NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final evaluation determination

Sebelipase alfa for treating lysosomal acid lipase deficiency

1 Recommendations

1.1 Sebelipase alfa is not recommended for long-term enzyme replacement therapy for treating lysosomal acid lipase (LAL) deficiency in babies with rapidly progressive disease. The committee recognised that sebelipase alfa is a potentially life-saving treatment in this population, and there is a compelling clinical need. It was concerned that, even with the company's proposed discount and cost cap, the cost of sebelipase alfa is exceptionally high and is too high to be considered value for money in the context of uncertainties about the potential long-term benefits of treatment.

1.2 Sebelipase alfa is not recommended for treating LAL deficiency in children or adults.

1.3 This guidance is not intended to affect the position of patients whose treatment with sebelipase alfa was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. For children and young people this decision should be made jointly by the clinician and the child or young person or the child or young person's parents or carers.

2 The condition

2.1 Lysosomal acid lipase (LAL) deficiency is an inherited autosomal recessive lysosomal storage disorder. Mutations in the lysosomal acid lipase gene result in deficiency of the LAL enzyme. This causes abnormal accumulation of lipids, mainly in the gastrointestinal, hepatic and cardiovascular systems.

2.2 The prevalence of LAL deficiency in England is unknown. The estimated incidence of LAL deficiency is 1 in 500,000 to 1 in 1,000,000 in children presenting in infancy and 1 in 40,000 to 1 in 300,000 in those presenting in childhood or adulthood.

2.3 The rate of progression of LAL deficiency and its mortality differs markedly depending on when people present with symptoms. Babies under 6 months who present with LAL deficiency generally have a rapidly progressive condition. The rate of progression in children and adults is slower and more variable than in babies. Most people present with symptoms during childhood: 83% of patients present by 12 years, with a median age of onset of 5 years.

3 The technology

3.1 Sebelipase alfa (Kanuma, Alexion Pharma UK) is a recombinant human lysosomal acid lipase. It has a marketing authorisation in the UK for long-term enzyme replacement therapy in patients of all ages with lysosomal acid lipase (LAL) deficiency. For babies under 6 months with rapidly progressive LAL deficiency, 1 mg/kg sebelipase alfa is administered by intravenous infusion once weekly. The dosage may be escalated to 3 mg/kg once weekly based on clinical response. For children and adults who do not present with rapidly progressive LAL deficiency before they are 6 months, 1 mg/kg sebelipase alfa is administered by intravenous infusion once every other week.

3.2 The summary of product characteristics lists the most serious adverse reactions for sebelipase alfa (seen in around 3 in 100 patients) as being signs and symptoms of severe allergic reactions. The summary of product characteristics also states that development of antibodies against sebelipase alfa has been reported, especially in babies, although the clinical impact of these is not yet known. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 Sebelipase alfa is available in vials containing 20 mg of sebelipase alfa, at a list price of £6,286 per vial (excluding VAT; company's evidence submission). The company estimated the annual cost of treatment for an 11-year-old child to be £491,992 (excluding VAT). The company proposed that sebelipase would have been made available with an annual per-patient cost cap (regardless of the dosing regimen used), a discount to the price per mg, and a total budget cap. The level of the caps and the discount are commercial in confidence.

4 Evidence submissions

The evaluation committee (section 7) considered evidence submitted by Alexion Pharma UK, a review of this submission by the evidence review group and evidence submitted by clinical experts, patient experts and NHS England.

Nature of the condition

4.1 Rapidly progressive lysosomal acid lipase (LAL) deficiency in babies is usually diagnosed within the first weeks of life. It causes gastrointestinal and liver problems including malabsorption, growth failure, profound weight loss, steatorrhoea (excretion of fat in stools) and hepatomegaly (enlarged liver). Survival is less than 12 months and the median life expectancy of a baby with rapidly progressive LAL deficiency is 3.7 months.

4.2 Children and adults with LAL deficiency frequently have abdominal pain, fatigue, diarrhoea, nausea, loss of appetite, itchy skin and a swollen abdomen. Lipid accumulation can lead to liver cirrhosis, liver failure, other systemic complications such as an enlarged spleen, anaemia and blood platelet deficiency and probably atherosclerosis. In around 87% of patients more than 1 organ is affected by LAL deficiency. It is estimated that approximately 50% of children and adults with LAL deficiency progress to have liver complications such as fibrosis or cirrhosis, or need a liver transplant within 3 years of the start of their symptoms. The life expectancy of people with LAL deficiency that presents after infancy is not clear because of the variability of symptom severity and rate of progression.

4.3 Because the condition is rare, delays in diagnosis are common. Parents of babies who have symptoms of LAL deficiency are usually adjusting to having a new baby and recovering from childbirth when the diagnosis is made. Delays in diagnosis are unbearable for them because they can see their child refusing feeds, crying in pain and vomiting continuously without knowing why. After diagnosis, parents have to come to terms with the prognosis of their child having weeks or months to live. They need to take large amounts of time off work and be away from home to be with their child in hospital, which may be far from the family home. People with symptoms presenting later in life find that their wellbeing is impaired by constant pain and nausea. Symptoms affect their ability to carry out everyday tasks, and can stop them working and taking part in sport. They may be anxious about being in crowded places because of the chance of being accidentally knocked, which increases their pain.

