NICE National Institute for Health and Care Excellence

NICE guidance

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

Highly specialised technologies guidance

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Your responsibility

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

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

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

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

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 type 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. And even when taking into account the substantial effect of olipudase alfa on quality and length of life, the cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources for highly specialised technologies. 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 is available in the summary of product characteristics for olipudase alfa.

Price

2.3 The list price of olipudase alfa is £3,612.00 per 20-mg vial (excluding VAT, BNF online, accessed November 2024).

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.

History of the evaluation

3.1 After the release of final draft guidance, NICE received 2 appeals from 2 patient organisations. The appeal was upheld on 1 point and referred back to the committee for further consideration. The upheld point was that the patient expert view was misrepresented by stating 'the patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD' (acid sphingomyelinase deficiency). At the appeal hearing, the patient experts indicated that the impact of caring for a child with ASMD is significant in all health states.

3.2 After the appeal, the company submitted an addendum containing additional long-term clinical efficacy and safety data based on longer follow up of the key clinical trials, and additional qualitative evidence on quality of life of carers of children with ASMD. The EAG also did analyses exploring variation in carer disutility between treatment arms. At the third meeting, the committee considered the appeal's upheld point and the new evidence and analyses presented.

The condition

Niemann–Pick type AB and type B

3.3 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 causes cells to die, resulting in damage to multiple organs, including the lungs, liver and spleen. There are about 40 to 50 people in total diagnosed in England with type A, B or AB. Both type AB and type B involve primary symptoms that include an enlarged spleen, low platelet count, 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. Interstitial lung disease is also common in people with ASMD. This often leads to shortness of breath, fatigue and difficulty performing daily activities. The disease is associated with increased risk of death, with the leading cause being respiratory or liver failure. Type AB and type B, together with type A (which is not included in this evaluation), are known collectively as ASMD. Other forms of Niemann–Pick disease include types C and D, but these are not classified as ASMD or covered in this evaluation.

Burden of the condition

3.4 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. A 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 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

3.5 The clinical experts explained that there is no licensed treatment that addresses the underlying causes of ASMD. Best supportive care involves supportive or palliative treatment for nutritional needs (with or without feeding tubes), respiration (including supplemental oxygen and treatment of infections) and liver disease (including consideration of a liver transplant), as well as 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

3.6 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. This would reduce the time needed for their carers' responsibilities, and may allow the carer to return to work and improve their quality of life. It may also reduce the risk of death in people with 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 type B.

Clinical effectiveness

Data sources and representativeness of the trial populations

3.7 Clinical-effectiveness data for olipudase alfa came from several clinical trials. ASCEND (n=36) was a phase 2 and 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 reported data for an additional year at the time of the original 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 of follow up. DFI13412 was an open-label trial in which 5 adults had olipudase alfa with a 26-week follow up. Finally, LTS13632 was an open-label extension study including people from the ASCEND-Peds and DFI13412 trials. This trial was ongoing at the time of submission, and reported data for 7 children with a follow up of 4 years, and 5 adults with a follow up of 6.5 years. For the third committee meeting, the company submitted an addendum with final follow-up data for ASCEND and LTS13632; the length of follow up is confidential and cannot be

reported here. The EAG noted that the inclusion and exclusion criteria of the trials were stringent, and it 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 having the treatment for some time, they would be similar 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 type 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. 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 type 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 reach similar levels to 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 suggested that people with type AB may be over-represented. This may result in a conservative estimate of the efficacy of olipudase alfa. At the second committee meeting, the clinical experts explained that the populations in the trials were representative of those seen in the NHS. But they noted that there would have been 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 the trials were representative of those seen in the NHS.

Clinical effectiveness in trials

3.8 Evidence from the clinical trials showed that olipudase alfa improved 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, the percentage-predicted DLco increased by a mean of 33% (95% CI 13.4% to 52.5%) from baseline for olipudase alfa. A responder analysis done by the company also showed that 5 out of 18 adults having olipudase alfa in ASCEND had a clinically significant improvement (defined by the company as an improvement of 15% or more) in lung diffusion capacity at week 52. The EAG noted that there could be further improvements after 52 weeks but there was 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 many missing outcome assessments at 2 years for this outcome (30% and above). But clinical advice to the EAG suggested that it was 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 in largely 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. At the second committee meeting, the clinical experts also explained that in their experience, people 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 than in 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 having olipudase alfa.

