NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Sebelipase alfa for treating Wolman disease

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

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: May 2023

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

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using sebelipase alfa in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 23 June 2023
- Second evaluation committee meeting: 13 July 2023
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Sebelipase alfa is not recommended, within its marketing authorisation, for treating Wolman disease (rapidly progressive lysosomal acid lipase deficiency [LAL-D]) in people who are 2 years or younger when treatment starts.

1.2 This recommendation is not intended to affect treatment with sebelipase 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. 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

Wolman disease is a rare genetic condition that presents in babies and children under 2 years old. It causes a build-up of fat in cells in the liver, heart, blood vessels, and digestive system. Without treatment, the baby or child will not survive. There are no treatments for Wolman disease available in the NHS. Standard care without sebelipase alfa is palliative. Sebelipase alfa is used as an enzyme replacement therapy alongside a restricted diet, and can allow a haematopoietic stem cell transplant to be done, if needed.

Clinical trial evidence suggests that sebelipase alfa increases how long people live. But it is not clear how much longer people will live or how their quality of life compares with people without the condition.

Haematopoietic stem cell transplant is an option for people having sebelipase alfa, those who can no longer have sebelipase alfa, or when sebelipase alfa stops working. But it is not clear when a transplant is done and what proportion of people have this. After a transplant, it is not clear how much the dose of sebelipase alfa can be reduced. It is also not known what dose of sebelipase alfa a person is likely to have over their lifetime.

Because of the clinical uncertainties and uncertainties around the likely treatment pathway when sebelipase alfa is used, the cost-effectiveness estimates are highly uncertain. Even when considering the condition's severity, and the effect of sebelipase alfa on quality and length of life, the most likely cost-effectiveness estimates are much higher than what NICE considers an acceptable use of NHS resources. So, sebelipase alfa is not recommended.

2 Information about sebelipase alfa

Marketing authorisation indication

2.1 Sebelipase alfa (Kanuma, Alexion) is indicated for 'long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of sebelipase alfa is £6,286 for a 20 mg vial (excluding VAT; company submission).

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

3 Committee discussion

The evaluation committee considered evidence submitted by Alexion, 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

Wolman disease

3.1 Wolman disease is a type of lysosomal acid lipase (LAL) deficiency, which is a rare, genetic disease where there is a marked decrease or loss in LAL enzyme activity. Wolman disease presents in babies and children under 2 years old as rapidly progressing multisystem disease. Wolman disease is characterised by intestinal failure and severe malabsorption, growth failure, hepatosplenomegaly and progressive liver fibrosis and cirrhosis (liver damage and scarring of liver). The condition normally causes death in the first 6 months of life, usually because of multiple organ failure. There is a smaller group of children diagnosed slightly later (under 2 years). For these children, there is still usually evidence of growth failure in the first 6 months of life. The condition can be diagnosed by identifying variants in the lipase A lysosomal acid (LIPA) gene, or deficient LAL enzyme activity, fibroblasts or dried blood spots, or through genetic testing. When symptoms of LAL deficiency occur after 2 years old, this is diagnosed as cholesteryl ester storage disease. This condition tends to have less severe presenting symptoms but can lead to hepatic and cardiovascular problems including hepatomegaly, cirrhosis, liver failure, dyslipidaemia and accelerated atherosclerosis. The scope of this evaluation is for Wolman disease only.

Impact of the condition on people with Wolman disease and their families

3.2 The committee considered the submissions from patient organisations and patient experts. The patient experts explained that Wolman disease has an extreme impact on both the child with the condition and their family and carers. A patient expert described that symptoms can present gradually, and that diagnosis is often delayed because of the rarity of the condition and lack of clinical knowledge about the condition. They highlighted the severe negative impact on the quality of life and length of life if Wolman disease is not treated, with death occurring very early in life.

