are uncertainties. The committee concluded that the reference case discount rate of 3.5% should be used in the cost-effectiveness analysis because of the uncertainties around whether olipudase alfa meets the 3 criteria to be eligible for the 1.5% discount rate.

Patient weight

3.16 The company and EAG differed in their method of modelling the weight of people with ASMD. The company modelled adult weight as being constant over time whereas for children it fluctuated over time by applying a z-score function estimated from the SPHINGO-100 study and applying this to UK growth weight charts. The EAG noted that the average weights for both adults and children seemed lower than the UK average if using other sources. The EAG preferred to use the 2019 Health Survey for England report to model weight and also applied a z-score function to the adult population, estimated from 18-year-olds in the SPHINGO-100 study. The patient and clinical experts agreed that it is common for people with ASMD to be shorter than their peers. Weight is also reduced because of this shorter height, though the difference compared with their peers is not as pronounced because the condition causes enlarged organs, which add weight. But the clinical experts noted that after several years' treatment, patients' weight would return to around the average range seen in the UK, but not to the extent of overweight or obese. The committee concluded that the EAG's approach was more appropriate but that weight for both children and adults was likely to be within the normal range but lower than the average of the UK general population. So, the starting weight should be at the lower end of the UK average in the model.

Carer disutilities

Applying carer's disutility

3.17 The company and EAG both included disutilities for carers of people with ASMD as part of their base case, but differed on a number of assumptions. The company only applied disutilities to carers in the best supportive care arm, assuming that there are no carer needs for people taking olipudase alfa. The EAG preferred that disutilities be based on the health state of the patient, irrespective of the treatment arm. It noted that carers for people with severe health states would have reduced quality of life regardless of the treatment used. The patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD. The committee concluded that carer's disutility should be based on the health state of the person with ASMD, irrespective of the treatment used.

Carer disutility values

3.18 There was an absence of published literature for carer disutility values in ASMD. Instead, the company sourced disutility values from Pompe disease, a condition in which the body cannot break down glycogen for energy, resulting in glycogen accumulation in tissues. It then applied a carer disutility of -0.15 for all health states. The EAG had clinical advice suggesting that Pompe disease would incur a higher carer disutility than ASMD, so it preferred that the values be sourced from a number of different chronic conditions, including multiple sclerosis and meningitis. Also, the EAG provided different values for children and adults, arguing that children need more attention than adults, and higher values for severe disease (defined as spleen volume 15 multiples of normal or greater). The carer disutility values used by the EAG range from -0.010 to -0.080. The committee agreed that it was more logical that children and people with more severe health states would incur greater carer disutility, also noting that it preferred carer disutilities to be applied based on the person's health state irrespective of treatment (see section 3.16). The

committee concluded that the EAG's approach of differentiating carers' disutilities by both the severity of health state, and children compared with adults, is appropriate for decision making.

Number of carers

3.19 The company assumed that children would have an average of 2.6 carers (including siblings) whereas the EAG preferred an average of 1 carer per person. The EAG noted that there is no precedent for assuming more than 2 carers even in evaluations for more severe LSDs, and that research into carer disutilities is limited, particularly within the context of sibling disutilities. The patient experts explained that there is considerable strain on quality of life for the person with the disease, the impact it has on functioning in everyday life and the corresponding impact on carers and their wider social network. Patient expert testimony also outlined the negative impact on siblings (see section 3.2). The committee acknowledged that the impact of the disease would be wider reaching than just the carer of the person with ASMD and would impact their wider social network. But it also considered that ASMD is not likely to produce such a profoundly large carer burden that 2 or more carers are needed to commit full-time efforts towards caring duties. The committee concluded that an average of 1 carer was appropriate for decision making.

Carer's disutility for mortality

3.20 The company assumed a carer disutility of -0.50 if the person with ASMD dies, and applied this disutility across the remainder of the time horizon used in the model. The EAG was concerned that there is no conclusive research into the application of carer disutilities after bereavement. Consequently, there is high uncertainty about whether disutilities should be applied in the event of the patient dying, how big the disutility should be and for how long. So, the EAG removed any disutility after death. The company explained that excluding carer's disutility for bereavement would be counterintuitive, leading to a result in which carers are not affected by the death of their loved ones. The committee noted that there may be a

carer's disutility associated with a patient dying, but that this would not be as high as -0.50 as assumed by the company. Also, it would not persist for the remainder of the time horizon of the model. The committee also noted that the EAG's approach may not capture the loss of utility associated with bereavement. Given the uncertainties and lack of research into the field, the committee concluded that it would be appropriate not to include carer's disutilities associated with bereavement numerically in the model, but rather to qualitatively consider the impact of a patient's death on carers in its decision making.