At the third committee meeting, the EAG stated that the additional evidence submitted by the company (with the longer follow up of the ASCEND and LTS13632 trials) on the outcome of spleen volume, liver volume and DLco was largely consistent with the results from previous data cut-offs. There was also no evidence of treatment waning (the exact results are confidential and cannot be reported here). But the EAG also noted the substantial missing data on these outcomes during the extended follow up of the ASCEND trial. The reasons for missing data were not explained by the company, and there was a high risk of bias in the evidence and increased uncertainty about the stability of the treatment effect of olipudase alfa in the longer term. The committee concluded that olipudase alfa improves clinical outcomes associated with ASMD, and the treatment effect can continue in the longer term but becomes more gradual as the person's condition moves towards full health. The committee took this into account in its decision making.

Treatment effect on health-related quality of life

3.9 The ASCEND and ASCEND-Peds trials collected health-related quality of life (HRQoL) data using the EQ-5D and the SF-36. There was no difference in HRQoL between the treatment arms in ASCEND. The company and EAG agreed that these results were inconsistent with the key outcome data from the trials and testimony from experts that suggested that 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 and 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 which 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 because ASCEND-Peds was open label there was a risk of bias when interpreting the evidence. But it noted that other studies not included in the submission also seemed to show a benefit, meaning the improvement in quality of life from baseline in children may be genuine. At 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 become 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

3.10 The company constructed a state transition model with 10 health states to model the disease course of ASMD being treated with olipudase alfa or best supportive care. The model had a time horizon of 100 years. Health states were categorised by 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 (between 40% and 80%) and severe reduction (40% and below). The model included 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 3.7), along with additional data from the SPHINGO-100 trial (see section 3.13) and a pooled chart review analysis. The committee concluded that the model structure was appropriate for decision making.

Modelling long-term treatment effect

3.11 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 until 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 of treatment. The committee considered that freezing the treatment effect after 2 years may be pessimistic, but it was concerned by the lack of justification for the company's approach. So, the committee asked the company to explore a scenario in which the treatment effect continued for 9 years and was frozen from year 10.

In response to the draft guidance, the company interviewed 6 clinicians to explore olipudase alfa's treatment effect in the longer term. Three of the clinicians felt unable to predict treatment effect waning, and another 3 estimated there would be none. But the EAG noted 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 became gradually healthier up to 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 becoming healthier at an earlier timepoint. It highlighted that the company presented no further data from clinical trials to support 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 states frozen from year 10 onwards. The EAG considered that this approach aligned with the scenario requested by the committee.

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, so have residual disease after treatment. Otherwise, people's quality of life becomes near normal. Taking into account that there may be an ongoing but more gradual improvement in the longer term, the additional evidence with longer follow up submitted by the company, and the associated uncertainties (see section 3.8), 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 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

3.12 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 (an observational study of 58 people with ASMD type B in North America over an 11-year period), 3 of 30 children died during the 11-year follow-up period, but the primary cause of death in all 3 children was pneumonia. The clinical experts explained that they had experienced children dying as a result of the disease for both ASMD type B and AB, and this was in line with the published literature. The committee concluded that it was appropriate to include disease-related mortality in children in the model.

Modelling mortality

3.13 The original company base case modelled mortality using the SPHINGO-100 trial. 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 small number of deaths occurring during follow up (9 people died; 8 deaths were related to ASMD) in the study, and categorising severe disease simply as whether or not the person had severe splenomegaly. 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. These included:

- extensive missing data on baseline severity markers such as spleen volume, liver volume and DLco in the chart review
- a lack of detail 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 kept the company's original approach in its base case, but noted there were uncertainties with this. At 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 et al. 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 3.11), 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:

- limited justification for using a 0.1 hazard ratio to model olipudase alfa mortality relative to the mortality of people having best supportive care
- the particularly low rates of mortality attributable to ASMD (10 out of 42 deaths) in children and young people

- the low mortality in adults (6 deaths; 2 related to ASMD).

