NICE National Institute for Health and Care Excellence

NICE guidance

Sebelipase alfa for treating Wolman disease

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 Sebelipase alfa is recommended as an option for long-term enzyme replacement therapy in Wolman disease (rapidly progressive lysosomal acid lipase deficiency [LAL-D]), only if people are 2 years or under when treatment starts. It is recommended only if the company provides sebelipase alfa according to the commercial arrangement.

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, 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 appropriate.

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 long-term 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. People may choose to have a transplant to reduce the need for a restricted diet and regular sebelipase alfa treatment, but there are risks associated with a transplant. It is not clear when transplants are done and what proportion of people have them. After a transplant, it is not clear how much the dose of sebelipase alfa can be reduced. These uncertainties are higher for transplants that happen later in life. It is also not known what proportion of people would remain on sebelipase alfa and what dose they are likely to have over their

lifetime.

Because of the clinical uncertainties, including those related to how sebelipase alfa is used in the treatment pathway for people with Wolman disease, the cost-effectiveness estimates are also uncertain. 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 within the range NICE considers an acceptable use of NHS resources. So, sebelipase alfa is 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. This makes sebelipase alfa available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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 rare, genetic condition in which there is a complete loss in lysosomal acid lipase (LAL) enzyme activity. It is the severest type of LAL deficiency, presenting in babies and children under 2 years old as rapidly progressing multisystem disease. 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. Wolman disease is characterised by intestinal failure and severe malabsorption, growth failure, hepatosplenomegaly and progressive liver fibrosis and cirrhosis (liver damage and scarring of the liver). It normally causes death in the first 6 months of life, usually because of multiple organ failure. For a smaller group of children diagnosed slightly later (under 2 years), there is usually evidence of growth failure in the first 6 months of life. 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, a subgroup of the company's marketing authorisation for sebelipase alfa.

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 explained that symptoms can present gradually, and that diagnosis is often delayed because of the rarity of Wolman disease and lack of clinical knowledge about the condition. The clinical experts explained that babies are usually severely unwell within weeks of being born and can be extremely malnourished. They noted that these babies usually need intensive multidisciplinary hospital care for long periods, during which they can have multiple intravenous lines and nasogastric tubes for blood transfusions and parenteral nutrition. They explained that babies are likely to have used several central veins in the first few months of life, which may lead to issues of venous access later in life (see sections 3.7 and 3.8). The patient experts outlined the severe negative impact on quality and length of life that untreated Wolman disease has, with death occurring very early in life (around 4 months old). They explained that families experience shock, confusion and feelings of helplessness and hopelessness when diagnosis of the condition is confirmed. Families also fear that other children may have the same inherited condition. The patient experts noted that there is limited information available about the condition locally. They also emphasised that enzyme replacement therapy with sebelipase alfa is important because it is a life-saving treatment. The clinical experts explained that treatment with sebelipase alfa allowed the possibility of a haematopoietic stem cell transplant (see sections 3.7 and 3.8), a treatment previously associated with a poor outcome. The committee acknowledged that Wolman disease is an ultra-rare, fatal condition, that has a significant negative impact on quality of life for people with the condition and their families and carers. It also 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 are generally not options without sebelipase alfa treatment, because clinical outcomes have been shown to be poor after these procedures when the condition is not first stabilised with sebelipase alfa. The company stated that sebelipase alfa is expected to be a first-line option for people with Wolman disease, with best supportive care being 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 explained that some people may have a haematopoietic stem cell transplant after treatment with sebelipase alfa. The decision to have a transplant is done on an individual basis, depending on clinical assessment, biochemical evidence, antibody response and patient and carer preference. The patient experts explained that, in general, families and carers had a strong preference for people with Wolman disease to remain on sebelipase alfa until it becomes ineffective rather than having a transplant. This is because of the mortality risks and uncertain long-term benefit of transplants, long hospital stays and the need to be isolated. So, a haematopoietic stem cell transplant was generally viewed as a rescue therapy and only considered when needed. In response to the draft guidance consultation, the company stated that it is unlikely that sebelipase alfa will be used over a lifetime. It stated that sebelipase alfa will likely be a bridging option to potential future treatment options, such as gene therapy. 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 haematopoietic stem cell transplants.