4.4 Approximately half the people diagnosed with LAL deficiency will need a liver transplant. A patient organisation explained the experiences of patients and their families facing the possibility of a liver transplant. For parents, there is the constant anxiety of knowing their child will need a liver transplant one day but not knowing when that is likely to be. The uncertainty about when a suitable liver will be available is stressful

because the child may die before a liver donor is found. Patients (and their families) need to be immediately available when a suitable liver is found, which affects daily activities and travel. People who have had a transplant need intensive care to recover and may be away from their family, school (or work) and friends for a long time. After transplant, people need to have drug treatment for the rest of their lives. Fear of liver transplant failure can be an ongoing source of anxiety for some people.

Clinical evidence

4.5 The company submission described 6 clinical trials (LAL-CL01, LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06 and LAL-CL08) and 2 retrospective cohort studies (LAL-1-NH01 and LAL-2-NH01). The submission focused on results from LAL-1-NH01, LAL-CL03 and LAL-CL02. The company explained that follow-up of people receiving sebelipase alfa in LAL-CL02 and LAL-CL03 is ongoing and that there are 2 further ongoing phase II clinical trials of sebelipase alfa for LAL deficiency (LAL-CL06 and LAL-CL08) which are expected to complete in 2017.

4.6 LAL-1-NH01 was a natural history study that retrospectively evaluated data from 35 children with confirmed LAL deficiency presenting before age 2 years (mean age of onset, 1.5 months) at 21 study sites. Diagnosis was from 1985 onwards. The company used a subgroup of 21 children in this study who had growth failure within the first 6 months of life, but who did not have a haematopoietic stem cell transplant or liver transplant, as a historical control for LAL-CL03.

4.7 LAL-CL03 is a single-arm, open-label multicentre study in 9 children aged 2 years or under with rapidly progressive LAL deficiency (defined primarily as growth failure within the first 6 months of life). Median age was less than 1 month at onset of symptoms and 3 months at the start of the study. Children receive sebelipase alfa 1 mg/kg every other week and dose escalation is permitted. Follow-up of children in this study is ongoing.

4.8 The primary outcome in LAL-CL03 was the proportion of babies who survived to 12 months of age. It was assessed in the 'primary efficacy analysis set', which was defined as all patients who received any amount of sebelipase alfa and were 8 months or younger at their first infusion. Six out of 9 babies survived beyond 12 months (67% survival, 95% confidence interval [CI] 30% to 93%). The median age at death for the 3 babies who died before they were 12 months was 2.92 months (range 2.80 to 4.30 months). Results from a later data cut submitted by the company during the evaluation showed 55% survival at 36 months (that is, 5 of the 9 babies survived beyond 3 years of age). The company also highlighted that the babies who survived developed normally and had improved growth and a reduced need for care during the trial. None of the historical control group from LAL-1-NH01 survived past 12 months (the median age at death was 3.00 months).

4.9 LAL-CL02 is a randomised, double-blind, placebo-controlled study in 66 people aged 4 years or older. Median age at symptom onset was 4 years; the median age at randomisation was 13 years. Thirty-six people had 1 mg/kg sebelipase alfa and 30 had placebo every other week for 20 weeks. An open-label follow-up period of up to 130 weeks is ongoing. The duration of each patient's treatment is expected to be at least 78 weeks. The primary outcome in the 'full analysis set' was defined as randomised patients who received any amount of sebelipase alfa or placebo.

4.10 The primary outcome in LAL-CL02 was normalisation of alanine aminotransferase (ALT) levels at week 20 (defined as ALT below the age- and sex-specific upper limit of normal provided by the central laboratory performing the assay). The company assessed ALT levels as a measure of liver injury because of lipid accumulation resulting from LAL deficiency. At 20 weeks, 31% of patients in the sebelipase alfa arm and 7% of patients in the placebo arm had ALT levels within the normal range. The difference between the groups was statistically significant (p=0.0271). The company also submitted results from the open-label period of the study.

After 76 weeks of sebelipase alfa treatment, 98% of patients had reduced ALT and 51% of patients had ALT levels within the normal range.

4.11 Secondary outcomes in LAL-CL02 included relative reduction in low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol, normalisation of aspartate aminotransferase (AST), relative reduction in triglycerides, relative increase in HDL cholesterol, relative reduction in liver fat content, improvement in liver histopathology and relative reduction in liver volume. There were statistically significant improvements favouring sebelipase alfa for all of the secondary outcomes apart from improvement in liver histopathology and reduction in liver volume. The company also submitted longer-term results, which showed that after 52 weeks of sebelipase alfa treatment, 67% of people had regression of liver fibrosis of at least 1 stage and 50% had regression of 2 or more stages (mean improvement in Ishak score of 1.58 points). After 76 weeks, AST and LDL cholesterol levels were 50.7% and 27.5% below baseline respectively and the level of HDL cholesterol was 22.9% above baseline.

Economic evidence

4.12 No published economic studies of LAL deficiency were found. The company adapted a cost–utility Markov model of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NAFLD and NASH; Mahady et al. 2012) to determine the costs and consequences of treatment with sebelipase alfa or best supportive care for people with LAL deficiency. The company stated that NAFLD and its progressive form NASH have a similar pattern of liver disease progression to LAL deficiency (from fibrosis to cirrhosis to hepatocellular carcinoma or liver transplant). However, the company noted that LAL deficiency may progress more rapidly than NAFLD. Although the company acknowledged that in patients with LAL deficiency the condition affects the cardiovascular, gastrointestinal and other systems, it considered it appropriate to focus on modelling liver disease progression because this is often the most prominent effect of the

condition. The model had a cycle length of 1 year, a half-cycle correction, a lifetime time horizon and an NHS and personal social services perspective. The company used a discount rate of 1.5% for costs and health outcomes in the base case because it considered that sebelipase alfa restored people who would otherwise die or had a very severely impaired life to full or near health, which would be sustained over a long period. A discount rate of 3.5% was used in scenario analyses.

