NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

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, and 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, such as improving nutrition and breathing, and treating infection, aims to manage the symptoms.

Clinical trial evidence shows that, 1 year after starting treatment with olipudase alfa, lung function is improved and the size of the spleen is reduced in adults and children

with ASMD. The improvements may continue in the longer term, but become more gradual as the condition stabilises.

There are uncertainties in the economic model. Also, the available cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources for highly specialised technologies, even after taking into account the decision to apply additional weight to the effect of olipudase alfa on quality and length of life. So, olipudase alfa is not 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 depends on the location of the affected cells but, over time, the accumulation of this fat causes 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 types 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 the lysosome, known as lysosomal storage disease. Both type AB and type B 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. Build-up of sphingomyelin can restrict lung capacity, causing extreme fatigue and limiting the ability to exercise and take part in everyday life. Patient experts also explained that the effect on energy levels means that the frequent trips for appointments can result in the person being unable to function properly for days afterwards, and that considerable planning is needed in the days running up to appointments.

An enlarged spleen can cause anaemia, limit the ability to eat usual size meals, and cause nausea and vomiting. This poses a substantial risk of malnutrition. The potential for contracting infections (which can be hard to recover from) 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. 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.

A new treatment option

3.4 Both the clinical and patient experts noted that olipudase alfa represents a transformative addition to supportive care for ASMD. 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 their carers' responsibilities. This may allow the carer to 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 was an open-label single-arm trial in which 20 children and young people under 18 years had olipudase alfa with 52 weeks follow up. DFI13412 was 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 people with a milder or more severe condition may have been excluded. The clinical experts explained that those with the most severe ASMD and a group of adults with mild ASMD, for example those with mildly reduced lung capacity, 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 body weight in these trials was lower than would be expected in the UK. The clinical and patient experts explained that some people with ASMD have reduced height and weight, but after some time on the treatment, they could catch up to the general population in both respects. The EAG also noted that although the marketing authorisation for olipudase alfa is 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 have 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 delays resulting from non-neurological manifestations of the disease (such as poor nutrition), and not necessarily indicative of type AB disease. For this reason, it is challenging to differentiate between type AB and B in practice, particularly in young people. A more certain diagnosis may only be reached in adulthood, after there has been time for those with developmental delay to catch up with their peers, and for the cause of the neurological symptoms to become clearer. Also, although the proportion of people with type AB disease is unknown, the high proportion of people with neurological symptoms in the trials suggests that people with type AB may be over-represented. This may result in a conservative estimate of the efficacy of olipudase alfa. During the second committee meeting, the clinical experts explained that populations in the trials are representative of those seen in the NHS. But they noted that there will be some children who were too young to be included in the trial, and that all adults present at the earliest stage of their disease in practice, most without fibrosis. The committee noted the variable clinical manifestations associated with ASMD and the spectrum of the disease. It concluded that the populations in trials are representative of those seen in the NHS.

Clinical effectiveness in trials

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 the percentage predicted DLco increased 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 the 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 again there were a lot 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 be maintained 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 adults (59.5%, n=5) and children (the data is confidential so cannot be reported here). Liver volume also showed a large decrease at both 6-month and 78-month follow up (the exact result is confidential so cannot be reported here). 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 improvements in clinical outcomes associated with olipudase alfa, but also noted the relatively short follow up periods in the trials. It questioned the treatment effect of olipudase alfa in the longer term. The clinical experts explained that olipudase alfa was associated with significant improvements in the first 6 to 12 months, and that the improvement could continue after 2 years. During the second committee meeting, the clinical experts also explained that in their experience, patients could still benefit from the treatment after years of taking it, with continuous improvement in spleen volume and lung capacity but at a slower rate of change compared with the earlier stages of treatment. The patient experts explained that treatment has a profound effect on key

clinical outcomes, improving the ability to function in everyday life, including regaining the ability to exercise regularly, which can further improve people's wellbeing. The EAG noted that although there were improvements in clinical outcomes, some effects of the disease did not resolve completely (for example, spleen volume remained several times larger than usual). The clinical experts explained that although people with ASMD with more severe damage, such as lung or liver fibrosis, are unlikely to return to full or near-full health, there will still be a considerable treatment benefit. They noted that people with apparently considerable lung fibrosis on scans subsequently improved after taking olipudase alfa. The committee concluded that olipudase alfa improves clinical outcomes associated with ASMD and the treatment effect can continue into the longer term, but becomes more gradual as the person's condition moves nearer to full-health. The committee took this into account in its decision making.