Clinical evidence

Key clinical evidence

3.4 The clinical effectiveness evidence for sebelipase alfa came from 2 single-arm, open-label, multicentre trials that included people diagnosed with LAL deficiency, some of whom were from the UK:

- LAL-CL08 was a phase 2 trial of 10 people diagnosed at 8 months old or younger with substantial clinical concerns. People had sebelipase alfa for up

to 3 years. The primary outcome was related to safety (severe treatment-emergent adverse events).

- LAL-CL03 was a phase 2/3 trial of 9 people diagnosed at 2 years old or younger with evidence of rapidly progressive disease based on growth failure before 6 months old. People had sebelipase alfa for up to 5 years. The primary outcome was the proportion of people alive at 12 months old.

  The company also used a natural history study to estimate outcomes for clinical management without sebelipase alfa:

- LAL-1-NH01 was a retrospective natural history study of 35 people diagnosed with Wolman disease between 1985 and 2012. They either had a haematopoietic stem cell transplant or liver transplant, or had no treatment. The primary outcome was time to death. The company used data from 21 people who had no treatment to inform outcomes for the comparator, which was clinical management without sebelipase alfa.

  The committee noted that the clinical trials restricted inclusion based on age of diagnosis or symptom onset. The clinical experts explained that diagnosis may happen up to 2 years old, but that this older population would have a similar poor prognosis to those diagnosed younger and there is usually evidence of earlier symptom onset. The committee acknowledged the limited number of people in the trials, and the differences between inclusion criteria.

Clinical effectiveness

Clinical outcomes up to 5 years from the sebelipase alfa trials

3.5 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% of people who had sebelipase alfa were alive at 12 months, with 80% alive at 24 months. 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 old. The sebelipase alfa clinical trials also reported improvements in weight and

length for age, nutritional outcomes and 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, starting doses (0.35 mg/kg in LAL-CL03 compared with 1 mg/kg in LAL-CL08), or the 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 Wolman disease between the trials, including faster dose escalation and increased dose frequency in early treatment of the most severe cases. The committee concluded that the clinical trial evidence suggests that sebelipase alfa improves survival and other disease-related outcomes for people with Wolman disease but noted the uncertainty around its longer-term effectiveness.

Economic model

Company model

3.6

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 reduced or loss of 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.

Early and late haematopoietic stem cell transplant

3.7 The company assumed that everyone who has sebelipase alfa will have a haematopoietic stem cell transplant in their lifetime. In the revised base case, the company assumed that a transplant will either happen early (defined as happening in the first few years of life; the exact timing is academic in confidence and cannot be reported here) or late (defined as happening at 30 years old). The clinical experts explained that early transplants are likely to be because of loss of clinical response from the development of anti-drug antibodies. One clinical expert explained that reduced effectiveness of sebelipase alfa is likely to happen in the first 2 to 4 years of life. They explained 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 clinical experts explained that people may have late transplants, usually because of a loss of venous access or because of lifestyle considerations and patient and carer preference to reduce the need for a restricted diet and regular treatment with sebelipase alfa. They noted that people with Wolman disease may have issues with venous access because of hospitalisations early in life (see section 3.2). But the experts also highlighted that there is limited data to assume that venous access would be lost because of weekly intravenous sebelipase alfa treatment over a lifetime. They explained that there may be an increased risk of thrombosis compared with other conditions that need enzyme replacement therapy, but venous access may be preserved for a long period of time, and possibly over a lifetime. One clinical expert explained that half of the people with Wolman disease on sebelipase alfa and their families are considering the possibility of late transplants because of lifestyle considerations. The clinical experts emphasised that because the population of people with Wolman disease is so small, and because the oldest person with the condition having sebelipase alfa was just over 10 years old, it was difficult to estimate the number of people who would have a transplant during their lifetime. But, they did not think that everyone would be likely to have a transplant during their lifetime.