4.13 The company's model had 6 health states:

- LAL deficiency without compensated cirrhosis (CC), decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC): This health state included people with LAL deficiency who did not have advanced liver complications. People in this state could have liver fibrosis.
- Compensated cirrhosis: This health state included people with cirrhosis (severe liver scarring) but with enough healthy liver remaining to perform all of its functions.
- Decompensated cirrhosis: This health state included people with cirrhosis with impaired liver function.
- Hepatocellular carcinoma: This is the most common type of liver cancer and may be secondary to liver cirrhosis.
- Liver transplant: It was assumed that patients who had a successful liver transplant would move back to the 'LAL deficiency without CC, DCC or HCC' state, but post-transplant costs and impact on quality of life were not tracked in the model.
- Death.

4.14 The model compared sebelipase alfa with best supportive care for treating LAL deficiency in people of all ages. The modelled cohort reflected the combined populations of LAL-CL02, LAL-CL03 and LAL-1-NH01, the historical control cohort for LAL-CL03. The modelled age when starting treatment was 11 years and the mean starting weight was 42.2 kg. In a scenario analysis the company modelled treatment in babies (reflecting the combined populations of LAL-CL03 and the natural history comparator

cohort) and in children and adults (reflecting the population in LAL-CL02) separately. All were modelled to have lifelong treatment with sebelipase alfa without any stopping rules or adjustment for treatment adherence.

4.15 People started treatment either in the 'LAL deficiency without CC, DCC or HCC' health state or the 'compensated cirrhosis' health state. Because liver biopsies were not routinely done in the clinical trials, the company estimated the proportion of people with cirrhosis when starting treatment using a published method that mapped AST and ALT levels and platelet count to a fibrosis or cirrhosis score called FIB-4 (Sterling, 2006). In its base case, the company assumed that an FIB-4 score of over 1.45 meant that people had compensated cirrhosis. A score lower than this meant that people did not have cirrhosis. In the base case, based on the AST or ALT scores in the combined population from the clinical trials (LAL-CL02, LAL-CL03 and LAL-1-NH01), it was assumed that 84% of people would start treatment in the 'LAL deficiency without CC, DCC or HCC' health state and 16% of people would start treatment in the 'compensated cirrhosis' state. The company assumed that no one with more advanced liver disease would start treatment because these people had been excluded from its clinical trials.

4.16 The company used different approaches to determine transition probabilities between the health states for people having sebelipase alfa or best supportive care. For sebelipase alfa, the company modelled the probability of moving from the 'LAL deficiency without CC, DCC or CC' to the 'compensated cirrhosis' health state based on data collected at baseline and week 20 in LAL-CL02. It noted that no one without cirrhosis at baseline in the sebelipase alfa arm developed cirrhosis by week 20. However, 1 of 4 people (25%) who had cirrhosis at baseline had an improved FIB-4 score (consistent with not having cirrhosis) at week 20. For best supportive care, this transition was calculated using data from the pre-trial period of LAL-CL02 in patients with a known baseline Ishak score (n=32). The company did a survival analysis of time from LAL deficiency onset to earliest mention of confirmed compensated cirrhosis.

The company noted that the FIB-4 results in the placebo-controlled phase of LAL-CL02 showed that no one in the best supportive care arm developed cirrhosis over the trial period using the 1.45 threshold, but argued that other FIB-4 thresholds and liver outcomes measured in the trial showed liver disease progression in the best supportive care arm.

4.17 The company assumed that no one would progress to more advanced liver disease in the sebelipase alfa arm because it considered that the clinical trials had shown that sebelipase alfa stopped disease progression. This meant that people receiving sebelipase alfa stayed in the 'LAL deficiency without CC, DCC or HCC' health state or the 'compensated cirrhosis' health state or moved from the 'compensated cirrhosis' to the 'LAL deficiency without CC, DCC or HCC' health state or died. People in the best supportive care arm progressed through the more advanced liver disease health states and could go on to have a liver transplant. The probabilities of moving between liver disease health states with best supportive care were from Mahady et al.

4.18 Rates of all-cause mortality were based on UK reference tables. Mortality rates associated with decompensated cirrhosis and liver transplant were from Mahady et al. Mortality associated with hepatocellular carcinoma was from Hartwell et al. (2011). The company's model did not include the risk of death associated with other non-liver related complications of LAL deficiency. The company took into account the higher risk of death for people presenting with LAL deficiency in childhood by allowing extra transitions. It assumed that patients under 1 year could die while in the 'LAL deficiency without CC, DCC or HCC' state. All patients under 1 year who received best supportive care died within the first year cycle of the model; the first-year mortality rate for patients receiving sebelipase alfa was 0.33 (based on data from LAL-CL03).

4.19 The company used utility values from Mahady et al. for liver outcomes. These were:

- LAL deficiency without cirrhosis or liver cancer: 0.92
- compensated cirrhosis: 0.82
- decompensated cirrhosis: 0.60
- hepatocellular carcinoma: 0.73
- liver transplant 0.69.

The company did not apply a disutility for caregivers in its modelling because it said there were no data that corresponded to the health states in its model. The company did not identify health state utility values for babies. It therefore assumed that quality of life was 0.25 for babies who die in the first year of life (averaged to a value of 0.07 for a full year, taking into account that babies will not live the full year) and 0.50 for babies who survive their first year. The company did not include disutilities for adverse events because treatment with sebelipase alfa (or placebo) had not negatively affected quality of life in LAL-CL02.