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 the EQ-5D or SF-36 are not sufficiently sensitive to show improvements 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

at 6 months and had increased further by 12 months. Children aged 5 to 7 had an increase near the minimally important difference threshold by 12 months. The EAG explained that ASCEND-Peds was open-label and so there is a risk of bias when interpreting 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. In the second committee meeting, the committee queried why some outcomes, particularly fatigue, showed limited improvement in the trial. The clinical experts explained that fatigue and quality of life were not well captured in the trial. They also reiterated the importance of many people with ASMD having got used to their reduced quality of life before starting treatment, which leads to higher than expected baseline scores and limits the sensitivity of tests to show the benefit of treatment. The patient experts agreed with this, noting that it was only after treatment that they realised how severely reduced their quality of life had been before treatment. They also noted that treatment has a transformative effect on quality of life. The committee understood that the evidence on olipudase alfa's treatment effect on HRQoL from the clinical trials was mixed, but there were limitations in the evidence given the different study designs, the small sample sizes, and the relatively short duration of trial follow up.

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 had 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 10 health states modelled were 9 different combinations of the spleen

volume and DLco health states, plus an additional health state for death. 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 (see 3.11) 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 and the EAG had different approaches to modelling long-term treatment effect. In its base case presented at the first committee meeting, the company assumed that everyone on olipudase alfa treatment would transition to the least severe health state (defined by spleen volume less than 6 multiples of normal and DLco 80% or above predicted value) from year 10, and would remain there for the rest of the modelled time horizon or death. The EAG was concerned about the uncertainties in treatment effect in the longer term and preferred to freeze the treatment effect from year 3 onwards in its base case, meaning that people stayed in the same health state after 2 years treatment. The committee considered that freezing the treatment effect after 2 years may be pessimistic, but was also concerned with the lack of justification for the company's approach. So, the committee asked the company to explore the scenario of a treatment effect that continues for 9 years and is then frozen from year 10.

In response to the draft guidance, the company interviewed 6 clinicians, exploring olipudase alfa's treatment effect in the longer term. Three of the clinicians felt unable to predict treatment effect waning, while another 3 estimated there would be none. But the EAG noted the limitations relating to the methods of the interviews, including lack of transcripts or quotes, and uncertainty in the methods used to analyse the qualitative data. In the company's revised model, health states were frozen from year 10, but people taking olipudase alfa got gradually healthier up until this point, so everyone was in the least severe health state by year 10. The EAG noted

that the company's revised approach was even more optimistic than its previous modelling of the long-term treatment effect because it saw people getting healthier at an earlier timepoint. It highlighted that the company presented no further data cut from clinical trials supporting olipudase alfa's treatment effect in the longer term. The EAG instead recycled the treatment effect seen in the clinical trials by maintaining constant transition probabilities from year 2 to year 10, with the health state of the patient frozen from year 10 onwards. The EAG considered that this approach aligned with the scenario the committee requested. The patient experts explained that the modelled health states were too simplistic, and by focusing on spleen volume and lung function the systemic nature of the condition was not properly captured, including the effects on malnutrition, fatigue, functioning and pain. They also advised that the ability to function in everyday life is a key area of improvement. They believed that these symptoms may not have been fully captured in the company's vignette study to inform the utility values of health states in the model. This was partly because the symptoms of ASMD are not fully understood. The clinical experts explained that in their experience spleen volume rapidly improved in the first few years then continued to improve but at a slower rate. They also noted that most people can be expected to move into the mild category for impaired lung function. They stated that around 10% to 20% of people will have neurological symptoms and so have residual disease after treatment, but otherwise patients' quality of life becomes near normal. Considering there may be an ongoing but more gradual improvement in the longer term, the committee agreed that it preferred the EAG's updated approach, which it considered to be in line with what would be expected. It noted that although spleen volume and lung function do not encapsulate the totality of the disease, they are still important outcomes, as well as being proxy indicators of other outcomes and overall health state. The committee concluded that the EAG's approach for modelling long-term treatment effect was appropriate for decision making. It acknowledged that health states defined by spleen

volume and lung function may underpredict the benefits associated with olipudase alfa and took this into account in its decision making.