They explained that families experience shock and confusion when diagnosis of the condition is confirmed and noted that there is little information available locally. The patient experts emphasised that enzyme replacement therapy with sebelipase alfa is important because it a life-saving treatment. They noted that nutritional management is a vital part of clinical management of the condition, with the need for a low-fat or fat-free diet. They highlighted that this can become more difficult when people with the condition reach adolescence, because people may be less willing to follow a diet that is significantly different to their peers. One patient expert explained that having sebelipase alfa means that, apart from restrictions in diet and not being able to do certain activities, their child is able to go to school and participate in most activities with their peers many years after diagnosis. The patient experts noted that while treatment with sebelipase alfa involves weekly intravenous infusions, it can be administered at home, which can reduce how much treatment interrupts school and home life. However, the experts also highlighted that the treatment can affect the ability to have family holidays and can result in the need for additional support for children who miss some school time. The clinical experts explained that treatment with sebelipase alfa allowed the possibility of a haematopoietic stem cell transplant. This transplant would be considered if sebelipase alfa efficacy reduced or if the person with Wolman disease and their carers considered it the most appropriate treatment option. The patient experts highlighted that, in general, there was a strong preference to remain on sebelipase alfa instead of having a haematopoietic stem cell transplant (see section 3.7). They explained that this was because of the risks of haematopoietic stem cell transplant. This meant that haematopoietic stem cell transplant was viewed as a rescue therapy and generally only considered if needed. The committee recognised the importance of sebelipase alfa as a life-saving treatment option for people with Wolman disease.

Clinical management

Treatment pathway

3.3 There are no NICE guidelines or NICE technology appraisal guidance for the management of Wolman disease. The current clinical management without sebelipase alfa involves supportive care and managing complications, but this is limited to palliative care. This can include lipid-lowering therapies and vitamin E supplementation. Haematopoietic stem cell transplant or liver transplant is generally not a treatment option without sebelipase alfa treatment, because clinical outcomes have been shown to be poor after these procedures when the disease is not first stabilised with sebelipase alfa treatment. The company stated that sebelipase alfa is a first-line treatment option for people with Wolman disease, with best supportive care as the alternative option (which results in early death). The clinical experts explained that sebelipase alfa would be used alongside nutritional support to implement the strict low-fat diet that is needed. They also stated some people may have a hematopoietic stem cell transplant, given after sebelipase alfa, if it is the most appropriate treatment option. The clinical experts explained that the decision about a haematopoietic stem cell transplant is made on an individual basis, which depends on clinical assessment, biochemical evidence, and antibody response (see sections 3.5 and 3.7). Because sebelipase alfa is given intravenously and usually administered weekly, there is a possibility that venous access is lost over time from repeated puncturing of the veins. The clinical experts stated that this may be a reason why a later hematopoietic stem cell transplant may be considered (see sections 3.5 and 3.8). The committee concluded that sebelipase alfa would be used as a first-line treatment option for babies and children with Wolman disease and may allow hematopoietic stem cell transplant.

Clinical evidence

Key clinical trials

3.4 The clinical effectiveness evidence for sebelipase alfa came from 2 single-arm trials that included some people from the UK. The company also used a natural history study to compare sebelipase alfa trial outcomes with clinical management without sebelipase alfa:

- LAL-CL08 was a phase 2 single-arm trial of 10 people who were 8 months old or younger when diagnosed with LAL-D and had substantial clinical concerns. The primary outcome was safety and tolerability.
- LAL-CL03 was a phase 2/3 single-arm trial of 9 people who were 2 years old or younger, with a LAL-D diagnosis and evidence of rapidly progressive disease based on growth failure within the first 6 months. The primary outcome in this study was the proportion of people surviving to 12 months of age.
- LAL-1-NH01 was a retrospective natural history study. In this study, people with LAL-D before the age of 2 either had a haematopoietic stem cell transplant or liver transplant or had no treatment. The primary outcome was to characterise survival and key aspects of the clinical course of Wolman disease. There were 21 people who did not have haematopoietic stem cell transplant or liver transplant in LAL-1-NH01. This population was used as comparative data by the company to inform outcomes for clinical management without sebelipase alfa.