4.20 The list price for sebelipase alfa is £314.30 per mg or £6,286 per 20 mg vial. The company proposed that sebelipase alfa would have been made available with an annual per-patient cost cap (regardless of the dosing regimen used), a discount to the price per mg, and a total budget cap. The level of the caps and the discount are commercial in confidence and cannot be reported here. The company suggested that it may make sebelipase alfa available in 5 mg vials in the future. In its modelling the company assumed that 5 mg vials would cost the same per mg as the 20 mg vials currently available. It said that these 5 mg vials will likely be available from January 2017 but this could not be confirmed. The company used the costs for 20 mg vials in the first year of its model and the costs for 5 mg vials thereafter (this assumption was revised after the second consultation; see section 4.33). The company also assumed the price of sebelipase alfa reduced by 30% after 10 years to account for the potential price reduction after loss of data exclusivity when generic versions may become available (this assumption was also revised after the second consultation; see section 4.33). The dosing regimen for

sebelipase alfa in the model was the same as in the marketing authorisation for sebelipase alfa. As patients aged, they were assumed to gain weight over time using UK growth charts. The company noted that sebelipase alfa may be administered in an outpatient setting or at home. It was assumed in the base case that everyone would get sebelipase alfa in an outpatient setting. The NHS reference costs for administration were £68.66 per infusion. Best supportive care drug costs and costs for treating adverse events were not included in the model.

4.21 The company did not identify published resource costs for LAL deficiency. It used cost data from a UK cost study and an economic evaluation for patients with hepatitis C (Backx 2014; Shepherd 2007) which were inflated to 2014 values using the Office for National Statistics Consumer Price Indices for Health. The company considered its health-state costs to be conservative because children with LAL deficiency may need additional specialist care and because the costs of treating symptoms in organs other than the liver were not included. The company assumed that babies who had treatment with sebelipase alfa and survived would have a 3-month hospital stay; babies who had treatment with best supportive care would stay in hospital for the duration of their lives (3.45 months, based on mean life expectancy in LAL-1-NH01).

4.22 The company presented the modelled survival curves for sebelipase alfa compared with best supportive care for the whole population (the whole modelled cohort) and for babies presenting with LAL deficiency (the infant-only cohort). When applying a discount rate of 1.5% to health benefits, people in the whole modelled cohort receiving best supportive care were modelled to live for 22.08 years on average (providing 19.14 quality-adjusted life years [QALYs]). People receiving sebelipase alfa were modelled to live for 43.24 years (providing 39.73 QALYs). The total costs associated with sebelipase alfa were commercial in confidence and cannot be reported here; the total costs with best supportive care in the base case were £46,748. In sensitivity analyses, factors that had a large impact on the costs and QALYs were the discount rate used (1.5%

or 3.5%) and the methods for estimating the number of people whose liver disease progressed in the sebelipase alfa or best supportive care arm. For the cohort of patients presenting with LAL deficiency as babies, the incremental (undiscounted) life years gained were 54.1 and the incremental QALYs were 28.6. For a cohort of children and adults with LAL deficiency (no babies) based on the LAL-CL02 population, incremental (undiscounted) life years gained were 38.2 and the incremental QALYs were 20.4. The costs of sebelipase alfa and the incremental costs for these subgroups were confidential and cannot be reported here.

4.23 The company estimated that the prevalence of LAL deficiency (the number of people with the condition at any one time) in people presenting with symptoms aged over 1 year in England was 4.38 per million (or 1 per 228,311). For patients presenting aged under 1 year, the company estimated the incidence (the number of new cases of LAL deficiency per year) to be 1.52 per million or (1 per 657,895). The company stated that the incidence and prevalence would be expected to be the same for the population presenting with LAL deficiency before age 1 because life expectancy is less than 1 year in this group. The company assumed that there would be 237 patients with LAL deficiency in the 1 year and over age group in 2016, including between 5 and 8 newly diagnosed patients. The company estimated 1 new patient in the 0–1 year age group per year.

4.24 The budget impact model had the following assumptions:

- **Weight by age and sex (for sebelipase alfa treatment cost).** The company estimated weight by age and sex as in its cost–consequence model, based on the expected weight for age percentile. The age distribution was based on Bernstein et al. (2013).
- **Death rates in the model.** Mortality in babies was based on LAL-CL03 and LAL-1-NH01 (33% in the first year if receiving sebelipase alfa; 100% if receiving best supportive care). For people over 1 year

presenting with symptoms, the company assumed that there was no additional mortality risk associated with LAL deficiency.

- **Diagnosis rate.** This was based on the company's experience with other ultra-rare conditions (including eculizumab for treating paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome). The diagnosis rate was assumed to increase when sebelipase alfa entered the market but remained less than 100%. The company stated that its estimates of diagnosis rates were confidential and cannot be reported here.
- **Treatment rate with sebelipase alfa.** The company assumed that not all people diagnosed as having LAL deficiency would receive sebelipase alfa in clinical practice. The company stated that its estimates of treatment rates were confidential and cannot be reported here.
- **Treatment continuation.** The company noted that dose modifications because of adverse events were uncommon in the sebelipase alfa clinical trials, but the company's experience from other ultra-rare diseases was that some patients may not continue treatment over the long term. The company stated that its estimates of treatment continuation rates were confidential and cannot be reported here.
- **Adherence rates.** The company originally assumed that all babies with LAL deficiency presenting in infancy and 85% of people with LAL deficiency presenting at 1 year or over would adhere to treatment. This assumption was revised after the first consultation (see section 4.32).
- **Drug dose.** The average weekly dose of sebelipase alfa for LAL deficiency presenting in infancy was 2.3 mg/kg in the first year of life (reflecting dose escalation from 1 mg/kg every week to 3 mg/kg every week) and 3 mg/kg every week in subsequent years. The dose for LAL deficiency presenting at 1 year or over was 1 mg/kg. As in the cost–consequence model the company assumed that 5 mg vials would be available in year 2. Therefore less drug wastage was assumed from year 2. This assumption was revised after the second consultation (see section 4.33).