  At 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 both have 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 people 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 have an increased risk of mortality.

Discounting rate

3.14 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

3.15 The first criterion for a 1.5% discount rate is that the treatment must be for people who would otherwise die or have a severely impaired quality of life. The committee recalled testimony from patient and clinical experts outlining the considerable impact the disease has on quality of life (see sections 3.3 and 3.4). The committee noted that despite some uncertainty, adults and children with ASMD have an increased risk of dying compared with the general population (see sections 3.12 and 3.13). So, this criterion was met.

Criterion 2

3.16 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 (Raebel et al. 2024) 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 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 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. At 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 that of the general population, those people with the condition they had seen 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 3.7). It agreed that most people would return to full or near-full health. So, this criterion was met.

Criterion 3

3.17 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 trial extensions provided data up to 4 years for children and up to 6.5 years for adults. It also explained that there was evidence in Gaucher disease that the effects of enzyme replacement therapy are maintained for 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 3.8 and section 3.11). It concluded that it was highly plausible the treatment effect may be maintained in the longer term, although the improvements may become more gradual over time as people's condition stabilises. 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.

Weight of people with ASMD

3.18 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 to UK growth weight charts. The EAG noted that the average weights for adults and children seemed lower than the UK average if other sources are used. 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, people's weight would return to within the average range seen in the UK, but not to the extent of being overweight or obese. The committee concluded that the EAG's approach was more appropriate, and that weight for 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 disutilities

3.19 The company and EAG both included disutilities for carers of people with ASMD as part of their base cases, but these differed in some assumptions. The company applied disutilities to carers in the best supportive care arm only, assuming that there would be no carer needs for people having olipudase alfa. The EAG preferred to base disutilities on the health state of the person, 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. At the third committee meeting, the EAG provided additional analyses in which:

- carer disutility was removed from the olipudase alfa arm and applied to the best supportive care arm only
- carer disutility in the olipudase alfa arm was reduced to half of carer disutility in the best supportive care arm
- a sliding disutility approach was used according to model health state as defined by spleen volume, in which carer disutility in the olipudase alfa arm relative to the best supportive care arm was:
  - reduced by half, at less than 6 multiples of normal
  - reduced by 25%, at 6 to less than 15 multiples of normal
  - equal to the disutility in the best supportive care arm, at 15 and above multiples of normal.

    One of the patient experts noted that nearly all caring functions and needs, for example fatigue, travel and anxiety, are not spleen related and cannot be captured by change in spleen volume. Another patient expert noted that additional benefits associated with olipudase alfa that were not fully captured may include improvements in emotional and mental health of carers, as indicated by the Raebel et al. study. The EAG noted that the scenario applying carer disutility to the best supportive care arm only contradicted previous statements from one of the patient experts (see sections 3.1 and 3.2) indicating that caregiver burden is an issue in

all health states and is not completely eliminated with the use of olipudase alfa. The EAG suggested that the scenarios with reduced caregiver burden in the olipudase alfa arm may be appropriate if there are additional benefits of olipudase alfa not already captured in the model. The patient experts highlighted that the health states in the model as defined by spleen volume do not fully capture the rapid improvement in symptoms and overall health improvements olipudase alfa provides, and consequently the rapid reduction in associated caregiver burden. The clinical experts agreed that overall improvement in symptoms such as fatigue happens rapidly and in a much shorter time period than reduction in spleen volume. The committee noted that health states in the model were defined by both spleen volume and DLco, and DLco normalises faster than spleen volume, so may have reflected some of the quick improvement associated with the treatment. But one of the patient experts explained that DLco still does not capture the improvement in anxiety and fatigue experienced by carers. The company explained at the meeting that spleen volume and DLco capture some improvement associated with carer burdens, and it considered that the EAG's first and second scenarios were more appropriate. The company also explained that the model was not designed to demonstrate the change in treatment effect over time as indicated by the patient experts. The committee was aware that the model might not fully capture the benefits associated with olipudase alfa (see section 3.11 and section 3.25). It acknowledged the concerns of the patient experts, but noted that the company's model based on health states and cycle length was not designed to capture the quick changes in carers' burden. Considering the evidence and the patient experts' testimonies, the committee concluded that, on balance, the scenario in which disutilities were based on the health state of the person with ASMD, and in which carer disutility in the olipudase alfa arm was half of the carer disutility in the best supportive care arm, was appropriate for decision making.