The committee was aware that in some cases, Wolman disease is diagnosed after 6 months of age. The clinical trials restricted inclusion based on age of diagnosis or of symptom onset. The clinical experts explained that diagnosis may happen up to 2 years of age, but that this population would also have a similar poor prognosis and there is usually evidence of earlier symptom onset. The company presented a naive (unadjusted) comparison of survival outcomes across the 2 sebelipase alfa trials and the natural history study. In LAL-CL08, 90%

and 80% of people who had sebelipase alfa were alive at 12 and 24 months, respectively. In LAL-CL03, 67% of people who had sebelipase alfa were alive at 12 months, with 56% alive at 24 and 60 months. In the natural history study (LAL-1-NH01), everyone who did not have treatment died before 12 months of age. The sebelipase alfa clinical trials reported improvements in outcomes such as weight and length for age and nutritional outcomes. The trials also showed improvements in important measures of liver damage. The company highlighted that differences in survival between the 2 sebelipase alfa trials may be because of differences in the populations within the trials, different starting doses (0.35 mg/kg in LAL-CL03 compared with 1 mg/kg in LAL-CL08), or faster dose escalation of sebelipase alfa in LAL-CL08. The company noted that the outcomes might have also differed because of an improved clinical understanding of the condition over the time between the clinical trials, including a more rapid escalation of dose or increased dose frequency in early treatment of the most severe cases. The committee acknowledged the limited number of people in the clinical trials, and the differences between trial inclusion criteria. It concluded that the results from LAL-CL03 and LAL-CL08 suggest that sebelipase alfa improves survival and other disease-related outcomes for people with Wolman disease.

Clinical effectiveness

Long-term effectiveness of sebelipase alfa

3.5 The clinical trial evidence provided outcomes for sebelipase alfa for up to 5 years. The company assumed that sebelipase alfa treatment continues until there is a lack of clinical response, for example because of anti-drug antibodies developing, or a loss of venous access because of repeated puncturing needed for intravenous infusions. If there is a lack of clinical response, or a risk of venous access being lost, haematopoietic stem cell transplant is considered (see section 3.7). The company also assumed that after haematopoietic stem cell transplant, sebelipase alfa treatment continues with a reduced dose and then is stopped completely (see

section 3.10). The company estimated that loss of venous access happens at 30 years old (see section 3.8). The clinical experts highlighted that clinical outcomes with sebelipase alfa also depend on adherence to a strict low-fat diet, which can be challenging. A patient expert explained that it can be increasingly difficult to adhere to this diet as the person with Wolman disease gets older (see section 3.2). The committee considered that the long-term effectiveness of sebelipase alfa depends on whether anti-drug antibodies develop, if venous access is preserved and how many people decide to have a haematopoietic stem cell transplant (including the timing and outcomes of this procedure). The committee concluded that there is substantial uncertainty around the long-term effectiveness of sebelipase alfa.

Economic model

Company model

3.6 The company presented a Markov model with 7 health states to estimate the cost effectiveness of sebelipase alfa compared with best supportive care for people with Wolman disease. The 7 health states were:

1. Diagnostic investigation
2. Rescue care
3. Trial follow up for up to 5 years
4. Stable monitoring until loss of venous access or haematopoietic stem cell transplant
5. Haematopoietic stem cell transplant in early life (because of losing response to sebelipase alfa) or transplant in later life (because of losing venous access)
6. Death from other causes
7. Death from Wolman disease

People having best supportive care in the model only transition through health states 1, 2, 3, and 7. People having sebelipase alfa can transition

through all model health states. The committee concluded that the company's model structure was suitable for decision making.