- **Non-drug direct medical costs.** Costs of treating liver complications, hospital stay and administration costs were the same as used in the cost–consequence model.

4.25 In its original analysis, the company estimated the total 5-year net budget impact to be £53,548,573, based on the list price of sebelipase alfa. This estimate increased to £63,866,314 if the company assumed only 20 mg vials were available rather than 5 mg vials. The estimate increased to £82,194,168 by assuming the age distribution of people presenting with LAL deficiency at 1 year or older was the same as in LAL-CL02 rather than as in Bernstein et al., in which people were younger on average.

Evidence review group review

4.26 The ERG commented that 2 of the sebelipase alfa clinical trials were non-comparative and may be subject to bias. It noted that the comparability between LAL-CL03 and the historical control cohort from LAL-1-NH01 was uncertain because of differences in eligibility criteria and the natural history study recruited people earlier (1985 compared with 2010). It stated that most people in LAL-1-NH01 (21 out of 36) were diagnosed before 1995 and it was likely that best supportive care options have since improved. The ERG noted that the average monthly weight gain for 4 patients in LAL-1-NH01 who were diagnosed after 2010 was 0.49 kg, whereas in LAL-CL03 this was 0.34 kg. However, the ERG also noted that monthly weight gain varied widely and there were very few other data to compare the prognosis for patients in each study.

4.27 The ERG noted that there were several outcomes listed in the final scope issued by NICE that were not assessed in the clinical trials (liver synthetic function, liver disease progression, liver transplant and cardiovascular events). The ERG agreed that sebelipase alfa reduced lipid levels, liver fat content and liver enzymes but was unclear how these surrogate outcomes related to key clinical outcomes. In particular, it was uncertain from the original clinical trial data if sebelipase alfa delayed or stopped progression to cirrhosis, hepatocellular carcinoma, need for liver transplant,

cardiovascular events or death. The ERG commented that, across the sebelipase alfa clinical trials, 9 babies had treatment for up to 208 weeks and 8 older patients had treatment for up to 156 weeks, but this was only a fraction of the expected lifelong treatment people in clinical practice would receive. The ERG therefore considered the long-term safety and efficacy profile of sebelipase alfa to be highly uncertain.

4.28 The ERG tested the impact of some of the company's assumptions in the cost–consequence model by doing sensitivity analyses; its main criticisms included:

- Different sources of data were used to determine transition probabilities for people receiving best supportive care or sebelipase alfa. The ERG stated that the company had used pre-trial data from LAL-CL02 to support its modelling assumption that liver disease progressed with best supportive care and data from the randomised phase of LAL-CL02 to support its modelling assumption that liver disease did not progress with sebelipase alfa. The ERG suggested that data from the 20-week randomised phase of LAL-CL02 were not long enough to determine whether liver disease had not progressed and it was inappropriate to use separate sources of data for sebelipase alfa and best supportive care. It further stated that the company's modelled treatment effect on liver disease progression, for sebelipase alfa compared with best supportive care, was not supported by the trial data.
- The ERG considered that the way the company had identified utility values used in its model had not been transparently described. The ERG presented utility data from Crossan et al. (2015). This was a systematic review and cost-effectiveness evaluation of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease. The ERG preferred these utility values:
  - LAL deficiency without cirrhosis or liver cancer: 0.66
  - compensated cirrhosis: 0.55

  - decompensated cirrhosis: 0.49
  - hepatocellular carcinoma: 0.49
  - liver transplant 0.51.
- The ERG also commented that the utility values used in the company's model were higher than those estimated for the general UK population. For example, in the company's model the utility value was 0.92 for 90% of people expected to be alive at age 65, whereas the estimated utility value is 0.78 for a person aged 65 in the UK. In its exploratory analyses, the ERG capped the utility values in the model so that they would not exceed those of the general population. Given there were no data for quality of life in babies, the ERG preferred taking a more conservative approach of assuming that quality of life would be 0.5 for all health states in the first year of life.
- The ERG considered that it was appropriate for the company to present costs and benefits using a 1.5% discount because NICE's guide to the methods of technology appraisal (2013) specifies that this rate may be used when cost-effectiveness results are very sensitive to the discount rate used, as was the case for costs and benefits here. However, the ERG considered it appropriate to also present results using the standard 3.5% discount rate.
- Assuming that the price of sebelipase alfa would reduce by 30% after 10 years because of the presumed availability of generic versions was not appropriate because it is highly uncertain if and when, and at what price, generic versions of sebelipase alfa would enter the market.
- The costs for sebelipase alfa should not be based on using 5 mg vials because they are not yet available.

4.29 The ERG's preferred base case:

- adjusted health-related quality of life to UK population norms
- used the utility values from Crossan et al.

- used the same approach as the company had used for best supportive care to model probability of liver disease progression in both the best supportive care and sebelipase alfa arms
- did not include a price reduction of sebelipase alfa after 10 years and
- assumed continued use of 20 mg vials.