Uptake of early and late haematopoietic stem cell transplant

3.8 In response to the draft guidance consultation, the company provided evidence of haematopoietic stem cell transplant uptake across 2 UK centres in people who

had sebelipase alfa and were alive. The data included the proportion of people having transplants and the age at which the transplant happened. The committee noted the difference in uptake of transplants in the Manchester and Birmingham treatment centres (the exact proportions are academic in confidence and cannot be reported here. The clinical experts considered that the difference in uptake across the 2 centres was likely to be because of the small number of patients, rather than variation in clinical practice or disease genotype. More than half the people who had sebelipase alfa had early transplants within the first couple of years of life. There was little data on late transplants. The clinical expert explained that a late transplant before adolescence was done because of patient preference. The exact proportion of people having transplants are considered confidential by the company and cannot be reported here. The committee acknowledged the limitations of the data because of the small number of patients, particularly for those who had late transplants. It considered that the model should use the data from the 2 UK centres for the proportion of people having early transplants and the average time when they happen. The committee considered that the estimates for late transplants were likely to be an underestimate because of the limited data and follow up. It acknowledged that late transplants may happen sooner than the 40 years that the committee had preferred after the first committee meeting (but later than 30 years). It agreed with the clinical experts that not everyone is likely to have a transplant and noted their views that half of the people were considering having a late transplant (see section 3.7). It considered that of the remaining people not having early transplants, half should have late transplants, with the other half remaining on sebelipase alfa over their lifetime. The committee acknowledged that late transplants can happen before adulthood. So, it agreed that the company's assumption in its revised base case that late transplants are likely to happen at 30 years was plausible. The committee considered that there is substantial uncertainty about the proportion of people having late transplants and those who will likely remain on sebelipase alfa over their lifetime. It acknowledged the company's arguments that sebelipase alfa may act as a bridging therapy to future novel interventions (see section 3.3). But, the committee had not been presented with any evidence or modelling options to support this assumption. It considered an assumption that the people not having early or late transplants would continue on sebelipase alfa is appropriate for decision making, because this is the only option currently available.

Sebelipase alfa dose and time on treatment

3.9 In response to the draft guidance consultation, the company provided revised assumptions on the use of sebelipase alfa after haematopoietic stem cell transplant, based on the data from the 2 UK treatment centres. The exact proportions are considered confidential by the company and cannot be reported here. The company assumed that people would reduce their dose at 12 months after transplant and that a large proportion would stop sebelipase alfa at 24 months after transplant. A clinical expert explained that data on average doses of sebelipase alfa used after transplant from the Manchester centre showed that everyone continued on the same dose for 12 months after transplant. They explained that this dose was reduced from 12 to 36 months after transplant for everyone. They further highlighted that by 36 months after transplant, everyone had stopped sebelipase alfa. The committee acknowledged the limitation of the evidence because of the small number of people who have had transplants. It also noted that there was a short duration of follow up in the data. The committee considered that this meant any estimates would be associated with uncertainty. It noted that the data mostly applied to people who had early transplants and that there was greater uncertainty regarding sebelipase use after late transplants. Despite this, the committee preferred to use the data provided by the clinical expert when assuming the dosage of sebelipase alfa after transplants in the model.

Vial management

3.10 The dosing of sebelipase alfa is weight based. In response to the draft guidance consultation, in its revised base case, the company assumed that clinicians adjust the dosing schedule to administer a full dose over a 2-week period to ensure less vial wastage. The clinical experts agreed that planned weekly alternate dosing is usual practice to manage sebelipase alfa dosing because the vial has 1 size. The committee agreed that the company's revised base case that included reduced vial wastage, in line with clinical practice, was appropriate for decision making.