Disease-related mortality in children

3.10 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, although 3 out 30 children died during the 11-year follow-up period, 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 the published literature. The committee concluded that it is appropriate to include disease-related mortality in children in the model.

Modelling mortality

3.11 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, and for severe disease (defined as involving 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 (9 people died, 8 related to ASMD) in the study, and categorising severe disease simply as whether the person had severe splenomegaly or not. After technical engagement, the company revised its approach to modelling mortality by using a parametric approach based on 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 highlighted 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
- a lack of details on the methods
- the source of the hazard ratio used to model the olipudase alfa arm
- a lack of analysis and reporting on the checking and suitability of chosen survival curves.

Given the lack of details and reporting of the analysis and methods used, the EAG preferred to maintain the company's original approach in its base case, but noted there were also uncertainties with this. During its first meeting, 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. So, it asked the company to present additional information and analysis for its parametric approach. After the first meeting, the company revised its parametric approach, and provided further information and analyses used in this approach. It also used a different source of data (McGovern 2013) to inform mortality estimates for children having best supportive care. This was a prospective cohort study of 61 children with type B disease. The company explained that in the interview with the 6 clinicians (see section 3.9), 5 agreed that they preferred the parametric approach to modelling mortality because the curve was more likely to be generalisable to the natural history of the disease (high mortality in children, followed by a plateau and another increase in mortality in people in their late 50s and above). They had no major concerns about the generalisability of the chart review study to the UK population. The EAG maintained its preferred approach, noting that there were still issues relating to the use of the parametric approach. These included the limited justification for using a 0.1 hazard ratio to model olipudase

alfa mortality relative to that in people having best supportive care, the particularly the low rates of mortality attributable to ASMD (10 out of 42 deaths) in children and young people, and the low mortality in adults (6 deaths, 2 related to ASMD). During the second committee meeting, the company explained that its original SMR approach did not capture mortality in children and young people. The clinical experts explained that children and young people with ASMD are more likely to die than adults, but that both are exposed to an increased risk. They also noted that the cause of death may not be accurately recorded for children with ASMD, and death in childhood in this group is likely to be ASMD related. The committee was aware that most participants in the chart review were children and young people at baseline, and the shape of the parametric curves for mortality aligned with the clinical experts' testimonies and the natural history of the condition. The committee concluded that the company's parametric approach was preferred for modelling mortality, noting that both adults and children are exposed to an increased risk of mortality.

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 if the committee is satisfied that the following 3 criteria are met.

Criterion 1

3.13 The first criterion for a 1.5% discount rate is that the treatment must be for people who would otherwise die or have a very severely impaired quality of life (see section 3.1 and 3.2). The committee recalled testimony from patient and clinical experts outlining the considerable impact the disease has on quality of life. The committee noted that despite some uncertainty, both adults and children with ASMD are exposed to an increased risk of

dying compared with the general population (see section 3.10 and 3.11). So, this criterion is met.

Criterion 2

3.14 The second criterion for a 1.5% discount rate is that 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 with 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 were still enlarged after treatment (at around 6 multiples of normal for spleen volume) and that meant that DLco at 52 weeks was around 70% of the predicted value, which may indicate that people are not restored to full health. The committee was concerned about the persistence of a significantly enlarged spleen and whether this prevents people returning to full or near-full health. During the second committee meeting, the patient experts explained that although an enlarged spleen is still possible after treatment, the reduction in size will be considerable and it is still likely that a person can live with near to normal quality of life despite having a spleen several times larger than normal size. The clinical experts also noted that, although lung capacity may still not be normal compared with the general population, all patients they see moved to mild impairment with improvements in cardiovascular function, exercise tolerance and fitness. The committee noted that people with type AB disease with neurological symptoms would not return to full health after treatment, and that it is often not possible to correctly differentiate between type AB and type B disease in childhood (see section 3.5). It agreed that most people would return to full or near-full health. So, this criterion is met.