The ERG presented results with both 1.5% and 3.5% discount rates. Sebelipase alfa was associated with no additional QALYs compared with best supportive care. The incremental costs were commercial in confidence and cannot be reported here. The ERG carried out an additional scenario analysis which used its preferred assumptions, but decreased the probability of developing cirrhosis with sebelipase alfa by 50% and increased the probability of cirrhosis improving with sebelipase alfa by 50%. This resulted in incremental QALYs of 1.53 for sebelipase alfa compared with best supportive care.

4.30 The ERG made the following comments on the company's budget impact model:

- The patient number calculations that took into account the incidence and prevalence of mutations in the lysosomal acid lipase gene were not transparent and because of this it could not validate them.
- An annual mortality rate of 100% for babies receiving best supportive care did not appear to have been included in the model.
- It considered that because of lack of data, basing diagnosis, uptake, adherence and treatment continuation rates on experience of other ultra-rare diseases may be appropriate. The ERG stated that how the company had applied its observations with eculizumab to sebelipase alfa was not completely transparent. It further noted that the estimated proportion of patients on sebelipase alfa in the fifth year was half the proportion of people on eculizumab with haemolytic uraemic syndrome.
- The ERG did not consider it appropriate to assume that people would not gain weight after 18 years or that 5 mg vials of sebelipase alfa would be available in the second year.

4.31 The ERG applied a 100% mortality rate for babies and recalculated non-drug costs in the model (£684 instead of £668 for sebelipase alfa and £1,444 instead of £1,699 for best supportive care). This increased the total net budget impact, using the list price, to £63,689,818. The ERG carried out further sensitivity analyses surrounding prevalence and incidence rates in the population aged over 1 year presenting with LAL deficiency. In these analyses it varied these estimates by 50%. The ERG considered that it was highly probable that all diagnosed babies would receive sebelipase alfa, but diagnosis and treatment rates in adults were more uncertain. The ERG carried out sensitivity analyses in which the diagnosis rates and treatment rates were varied by 10 and 20% around the company's base-case assumptions in the population aged over 1 year presenting with LAL deficiency. The results of these analyses ranged between £23,439,245 and £126,845,895 for total 5-year net budget impact. The ERG also carried out sensitivity analyses around treatment adherence and continuation, in which both were set to 100%. It combined this with its sensitivity analyses around diagnosis and treatment rates. The 5-year net budget impact, using the list price, varied between £36,137,359 and £206,367,686. Overall the ERG thought that it was most plausible to increase the company's base-case treatment rates by 10%, the company's diagnosis rates by 20% and to set the continuation and adherence rates to 100%. This resulted in a 5-year net budget impact of £178,527,667.

Response to first consultation

4.32 The MPS Society (a group representing patients with LAL deficiency) stated that it considered the ERG's estimates of patient numbers in the budget impact modelling to be too high. It stated that in England there are:

- 7 babies born in the last 5 years with the rapidly progressive form of LAL deficiency
- 2 paediatric patients

- 16 adult patients (10 of whom were diagnosed when they were children).

The company stated that of 31 patients it knows to have been diagnosed with LAL deficiency in the UK, 11 were receiving sebelipase alfa in an ongoing clinical trial (including 4 people who presented as babies), 1 person was receiving sebelipase alfa through a compassionate use programme and a further 19 people had been diagnosed with LAL deficiency but were not receiving sebelipase alfa. The company expected that all people receiving sebelipase alfa in a clinical trial would continue to do so. Of those 20 patients not in a clinical trial the company estimated that, based on a review of patients in the UK, 11 people would already have fibrosis and be eligible to start treatment. If 22 people received sebelipase alfa, the company estimated a 5-year budget impact of £57 million, using the list price. If all these people continued and adhered to treatment then the 5-year budget impact would be £67 million, using the list price. The company also stated that it asked 6 consultants in metabolic medicine and 2 consultants in paediatric hepatology about the assumptions in the budget impact base case in the company submission. These clinical experts suggested lower rates of future diagnosis and treatment than those in the company base case. Their new estimates resulted in fewer patients who would have sebelipase alfa over the course of 5 years than previously estimated by the company. The company stated that the new estimates of diagnosis and treatment rates were commercial in confidence and cannot be reported here.

Response to second consultation

4.33 The company submitted a revised cost–consequence analysis, with the following changes to the model:

- adjusted health-related quality of life to UK population norms, consistent with the committee's preferred assumptions described in the second evaluation consultation document (the company commented

that this approach, proposed by the ERG, was based on utilities taken from a sample of people aged 45–85 with heart disease)

- removed the assumption that the price of sebelipase alfa would decrease after 10 years
- included only the 20 mg vial in the analysis, given that the 5 mg vial is not yet available.

The company considered that the ERG's utility values (from Crossan et al. see section 4.28) were underestimates for this population, and therefore retained its preferred utility values from Mahady et al. (see section 4.19) for the revised analysis. The company also maintained its view that sebelipase alfa meets the criteria for applying a 1.5% discount rate (see section 4.12) and therefore used this in the revised base case (although a 3.5% discount rate was presented in a scenario analysis). The company presented results for the whole population and separate results for people presenting as babies (the infant-only cohort), people presenting as children or adults, and for a population consistent with the proposed managed access agreement (see section 4.37). In the revised base-case analysis for the population consistent with the managed access agreement, sebelipase alfa was associated with an additional 21.4 QALYs compared with best supportive care. The total and incremental costs associated with sebelipase alfa were commercial in confidence and cannot be reported here.