Criteria for applying QALY weighting

3.21 The committee understood that NICE health technology evaluations: the manual (2022) specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per quality-adjusted life year (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. This is seen through the number of additional QALYs gained and by applying a 'QALY weight'. A weight of between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee understood that olipudase alfa improves clinical outcomes in people with ASMD. But it noted the uncertainties in the clinical evidence and surrounding the assumptions in the model. Also, it had not currently been provided with an ICER range reflecting all its preferred assumptions (see section 3.22). The committee considered that some of the criteria for applying a QALY weighting are likely to be met, but until it had seen the size of the QALY gain suggested by a model incorporating its preferred assumptions it was unable to reach a final conclusion.

Cost-effectiveness estimates

Committee preferred assumptions and further analyses needed

3.22 The company's base-case results after technical engagement resulted in an ICER over £100,000 per QALY gained (that is, the maximum ICER normally considered to be a cost-effective use of NHS resources in a highly specialised technology evaluation). This did not account for the committee's preferred assumptions. Considering the company's and EAG's analyses, the committee's preferred assumptions included the following, with further analyses requested:

- Long-term treatment effect: the EAG's scenario analysis of treatment effect continuing after year 2 may be an option, but the company should present further analysis exploring the scenario of continuing treatment effect then freezing it at year 10 (see section 3.9).
- Modelling mortality: the EAG's approach to modelling mortality is preferred but the company should present additional information and analysis in its revised approach for decision making (see section 3.10).
- Disease-specific mortality for children is appropriate to include in the model (see section 3.11).
- Discount rate: 3.5% for the cost-effectiveness analysis (see section 3.12).
- Patient weight: the EAG's approach to modelling weight is preferred but the starting weight should be at the lower end of the UK average in the model (see section 3.16).
- Carer disutilities should be applied depending on the health state of the person with ASMD, regardless of which treatment they have (see section 3.17).
- The EAGs approach of differential carer disutilities depending on severity of disease and whether the person with ASMD is an adult or child is preferred (see section 3.18).
- An average of 1 carer per child with ASMD is preferred (see section 3.19).

- There may be carer disutilities associated with patient death but this should be considered qualitatively in decision making instead of numerically in the model (see section 3.20).

Both the company and EAG ICERs were over £100,000 per QALY gained. The committee reasoned that its preferred assumptions were unlikely to reduce these values to a range considered a cost-effective use of NHS resources, but was open to reconsider revised analyses.

Managed access

Recommendation with managed access

3.23 The committee considered whether a recommendation with managed access could be an appropriate option for addressing uncertainty in the clinical evidence and assumptions. It noted that the company had submitted a managed access proposal. In this it proposed to address the uncertainties in the long-term treatment effect through data collection from the ongoing extension study of LTS13632 and the extension study of ASCEND, as well as an international Niemann-Pick disease registry. The company also planned qualitative studies to understand the quality of life for carers and the burden of the disease on patients and carers. The committee was aware that assumptions on long-term treatment effect and carer's disutilities, especially carer's disutilities associated with patient death, are key drivers for ICERs in this evaluation. It discussed whether further data collection from a managed access agreement could help resolve the key drivers of ICERs and the surrounding uncertainties. For long-term treatment effect, it noted that both the ongoing studies are due to complete in 2024, which would not be long enough to resolve all uncertainties relating to long-term treatment effect. Data from the Niemann-Pick international registry could be retrieved outside a managed access agreement. For uncertainties relating to carer's disutilities, there is a lack of detail on the methods of the planned qualitative study. But, the committee was concerned that the study may be subject to small sample size and uncertainties related to it. The committee noted that that some

data may be collected from the ongoing or planned studies, but it is unclear how much additional value they would bring to resolving uncertainties in the model. So it concluded that a recommendation with managed access is not an appropriate option for addressing uncertainties in this evaluation.

Other factors

Equalities

3.24 No equality issues were identified in the evaluation.

Innovation

3.25 The committee recognised that olipudase alfa is the first treatment addressing the underlying causes of ASMD. The evidence shows that it was associated with improvement in several clinical outcomes and the treatment effect may continue. The clinical experts stated that symptoms that patients regard as normal (limited exercise capacity, pain, fatigue) may disappear with treatment and people develop a new understanding of what 'normal' life is. QALY calculations cannot fully capture this and so may underestimate the benefit of olipudase alfa. The committee considered that it is uncertain whether this has been fully captured in the model, given the uncertainties in the evidence and on several assumptions. It concluded that there might be benefits not fully captured but this was uncertain.

Conclusion

Recommendation

3.26 The committee had not been presented with an ICER that included all of its preferred assumptions (see section 3.22). But it concluded that any ICER with these assumptions was unlikely to be below the threshold normally considered an effective use of NHS resources for a highly specialised technology. So, it could not recommend olipudase alfa for routine commissioning to treat ASMD type AB or B. The committee

concluded that the company and stakeholders should provide additional information for consideration at the next evaluation committee meeting (see section 3.22).

4 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Peter Jackson
Chair, highly specialised technologies evaluation committee

NICE project team

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

Tom Jarratt
Technical lead

Yelan Guo
Technical adviser

Vonda Murray

Project manager

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