Carer disutility values

3.20 There was a lack of published literature on 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 adults with more severe health states would incur greater carer disutility. It also noted that it preferred carer disutilities to be applied based on the person's health state irrespective of treatment (see section 3.19). 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 that 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 was likely that this would overestimate the disutility associated with caring for someone with ASMD, and would bias the analysis in favour of olipudase alfa. It concluded that the EAG's approach to sourcing utility values (which remained unchanged after the first meeting) was still preferable.

Number of carers

3.21 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 was little precedent for assuming more than 2 carers, even in evaluations for more severe lysosomal storage diseases, and that research into carer disutilities was 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, and explained 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 3.4), and the degree of support that may be split between multiple carers.

At 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 full-time carers are needed. In response to consultation, the company maintained that an average of 2.6 carers better reflected the caring needs for ASMD. It also explored a 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 people with the condition and their carers, as outlined by the company in its submission and supported by the clinical and patient experts. It also acknowledged the earlier statements from the patient experts outlining how ASMD may impact multiple caregivers. 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 depending on health state, and an average of 1 would be reasonable. The committee concluded that an average of 1 carer was appropriate for decision making.

Carer disutility after bereavement

3.22 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 carer disutilities after bereavement. Consequently, there was high uncertainty about whether disutilities should be applied after someone dies, how big the disutility should be, and for how long. So, the EAG removed any disutility after death. The company explained that excluding carer 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 disutility

associated with someone dying, but 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 noted that the EAG's approach may not have captured the loss of utility associated with bereavement. Given the uncertainties and lack of research in the field, the committee concluded that it would be appropriate not to include carer disutilities associated with bereavement numerically in the model, but it acknowledged the impact of a person'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 it did not change its base-case assumption. The patient experts stated that there would be a considerable disutility for the carer if a person died, and this would reduce somewhat over time. The committee noted this, but thought that because of how the model was designed (see section 3.10), the company's built-in assumption that carers would live for 100 years and experience such a high disutility for this entire period of time was inappropriate. The committee concluded that it would qualitatively consider the impact of a person's death on carers in its decision making.

Qualitative evidence on carer health-related quality of life

3.23 At the third committee meeting, the company presented qualitative evidence on the impact on carer quality of life when caring for children with rare, progressive and life-limiting conditions (the company considers the methodology and results of this evidence to be confidential, so they cannot be described here). The company and the patient experts highlighted that the rarity of the condition affects the quality of life of carers because of the limited availability of support and resources. The committee acknowledged the challenges in generating evidence on the impact on carer HRQoL in ultra-rare diseases, but considered that the evidence presented did not specifically capture elements unique to ASMD. It concluded that the qualitative evidence presented by the company was not specific to ASMD and was therefore of limited use for decision making.

Recently diagnosed subgroup

3.24 After the first committee meeting, the company presented a new subgroup analysis of people newly diagnosed with ASMD. The company argued that people who have had the disease for a longer period of time before treatment are more likely to have 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 than those with longer-standing disease, so are more likely to have permanent organ damage and reach the least severe health state. The clinical experts also explained that some people with ASMD only get 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 (see section 3.7). It recognised the difficulties in defining a 'recent' diagnosis in practice, and was concerned that some young people 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 people. There would also be ethical concerns if the treatment was recommended only for people who have recently been diagnosed and people with longer-standing disease were excluded, given the unmet need. It concluded that the recently diagnosed subgroup proposed by the company was not appropriate for decision making.

QALY weighting

3.25 The NICE health technology evaluations manual 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 will take account of the size of the incremental therapeutic improvement and the degree of certainty around the ICER. The incremental therapeutic improvement 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. At its first meeting, the committee thought 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 at its third meeting. It recalled the uncertainties in the evidence (see section 3.8) and around some assumptions in the model (see section 3.11, section 3.16 and section 3.17). It also noted that that there might be benefits associated with olipudase alfa not fully captured in the model (see section 3.11), and it would qualitatively consider the impact of a person's death on carers in decision making (see section 3.22). The size of the undiscounted QALY gains was 28 in the scenario the committee thought was most plausible. In this scenario, the company assumed the patient population would be 50% children and 50% adults. Considering the evidence as a whole, the committee agreed that a QALY weighting of 2.8 should be applied.