4.34 The company also presented a revised budget impact analysis. This analysis updated estimates for the number of people having sebelipase alfa consistent with the proposed managed access agreement (see section 4.37). The number of people for whom sebelipase alfa treatment would be indicated according to the managed access agreement criteria was confidential and cannot be reported here. The results of the revised budget impact model showed a 5-year net budget impact for sebelipase alfa of £59 million (including the proposed per-patient cost cap). The proposed per-mg price discount and total budget impact cap were confidential and cannot be reported here.

4.35 The ERG provided a critique of the company's revised cost–consequence analysis and estimates of patient numbers. It disagreed with the company's claim that the ERG's utility adjustment reflects the health-related quality of life of patients aged 45–85 with heart disease.

4.36 Further comments were received from patient and carer groups, patient and clinical experts, and members of the public. The comments emphasised that sebelipase alfa has a positive effect on burden of disease, life expectancy and quality of life. They also reiterated that sebelipase alfa is a life-saving treatment for babies with LAL deficiency, for whom there is no alternative. Patient and carer groups, along with clinical experts, confirmed that they were involved in the discussions and design of the proposed managed access agreement (see section 4.37) and therefore fully supported the company's proposals. They also found that there were 25 patients with LAL deficiency in England (7 children and 18 adults) at specialist centres, of whom 23 at most would be eligible for treatment with sebelipase alfa under the managed access criteria. Members of the public noted that making sebelipase alfa available to patients may help reduce uncertainty about its long-term benefits.

Managed access agreement

4.37 The company proposed a managed access agreement, which it revised after feedback from the committee in the second evaluation consultation document. The revised agreement was developed together with patient and carer groups along with clinical experts and it was proposed to last 5 years, and defined criteria for starting and stopping sebelipase alfa treatment and for monitoring and collecting data:

- **Starting criteria**: The managed access agreement specified that all babies presenting with LAL deficiency aged under 1 year would start treatment with sebelipase alfa. Sebelipase alfa would also be considered for people who present with LAL deficiency aged 1–18 years with malabsorption, hepatomegaly with persistently elevated transaminases, signs of liver fibrosis (defined by an Ishak score of at

least 1) or signs of liver dysfunction, and for people who present with LAL deficiency aged over 18 years with liver fibrosis (defined by an Ishak score of at least 3). Sebelipase alfa would not be considered for adults with a functioning liver transplant.

- **Stopping criteria**: The company noted that the minimum treatment period for defining response has not been determined. It proposed that lifelong therapy is likely to be needed unless the disease does not respond to therapy. This is defined as: persistent failure to thrive or progression to liver failure (babies under 1 year), not crossing an upwards centile line (children with malabsorption), an increase in spleen volume of greater than 10% or progressive liver disease (children over 1 year and adults). Treatment would also be stopped if the person does not attend clinics or has a liver transplant.
- **Monitoring and collecting data**: The managed access agreement specified that data would be collected from everyone having sebelipase alfa within the managed access agreement. The data would normally be recorded in the company's global LAL deficiency registry. This collects data on the progression of LAL deficiency, the progression of liver and cardiovascular diseases, changes in anthropometric assessments, the long-term effectiveness and safety of sebelipase alfa and other therapeutic interventions, and the effects of sebelipase alfa on other patient populations for whom limited information is available. The managed access agreement specified a number of clinical assessments to be completed at baseline and every 6 or 12 months, including liver function, liver and spleen volume, liver fibrosis, cardiovascular assessments and quality of life. The company stated that NHS England will be provided with relevant data extracts from the registry database to assess sebelipase alfa.

4.38 Full details of all the evidence are in the submissions received for this evaluation, and in the ERG report, which are all available in the committee papers.

5 Consideration of the evidence

The evaluation committee reviewed the data available on the benefits and costs of sebelipase alfa, having considered evidence on the nature of lysosomal acid lipase (LAL) deficiency and the value placed on the benefits of sebelipase alfa by people with the condition, those who represent them, and clinical experts. It also took into account the value for money that sebelipase alfa represents and the effective use of resources for specialised commissioning.

Nature of the condition

5.1 The committee discussed the natural history of LAL deficiency. It noted that LAL deficiency with symptoms presenting in babies under 6 months was typically rapidly progressive. It heard that symptoms included pain, poor feeding, growth failure and severe hepatic disease, and were associated with a very short life expectancy of less than a year. Conversely, the committee heard that the natural history, and particularly the rate of symptom progression, was highly variable in people presenting with symptoms of LAL deficiency later in childhood or adulthood. The committee heard that the possible long-term effects of LAL deficiency included liver cirrhosis and liver failure (clinical features that are shared with non-alcoholic steatohepatitis [NASH]). The clinical experts explained that the type of lipid dysregulation seen in people with LAL deficiency would be expected to be a risk factor for cardiovascular disease, but the long-term cardiovascular effects of LAL deficiency have not been established. The clinical experts stated that a person's genotype or presenting symptoms did not predict the rate of disease progression. The committee concluded that the severity of symptoms varied widely in people with LAL deficiency. It further concluded that although the rate of disease progression was rapid when symptoms started in babies under 6 months, in people presenting with symptoms later in life the rate of progression was more variable.

5.2 The committee heard from patients and carers about their experiences of living with LAL deficiency. It heard about the extreme distress to parents of having a child with the symptoms of LAL deficiency without an effective treatment option and of losing a child to LAL deficiency. The committee heard about the impact of the symptoms on older patients and how the pain and nausea affected their ability to take part in everyday activities including work and the impact on their quality of life. The committee discussed whether patient experience would vary because it heard that the course of the disease in people who did not present with rapidly progressive LAL deficiency before 6 months varied widely. The committee noted that the patient experts had taken part in, or had a child who had taken part in, the sebelipase alfa trials. As such, the committee considered that their perspectives may represent those of a population with more severe LAL deficiency because not all people need treatment (see section 5.3). The committee concluded that LAL deficiency had a very large impact on some patients with the condition, but it was unclear about the quality-of-life impact of symptoms of less severe forms of LAL deficiency.