Haematopoietic stem cell transplant

3.7 The company assumed that everyone with Wolman disease who has sebelipase alfa has a haematopoietic stem cell transplant at some point over their lifetime. The patient experts explained that the decision to have a hematopoietic stem cell transplant is a difficult one and most parents and people with Wolman disease would only choose to have a transplant if sebelipase alfa was not providing adequate benefits (see section 3.2). Also, there was a difference in views between clinical experts about the use of haematopoietic stem cell transplant. One of the clinical experts estimated that up to 50% of people with Wolman disease would have a haematopoietic stem cell transplant. Another clinical expert had stated that none of the people with Wolman disease in their practice had a transplant after sebelipase alfa. The clinical experts emphasised that because the population of people with Wolman disease is so small, and because the oldest person with Wolman disease having sebelipase alfa was around 10 years old, it was difficult to estimate the number of people who would go on to have a haematopoietic stem cell transplant. A patient expert explained that because of the mortality risks with transplant, long hospital stays, being in isolation, and the uncertain long-term benefits, most people with Wolman disease and their carers would prefer to continue sebelipase alfa until the treatment becomes ineffective. The committee acknowledged that a significant proportion of people with Wolman disease do not have a haematopoietic stem cell transplant, and it is uncertain how many people do. Considering clinical expert input, the committee concluded that up to 50% would be the most appropriate estimate for the proportion of people who would have haematopoietic stem cell transplant after sebelipase alfa.

Early or late haematopoietic stem cell transplant

3.8 The company assumed that a haematopoietic stem cell transplant happened either early (defined as 2 years of age, which the company assumed would happen for most people) or late (defined as 30 years of age). The exact proportions are considered confidential by the company and cannot be reported here. Early transplant was assumed to be because of development of anti-drug antibodies, and late transplant was assumed to be primarily because of a loss of venous access. One clinical expert explained that the proportion of people having a haematopoietic stem cell transplant early will depend on the response to enzyme replacement therapy, which may be reduced, often in the first 3 or 4 years of life. The clinical expert added that immunomodulatory agents (rituximab or bortezomib) may be used to target anti-drug antibodies, but this impact is limited and repeated use has risks. The expert also explained that factors such as venous access and lifestyle considerations (such as having to follow a strict diet) affect the decision to have transplant later in life. Another clinical expert added that haematopoietic stem cell transplant is used as a rescue treatment, and sebelipase alfa is the preferred treatment option as long as there is treatment benefit and no complications. A clinical expert stated that 1 out of 6 people with Wolman disease who had haematopoietic stem cell transplant in their practice had the procedure because of loss of venous access. The clinical experts said that it can be challenging to preserve central venous access in early life when other clinical issues are present (such as nutrition, protein depletion, or infections). In these cases, alternative ways of gaining venous access may be explored, or a haematopoietic stem cell transplant may be considered. But the clinical experts highlighted that there is little data on whether it could be assumed that venous access would be lost after weekly intravenous treatments with sebelipase alfa over a lifelong period. They noted that there may be an increased risk of thrombosis as seen in other conditions but venous access may be preserved for a long period of time, and possibly over a lifetime. The EAG explored scenarios where venous access is lost at 20 years and 40 years of age, as well as a

scenario where venous access is never lost. The EAG also provided scenario analyses that assumed early haematopoietic stem cell transplant is given for 0%, 50%, and 100% of people. The committee acknowledged that having haematopoietic stem cell transplant depends on multiple factors (see section 3.5). The committee concluded that some people have haematopoietic stem cell transplant early, but the proportion of early transplants is uncertain and early transplant would likely occur, on average, after 3 to 4 years. It acknowledged that some people with Wolman disease having transplant would have it late, primarily because of losing venous access. The committee concluded that some people may have a haematopoietic stem cell transplant in later life, but the proportion is unknown. It concluded that if a transplant in later life is done, it is likely to happen after a person is 30 years old.