Survival extrapolations

3.11 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 assumed no additional risk of death because of Wolman disease. The company also provided a scenario in which an increased mortality risk of 20% was assumed, compared with that of the general population without the condition. The EAG noted that while the Kaplan–Meier curves provided 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 transplant. The EAG noted that this study provided limited data on survival after transplant. The clinical experts stated that there would be an increased risk of death in the first 2 years after transplant, but after this time the risk of death would fall substantially. At the second committee meeting, the clinical experts explained that based on evidence from other lysosomal conditions such as mucopolysaccharidosis type I and Gaucher's disease, they expected mortality risk to be in line with the general population at 35 years after transplant (longest available data). But there may be a higher incidence of type 2 diabetes and insulin resistance, which will likely have an impact on mortality 50 to 60 years later. The clinical experts noted that long-term data on later mortality is not available. The committee considered that there was substantial uncertainty surrounding the assumptions of long-term survival. It considered that the EAG's parametric survival extrapolations using the trial Kaplan–Meier curves were highly uncertain because of the limited trial data. The committee considered that people with Wolman disease would have an increased risk of mortality compared with people without the condition. The committee preferred to apply an increased mortality risk of 20% compared with the UK general population.

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 Paediatric 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 of people who have had sebelipase alfa and then a haematopoietic stem cell transplant. The committee noted that this study was based on small numbers, and most had been diagnosed and started treatment unusually early because of a sibling with the condition. The study also had differing results between people with Wolman disease and their carers, 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 highlighted that frequent infusion with sebelipase alfa may affect quality of life, as seen in other conditions that need enzyme replacement therapy. It had concerns that the health-related quality of life may be overestimated and included a scenario analysis where a 0.8 weighting was applied to the utility values (20% reduction in quality of life compared with that of the age-matched general population) in the model. In its base case, the company included utility decrements associated with parenteral nutrition. It also included utility decrements for haematopoietic stem cell transplant and for family bereavement in scenario analyses. The EAG provided a scenario analysis that applied a carer 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 sebelipase alfa treatment can be challenging, which affects the child more as they grow older. But the experts emphasised that 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 grow older and can eat orally, adherence to a low-fat diet may improve, particularly after experiencing the negative symptoms of eating

fat. 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 similar to their peers many years after diagnosis. The patient experts noted that while sebelipase alfa involves weekly intravenous infusions, it can be administered at home, which can reduce disruption to school and home life. But 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. In response to the draft guidance consultation, the company included utility decrements associated with haematopoietic stem cell transplant in its revised base case, but continued to assume general population utility values in its model. It also provided an additional scenario analysis that applied a 0.95 weighting to the utility values (5% reduction in quality of life compared with the age-matched general population). In response to the draft guidance consultation, the MPS Society did a survey of 15 children with and without Wolman disease to compare function and quality of life (using the EQ-5D). This survey was completed online by carers. The patient organisation reported data separately for people aged 6 to 8 years and 9 to 12 years. The exact data are considered confidential by the patient organisation and cannot be reported here. The patient organisation considered that the data showed that people with LAL-D have good to normal developmental gains and are close to the healthy population in terms of abilities and quality of life. The committee acknowledged the small number of people included in the survey and that it was unclear how many had haematopoietic stem cell transplants. It noted that, overall, function and quality-of-life indicators were generally lower for people with Wolman disease than for the age-matched population without the condition. The committee recalled that some people on sebelipase alfa were considering having transplants because of lifestyle considerations relating to their diet and intravenous administration of sebelipase alfa (see section 3.7). It acknowledged the high uncertainty surrounding the quality-of-life assumptions. But it agreed that the company's scenario analysis applying a 0.9 weighting to the general population utility values was more plausible than assuming general population utility values as in the company's base case.

Discount 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 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 considered that there was a high level of uncertainty as to whether sebelipase alfa restores people to full or near-full health considering, for example, that people who do not have haematopoietic stem cell transplants continue to need severe dietary restrictions alongside sebelipase alfa infusions. But, while having a transplant may address clinical issues when sebelipase alfa's efficacy is reduced, and may remove the need for a low-fat diet, haematopoietic stem cell transplant is associated with a risk of early death and for some, significant adverse effects. The clinical experts stated that not everyone would have a transplant, while patient experts expressed concerns about the risks of a transplant compared with continuing with sebelipase alfa (see section 3.3). The committee recalled that people with Wolman disease may have an increased risk of type 2 diabetes and insulin resistance (see section 3.11). It 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's model underestimated uncertainty in clinical outcomes such as survival and noted that the company's probabilistic sensitivity analysis did not vary key model parameters such as the increased risk of death. But, the committee acknowledged the heterogeneity of response, so while some people with Wolman disease may stabilise and survive on sebelipase alfa to enable a transplant, others may not. The committee also noted that it is

unknown if the benefits of sebelipase alfa are sustained over a long period, given the limited longer-term evidence. It 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 substantially greater than 30 in the base-case analysis. It noted that there was uncertainty around this estimated gain because of the small number 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 so considered a QALY weighting of 3 to be applied in its decision making.