Cost-effectiveness estimates

The committee's preferred assumptions

3.26 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 3.11).
- Including disease-specific mortality for children in the model (see section 3.12).
- The company's parametric approach to modelling mortality (see section 3.13).
- A discount rate of 1.5% for the cost-effectiveness analysis (see sections 3.14 to 3.17).

- The EAG's approach to modelling body weight, with the starting weight at the lower end of the UK average (see section 3.18).
- Applying carer disutilities depending on the health state of the person with ASMD, with carer disutility in the olipudase alfa arm equal to half of carer disutility in the best supportive care arm (see section 3.19).
- Using carer disutilities that depend on disease severity and whether the person with ASMD is an adult or child (see section 3.20).
- Using an average of 1 carer per child with ASMD (see section 3.21).
- Not including carer disutilities associated with death of someone with ASMD in the model. The committee agreed to consider this qualitatively in its decision making instead (see section 3.22).

  Both the company's 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 noted that it had not been presented with any ICERs that were likely to be within the range NICE normally considers a cost-effective use of NHS resources for a highly specialised technology. This was even when taking into account the decision to apply a QALY weighting of 2.8, which meant that the committee was willing to accept a higher ICER than usual (see section 3.25).

Managed access

Recommendation with managed access

3.27 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. In its original submission, the company proposed to address the uncertainties about the long-term treatment effect through data collection from the ongoing extension study of LTS13632, the extension study of ASCEND, and an international Niemann–Pick disease registry. It also planned qualitative studies to understand the quality of

life of carers and the burden on people with the condition and their carers. Assumptions about long-term treatment effect and carer disutilities, especially carer disutilities associated with patient death, substantially affected the ICERs.

At its third meeting, the committee noted that both of the ongoing studies had been completed, but there were still substantial uncertainties in the evidence relating to the long-term treatment effect of olipudase alfa (see section 3.8). It also noted that data from the Niemann–Pick international registry could be retrieved outside a managed access agreement. For uncertainties relating to carer disutilities, there was a lack of detail on the methods of the planned qualitative study in the company's proposal, and the committee acknowledged the challenges in generating such evidence for an ultra-rare disease such as ASMD (see section 3.23). The committee noted that some data may be collected from planned studies, but it was unclear how well this would resolve the uncertainties in the model. Also, 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

3.28 There were no equality issues raised or identified in the evaluation.

Uncaptured benefits

3.29 The committee considered whether there were any uncaptured benefits of olipudase alfa. It recognised that olipudase alfa is the first treatment to address 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. At the first committee meeting, the clinical experts stated that

symptoms that people with ASMD regard as normal (such as limited exercise capacity, pain and 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 (see section 3.11) may have helped to account for these symptoms, but it is unlikely that the QALY calculations fully captured them, 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 that the company used to inform health state utilities. These included 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 for people with ASMD and their carers associated with treatment because of how the health states were defined (see section 3.10 and section 3.11). The committee noted that some of these uncaptured benefits may also have been accounted for by its conclusion about olipudase alfa's treatment effect in the longer term (see section 3.8), the 1.5% discount rate (see sections 3.14 to 3.17), and the QALY weighting of 2.8 (see section 3.25). It agreed that there were no other benefits that had not been captured in the model, and took this into account in its decision making.

Conclusion

Olipudase alfa is not recommended

3.30 The committee was not presented with a plausible cost-effective estimate after taking into account all of its preferred assumptions and other considerations (see section 3.26). 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 of the members who attended and their declarations of interests, are posted on the NICE website.

Chairs

Paul Arundel and Peter Jackson
Chairs, highly specialised technologies evaluation committee

Iolo Doull
Vice 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, a project manager and an associate director.

Tom Jarratt and Emma McCarthy
Technical leads

Yelan Guo

Technical adviser

Vonda Murray
Project manager

Richard Diaz
Associate director

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