Survival extrapolations

3.9 The company used clinical trial data from LAL-CL03 and LAL-CL08 to model Wolman disease-related mortality for sebelipase alfa using Kaplan–Meier data within the first 5 years. After the 5-year trial period, the company assumed that mortality was the same as that of the general UK population (so assuming no additional risk of death because of Wolman disease). The EAG noted that while the Kaplan–Meier curves had the best estimates of expected survival during the trial follow up, it considered that the estimated overall survival over a lifetime was too optimistic and highly uncertain because of the limited data and long-term assumptions. The EAG applied parametric survival extrapolations to the Kaplan–Meier curves in scenario analyses. The company used data from Potter et al. (2021) to model survival after sebelipase alfa treatment followed by haematopoietic stem cell transplant. The Potter et al. study included survival outcomes for 5 children after sebelipase alfa treatment followed by haematopoietic stem cell transplant. The EAG also noted that survival after haematopoietic stem cell transplant was based on limited data from Potter et al. (2021). The clinical experts stated that there would be an increased risk of death in the first 2 years after the procedure, but after

this the risk of death would fall substantially. The committee concluded that the limited data available to extrapolate survival with sebelipase alfa treatment over a lifetime horizon meant that the survival estimates after 5 years are uncertain.

Sebelipase dose and time on treatment

3.10 The company assumed that after haematopoietic stem cell transplant, the dose of sebelipase alfa would be reduced and people would stop treatment after 18 months. The EAG highlighted that the company assumptions around dose reduction and treatment stopping were highly uncertain. So, the EAG explored scenario analyses where only 50% of people having sebelipase alfa have a dose reduction after and only 50% of people stop sebelipase alfa after early haematopoietic stem cell transplant. The EAG also noted that the proportion of people on different doses of sebelipase alfa was uncertain in the model because these were based on limited data. One clinical expert stated that 3 out of 4 (75%) people with Wolman disease in their clinic had a stable condition reported on a 3 mg/kg sebelipase alfa dose. The clinical experts added that the potential to stop treatment is less well known for Wolman disease than for other lysosomal disorders. The clinical experts stated that after 1 year since haematopoietic stem cell transplant, the sebelipase alfa dose could be reduced gradually, and treatment could be stopped for people who show clinical improvement. One clinical expert explained that out of 5 people having sebelipase alfa, 1 had continued with the standard dose, 2 were on a reduced dose, and 2 stopped sebelipase alfa treatment within 2 to 2.5 years after haematopoietic stem cell transplant. The committee considered that the assumptions around sebelipase alfa dosing over a lifetime was highly uncertain. The committee concluded that up to 40% of people with Wolman disease would stop sebelipase alfa after haematopoietic stem cell transplant. The committee acknowledged they would do so gradually, likely between 2 to 2.5 years after transplant, rather than at 18 months as assumed by the company. The committee

agreed that the company's base-case assumptions significantly underestimated the time on sebelipase alfa treatment.

Vial management

3.11 The dosing of sebelipase alfa is weight based. The company assumed that each partly used 20 mg vial was disposed of and so it rounded up vial numbers when estimating drug acquisition costs. The company highlighted that in clinical practice, clinicians may adjust the dosing schedule to administer a full dose over a 2-week period to ensure less vial waste. The company stated that its base case was a conservative analysis. The company and EAG also presented scenarios that adjusted the vial use over 2 weeks. The clinical experts agreed that planned weekly alternate dosing is usual practice to manage sebelipase alfa dosing as the vial has one size. The committee recognised that in clinical practice, doses are managed to minimise vial wastage and agreed to consider this scenario in its decision-making.