Cost-effectiveness estimates

The committee's working assumptions

3.15 Because of the uncertainty in so many areas, the committee considered a large number of scenarios. While it considered some of these scenarios to be plausible assumptions, it noted the very high level of uncertainty in all of them. The committee acknowledged that the extreme uncertainty is mainly because of the

very small population and took this into consideration. For the purposes of decision making, the committee selected what were likely to be the most reasonable, working assumptions. The company and EAG revised base-case analysis included the same key assumptions apart from the choice of discount rate used for cost and benefits (see section 3.13). The base-case analysis from the company and EAG did not include the committee's working assumptions, which were:

- Just over 50% of people would have an early haematopoietic stem cell transplant after sebelipase alfa treatment. This, on average, would happen in the first few years of life (see section 3.8).
- 50% of the remaining people who did not have an early transplant would have a late transplant after sebelipase alfa. This, on average, would happen at 30 years old (see section 3.8).
- The remaining people not having an early or late transplant would remain on sebelipase alfa over their lifetime (see sections 3.7 and 3.8).
- Everyone would continue on the same dose of sebelipase alfa for 12 months after transplant (see section 3.9).
- Everyone would then continue on a reduced dose of sebelipase alfa from 12 to 36 months after transplant (see section 3.9).
- Everyone would stop sebelipase alfa at 36 months after transplant (see section 3.9).
- An increased mortality risk of 20% should be applied to the UK age-matched general population values to represent the mortality risk for people with Wolman disease after the 5-year trial period (see section 3.11).
- A 0.9 weighting should be applied to the UK general population utility values to represent the quality of life of people with Wolman disease (see section 3.12).
- A discount rate of 3.5% should be applied to costs and benefits (see section 3.13).
- A QALY weighting of 3 should be applied (see section 3.14).

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

- proportion of people having a haematopoietic stem cell transplant and when the transplant happens (see sections 3.7 and 3.8)
- dose of sebelipase alfa over a lifetime (see section 3.9)
- survival outcomes for sebelipase alfa treatment followed by haematopoietic stem cell transplant (see section 3.11)
- health-state utility values and how they were incorporated in the model (see section 3.12)
- probabilistic sensitivity analysis, which did not vary key parameters such as inputs related to mortality (see section 3.13).

The committee reviewed all the scenarios including 1 based on its set of working assumptions. After the second committee meeting, the company revised its patient access scheme discount. The revised cost-effectiveness estimates using the committee's set of working assumptions were within the range that NICE considers an acceptable use of NHS resources for a highly specialised technology, when considering the QALY weighting (see section 3.14), the potential for some benefits to be uncaptured and the extreme level of uncertainty in the working assumptions.

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. This largely occurs in South Asian ethnicities. Disease severity may be increased 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 South Asian groups differently.

Innovation

3.17 The committee considered whether sebelipase alfa was innovative. The committee noted that it had identified additional benefits of sebelipase alfa not captured in the economic modelling but had already considered this in its decision making (see section 3.13 and section 3.15).

Conclusion

Recommendation

3.18 The committee concluded that the revised cost-effectiveness estimates for sebelipase alfa for the set of scenarios it considered to be plausible assumptions are within the range considered an acceptable use of NHS resources for a highly specialised technology. So, sebelipase alfa is recommended for treating Wolman disease (rapidly progressive lysosomal acid lipase deficiency [LAL-D]), only if people are 2 years or under when treatment starts.

4 Implementation

4.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has Wolman disease and the doctor responsible for their care thinks that sebelipase alfa is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

Sharlene Ting and Summaya Mohammad
Technical leads

Alan Moore
Technical adviser

Leena Issa, Daniel Davies and Vonda Murray
Project managers

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Accreditation