Criterion 3

3.15 The third criterion for a 1.5% discount rate is that 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 are maintained up to 20 years after starting treatment. One of the clinical experts noted that some people in the extensions 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, with their experience indicating that the effect is sustained in the long term. The EAG highlighted the small number of people with data available at the longer-term follow-up time points in the clinical trials. The committee recalled its discussions on the treatment effect of olipudase alfa in the longer term (see section **Error! Reference source not found.** and section 3.9). It concluded that it is highly plausible the treatment effect may be maintained in the longer term, although the improvements may become more gradual over time as people's conditions stabilise. Considering the entirety of the evidence and the clinical and patient expert testimonies, the committee concluded that olipudase alfa met the criteria to be eligible for a 1.5% discount rate to be applied to both costs and benefits.

Patient weight

3.16 The company and EAG modelled the body weight of people with ASMD differently. 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 would be reduced because of this shorter height, although 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 of treatment, patients' weight would return to within 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, and 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 cases, 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 burden and therefore a higher disutility than ASMD, so it preferred to source the values from 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 utility decrements for severe disease (defined as spleen volume 15 times normal or greater). The EAG's carer disutility values ranged from -0.010 to -0.080. The committee agreed that it was reasonable 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 3.17). The committee concluded that the EAG's approach of differentiating carers' disutilities by both the severity of health state, and whether the person treated is a child or an adult, was appropriate for decision making. After the first meeting the company revised its approach, so carers experienced differential disutility depending on whether the child was in a mild, moderate or severely impaired health state (determined by a combination of spleen volume and liver function), but the values were again derived from Pompe disease. The committee was concerned with sourcing disutility values from Pompe disease because it is likely that this would result in overestimating the disutility associated with caring for someone with ASMD, and so bias the analysis in favour of olipudase alfa. It concluded that the EAG's approach (which remained unchanged after the first meeting) was still preferable.

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 little precedent for assuming more than 2 carers, even in evaluations for more severe lysosomal storage diseases, and that research into carer disutilities is limited, particularly in 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. They also outlined the negative impact on siblings (see section 3.2). During its first meeting, the committee noted 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. In response to consultation, the company maintained that an average of 2.6 carers better reflected the caring needs for ASMD. The company also explored the scenario of an average of 1.5 carers, in line with suggestions from a patient group survey that suggested that 1.5 carers was the most appropriate assumption. The committee recognised the substantial impact ASMD has on both patients and carers, as outlined by the company in its submission and supported by the clinical and patient experts. But, considering the precedent in other highly specialised technology guidance for ultra-rare diseases, the committee did not agree that the evidence and information presented in this evaluation should be dealt with differently. It also noted that ASMD severity is on a spectrum, so caring needs would differ between the less and more severe health states and an average of 1 would be reasonable. The committee concluded that an average of 1 carer was appropriate for decision making.

Carer's disutility after bereavement

3.20 The company assumed a carer disutility of -0.50 if the person with ASMD died, and applied this disutility across the remainder of the time horizon used in the model. The EAG was concerned that there was no conclusive research into the application of carer disutilities after bereavement. Consequently, there is high uncertainty about whether disutilities should be applied after a 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 it acknowledged the impact of a patient's death on carers and would qualitatively consider it in its decision making. In the second committee meeting, the company maintained its view that not including a disutility associated with the patient dying was counterintuitive and inappropriate, so did not change its base-case assumption. The patient experts stated that there would be a considerable disutility for the carer if a patient died, and that this would reduce somewhat over time. The committee noted this, but considered that the company's assumption that carers would live for 100 years and experience such a high disutility for this entire period of time inappropriate. The committee concluded that it would qualitatively consider the impact of a patient's death on carers in its decision making.

Recently diagnosed subgroup

3.21 After the first committee meeting, the company presented a new subgroup analysis of people newly diagnosed with ASMD. The company argued in its response that people who have had the disease for a longer period of time before treatment have a greater likelihood of having irreversible organ damage, which may limit the effects of treatment on key outcomes. The clinical experts explained that people with extensive lung fibrosis and liver cirrhosis may not return to full health after treatment because of the extent of the damage they have experienced. So, it is possible that people who have treatment immediately after diagnosis would experience greater benefits and be more likely to reach the least severe health state. The

clinical experts also explained that some people with the disease still only receive a diagnosis in adulthood, but noted that with increasing awareness of the disease the chances of this happening will decrease in the future and become rare. Regarding severity, the EAG noted that the subgroup analyses in the pivotal trial did not show variation in treatment effect according to baseline severity, although the analyses were limited because of small sample sizes. The committee recalled the challenges in diagnosing children and young people (section 3.5 and section 3.14). It recognised the difficulties in defining a 'recent' diagnosis in practice, and was concerned that some young patients may be missed. It recognised the appeal of starting treatment before organ damage occurs, but had not been provided with any direct evidence of greater effectiveness in newly diagnosed patients. There would also be ethical concerns if recommending the treatment only for people who have recently been diagnosed and excluding people with longer standing disease, given the unmet need. It concluded that the recently diagnosed subgroup proposed by the company was not appropriate for decision making.