Health-related quality of life

Utility values

3.12 LAL-CL03 and LAL-CL08 did not measure health-related quality of life. The company referenced a retrospective cohort study by Demaret et al. (2021), which included 5 people with Wolman disease who had sebelipase alfa treatment in France. This study reported results using the Pediatric Quality of Life Inventory questionnaire. The company stated that the results showed normal or near normal development and health-related quality of life. This study was used by the company as supportive evidence for its assumption that the quality of life of people having sebelipase alfa is the same as that of the age matched general population in the UK. The company also assumed this for the quality of life for people who have had sebelipase alfa and then a haematopoietic stem cell transplant. The committee noted that this study was based on small numbers, had differing results between people with Wolman disease and their caregviers, and had limited follow up. The company included a

scenario analysis that applied a 0.9 weighting to the utility values (10% reduction in quality of life compared with the age matched general population). The EAG reported that frequent infusion with sebelipase alfa may affect quality of life, as seen in other conditions that need enzyme replacement therapies. The EAG had concerns that the health-related quality of life may be overestimated and included a scenario analysis where a 0.8 weighting (20% reduction in quality of life compared with that of the age matched general population) was applied to the utility values in the model. In its base case, the company included utility decrements associated with parental nutrition. Utility decrements were also included for haematopoietic stem cell transplant and for family bereavement in the scenario analyses (the EAG provided a scenario analysis that applied a caregiver disutility for ongoing enzyme replacement therapy). The patient experts explained that the strict low-fat diet that people with Wolman disease have to follow alongside treatment with sebelipase alfa can be challenging, which affects the child more as they get older. However, the experts emphasised this is highly individualised, and depends on factors such as family and support networks. The clinical experts explained that some people may need a gastrostomy when young, but when children get older and can eat orally, adherence with a low-fat diet may improve, particularly after experiencing the symptoms resulting from fat consumption. The committee agreed that utility decrements associated with haematopoietic stem cell transplant should be included in the base-case analysis. It agreed that the EAG's scenario analyses applying a 0.8 weighting to the general population utility values were more plausible than the company's base case that assumed general population utility values. However, the committee considered that the health-related quality of life was not captured accurately over the lifetime of the model. The committee concluded that it would prefer to see analyses that model health-related quality of life changes more accurately over the lifetime of the model.

Discounting rate for costs and health benefits

3.13 NICE's health technology evaluations manual (2022) specifies that the discount rate that should be used in the reference case is 3.5% for costs and health effects. But it also states that a non-reference case rate of 1.5% for costs and health effects may be used instead when all of the following criteria are met:

- the technology is for people who would otherwise die or have very severely impaired life
- is likely to restore them to full or near-full health
- the benefits are likely to be sustained over a very long period.

The company used a 1.5% discount rate in its base case, whereas the EAG used a 3.5% discount rate in its base case. The committee acknowledged the substantial health benefits of sebelipase alfa compared with best supportive care. But it noted that the company model did not appropriately model health-related quality of life changes over a lifetime (see section 3.12). The committee was uncertain whether sebelipase alfa restores people to full or near-full health. Also, having a haematopoietic stem cell transplant may address clinical issues when sebelipase alfa's efficacy is reduced, and may remove the need for a low-fat diet, but would have its own associated risks. However, clinical experts stated that not everyone would have a haematopoietic stem cell transplant, and patient experts expressed concerns about the risks of transplant compared with continuing with enzyme replacement therapy (see sections 3.2 and 3.7). The committee noted that the evidence informing outcomes for haematopoietic stem cell transplant after sebelipase alfa treatment was limited and so was highly uncertain. The committee also considered that the company model significantly underestimated uncertainty in clinical outcomes including the company's probabilistic sensitivity analysis, which did not vary key model parameters. The committee highlighted that it is unknown if the benefits of sebelipase alfa are

sustained over a long period, given the limited longer-term evidence. The committee concluded that sebelipase alfa did not meet the criteria for using a 1.5% discount rate.

Applying quality-adjusted life year weighting

3.14 NICE's health technology evaluation manual (2022) specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgments about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying 'QALY weight'. The committee noted that NICE's health technology evaluations manual states that, for this weight to be applied, there needs to be compelling evidence that the treatment offers significant QALY gains. It is understood that a weight of between 1 and 3 can be applied when the QALY gain is between 11 and 29 QALYs. The committee noted that the number of undiscounted QALYs gained with sebelipase alfa was likely to be over 30 in the base-case analysis. It noted that there was uncertainty around this estimated gain because of the small numbers of people in the clinical evidence base and the limited long-term evidence. But, the committee agreed that despite the uncertainty sebelipase alfa is likely to provide a QALY gain greater than 30 and therefore considered a QALY weighting of 3 to be applied in its decision making.

Cost-effectiveness estimates

The committee's preferred assumptions

3.15 The company and EAG base-case analysis included the same key assumptions apart from the choice of discount rate used for cost and benefits (see section 3.12). The committee recalled that the base-case

analysis from the company and EAG did not include its preferred assumptions, which were:

- assuming that up to 50% of people would have haematopoietic stem cell transplant after sebelipase alfa treatment (see section 3.7)
- people with Wolman disease who have an early haematopoietic stem cell transplant after sebelipase alfa would, on average, have this between 3 to 4 years of age (see section 3.8)
- people with Wolman disease who have a late haematopoietic stem cell transplant after sebelipase alfa are likely to have this after 30 years of age (see section 3.8)
- 40% of people with Wolman disease would likely stop sebelipase alfa after haematopoietic stem cell transplant and would take between 2 and 2.5 years after the transplant to stop treatment (see section 3.10)
- not everyone with Wolman disease would reduce their dose of sebelipase alfa after haematopoietic stem cell transplant (see section 3.10)
- the EAG's scenario analysis applying a 0.8 weighting to general population utility values was more plausible than assumed general population utility values, but the committee would prefer to see analysis that more accurately captured the quality-of-life changes over the lifetime of the model (see section 3.12)
- applying discount rate of 3.5% to costs and benefits (see section 3.13)
- applying a QALY weighting of 3 (see section 3.14).

There was a high level of uncertainty in the cost-effectiveness results because of:

- the probabilistic sensitivity analysis, which did not vary key parameters and so underestimated the uncertainty in the ICER estimates
- the proportion of people having a haematopoietic stem cell transplant and when a haematopoietic stem cell transplant happens (see sections 3.7 and 3.8)

- the limited evidence informing survival outcomes for sebelipase alfa treatment followed by haematopoietic stem cell transplant (see section 3.9)
- the dose of sebelipase alfa after a haematopoietic stem cell transplant (see section 3.10)
- how health-state utility values were incorporated in the model (see section 3.12)

The committee considered that none of the cost-effectiveness estimates it had been presented with from the company and EAG fully accounted for its preferred assumptions. It concluded that while it could not determine the most plausible ICER estimate, it believed that this ICER would be substantially above what NICE considers acceptable use of NHS resources for a highly specialised technology.

Other factors

Equality

3.16 A clinical expert explained that some people have a genetic mutation in the LIPA gene which can cause increased disease severity, and predominantly occurs in people from South Asian family backgrounds. This is because an increased amount of anti-drug antibodies can be produced, which may impact the effectiveness of enzyme replacement therapies. The clinical experts noted that this may increase the need for haematopoietic stem cell transplant in this population. The committee considered this issue and noted that the recommendations for sebelipase alfa would not affect people from South Asian family backgrounds differently.

Innovation

3.17 The committee considered if sebelipase alfa was innovative. It did not identify additional benefits of sebelipase alfa not captured in the economic modelling. So the committee concluded that all additional benefits of sebelipase alfa had already been taken into account. The committee

noted that as the cost-effectiveness estimates were substantially above the level considered an acceptable use of NHS resources, accounting for any benefits not captured in the model would not change this conclusion.

Conclusion

Recommendation

3.18 The committee concluded that its preferred assumptions would result in cost-effectiveness estimates for sebelipase alfa that would be above the range considered an acceptable use of NHS resources for a highly specialised technology. So, sebelipase alfa is not recommended for treating Wolman disease.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Dr 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.

Summaya Mohammad
Technical lead

Alan Moore
Technical adviser

Daniel Davies
Project manager

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