QALY weighting

3.22 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 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. During its first meeting, the committee considered that some criteria for applying a QALY weighting were likely to be met, but there were uncertainties in the size of the QALY gain. The committee discussed the undiscounted QALY gains associated with

olipudase alfa during its second meeting. It noted this was 27.6 in the scenario considered the most plausible. In this scenario, the company assumed a 50% split between children and adults for the patient population. Considering the entirety of the evidence, the committee agreed that a full QALY weighting of 2.7 should be applied.

Cost-effectiveness estimates

The committee's preferred assumptions

3.23 The committee's preferred assumptions included the following:

- The EAG's approach to modelling long-term treatment effect of continuing the treatment effect for 9 years, then freezing it at year 10 (see section 3.9).
- Including disease-specific mortality for children in the model (see section 3.11).
- The company's parametric approach to modelling mortality (see section **Error! Reference source not found.**).
- A discount rate of 1.5% for the cost-effectiveness analysis (see sections 3.12 to 3.15).
- The EAG's approach to modelling body weight, with the starting weight at the lower end of the UK average (see section 3.16).
- Applying carer disutilities depending on the health state of the person with ASMD, regardless of which treatment they have (see section 3.17).
- Using carer disutilities that depend on disease severity and whether the person with ASMD is an adult or child (see section 3.18).
- Using an average of 1 carer per child with ASMD (see section 3.19).
- Not including carer disutilities associated with patient death in the model. The committee agreed to consider this qualitatively in its decision making instead (see section 3.20).

Both the company and EAG's base-case ICERs for olipudase alfa compared with standard care were over £300,000 per QALY gained (the

exact ICERs are confidential and cannot be reported here). The committee considered that it had not been presented with any ICERs that were likely to be within the range NICE normally considers an effective use of NHS resources for a highly specialised technology, even when taking into account the decision to apply a QALY weighting of 2.7, which meant that the committee were willing to accept a higher ICER than usual (see section 3.22).

Managed access

Recommendation with managed access

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

was unclear how much additional value they would bring to resolving the uncertainties in the model. Further, it would need to be shown that olipudase alfa was plausibly cost effective in the context of a highly specialised service. But the committee recognised that, at the price the company had chosen to charge, olipudase alfa was not plausibly cost effective. So, it concluded that a recommendation with managed access was not appropriate for addressing the uncertainties in this evaluation.

Other factors

Equalities

3.25 No equality issues were identified in the evaluation.

Innovation

3.26 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 that the treatment effect may continue. During the first committee meeting, 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. The general public's preference weighting in the company's vignette study may help to account for these symptoms, but it is unlikely that the QALY calculations fully captured them, and so the benefit of olipudase alfa may be underestimated. In response to the draft guidance consultation, the company listed a series of other benefits associated with the treatment that may not be fully captured in the model. But the EAG noted that although these benefits may not be fully captured in the model, several others were incorporated into the vignette study the company used to inform health state utilities. These included, for example, fatigue, ability to function, abdominal pain and discomfort, exercise tolerance, emotional impacts, hospitalisations, infections, bleeding events, ability to eat normally, reduced height, muscle strength and school attendance. The

company's model may have underestimated the benefits associated with the treatment because of how the health states were defined (see section 3.9). The committee considered that there were no other benefits that had not been captured in the model. It concluded that olipudase alfa is innovative in treating ASMD and took this into account in its decision making.

Conclusion

Recommendation

3.27 The committee was not presented with a plausibly cost-effective estimate after taking into account all of its preferred assumptions and other considerations (see section 3.23). So, it could not recommend olipudase alfa for routine commissioning to treat ASMD type AB or type B.

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 o 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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