5.3 The committee asked the clinical experts whether all people with LAL deficiency would benefit from treatment with sebelipase alfa. The clinical experts stated that all babies presenting with symptoms before 6 months needed sebelipase alfa because it is the only treatment that can prevent early death. However, the committee heard that treatment would not routinely be offered to older patients whose symptoms are less severe and whose condition is less rapidly progressive. The clinical experts explained that the presence of fibrosis would indicate a need for treatment and that a review of published case reports of people with LAL deficiency suggested that around 80% had fibrosis. The committee noted that such a review may be subject to bias (that is, it may overestimate the proportion of people with fibrosis at diagnosis) because case reports would be likely to report on people with more severe LAL deficiency with complications needing diagnosis and treatment. The committee stated it was not

possible to determine the extent of the potential bias. The clinical experts stated that they would not start treatment with sebelipase alfa in people who had other explanations for liver disease, such as alcohol misuse or obesity. Also the clinical experts stated that they would not offer sebelipase alfa to people who had received a liver transplant or who had cardiovascular complications without significant liver disease because there were no data on the efficacy of sebelipase alfa in these people. The committee concluded that if sebelipase alfa were available in clinical practice in England, it would be offered to all babies diagnosed with LAL deficiency, but that treatment in older people would only be started when evidence of significant liver disease is present.

Impact of the new technology

5.4 The committee acknowledged the patient experts' view that sebelipase alfa offered a lifeline for babies presenting with rapidly progressive LAL deficiency. It also noted the views of patient experts with symptoms starting later in life; how sebelipase alfa had stopped their symptoms, enabled them to do day-to-day activities again and restored their quality of life. The committee heard from the clinical experts that because sebelipase alfa is the first therapy that specifically targets the underlying cause of LAL deficiency, they considered it to be a step change in managing the condition.

5.5 The committee discussed the evidence for the efficacy of sebelipase alfa for babies presenting before 6 months with rapidly progressive LAL deficiency. It noted that the company had compared 12-month death rates from the single arm study LAL-CL03 with data from a historical control. It also noted that the evidence review group considered that people receiving best supportive care in the past potentially may have had poorer outcomes than people receiving best supportive care now because of changes in available treatments over time. The clinical experts stated that any changes in best supportive care had not improved survival in this patient population. The committee noted that no one receiving best

supportive care in the historical cohort survived past 12 months whereas two-thirds of the babies in the sebelipase alfa trial had survived past 12 months. The committee further considered the patient submissions which reported that, with continued use of sebelipase alfa beyond 12 months, children had shown improved feeding and growth and were meeting developmental milestones. The committee also considered the longer-term results, which showed that 5 out of 9 babies survived past 3 years (see section 4.8). It heard from the clinical and patient experts that this evidence was compelling. The committee noted that the oldest child in LAL-CL03 is now 6 years old and is doing well. The committee considered that the clinical trial evidence suggested that sebelipase alfa was effective for treating rapidly progressive disease in babies presenting before 6 months. It was reassured that the evidence collected with follow-up for up to 6 years reduced some of the uncertainty about the duration of the treatment benefits, although it highlighted that this is still a relatively short period for a potentially lifelong treatment. Furthermore, because numbers were small and because no robust comparative data were available, the committee was unable to determine the variability in response to treatment, whether the response could be maintained and whether it was sufficient to prevent long-term complications of LAL deficiency and fully restore life expectancy. It concluded that sebelipase alfa is a potentially life-saving treatment for some babies with rapidly progressive LAL deficiency, but that there are still important uncertainties about the proportion of babies whose disease would respond and the long-term benefits of treatment.

5.6 The committee discussed the evidence for the efficacy of sebelipase alfa for children and adults who did not present with rapidly progressive LAL deficiency before 6 months. It noted that the randomised control period of LAL-CL02 was 20 weeks. In this study a number of biochemical markers were measured (including alanine aminotransferase [ALT] and aspartate transaminase [AST], lipids and lipoproteins). The committee agreed that there was a response to sebelipase alfa over 20 weeks in these markers.

The committee discussed the relationship between raised ALT and AST levels and liver fibrosis. It noted that liver damage was associated with raised ALT and AST in most, but not all, conditions affecting the liver. The committee noted that direct measurement of liver damage by biopsy was more robust. However, it accepted that repeated biopsies were not feasible in the clinical trial and are not always acceptable to patients. Biopsies in children are particularly challenging because they need general anaesthetic. Nevertheless, the committee was reassured that the available evidence after 52 weeks of sebelipase alfa treatment (see section 4.11) showed regression of liver fibrosis in 67% of patients, and it heard from the clinical and patient experts that this improvement was compelling. The committee noted that sebelipase alfa improved patients' lipid profiles, but noted it was unclear how this related to long-term clinical outcomes such as loss of liver function, the need for a liver transplant or future cardiovascular disease. The committee concluded that the clinical trial evidence showed that sebelipase alfa had a positive effect in the short term on biochemical markers of liver disease, and appeared to stabilise or improve liver fibrosis, in children and adults who did not present with rapidly progressive LAL deficiency before 6 months. It also concluded that the additional results from the open-label period of LAL-CL02 reduced some of the uncertainty around the effectiveness of sebelipase alfa over 1 to 2 years. However, the committee remained uncertain about how sebelipase alfa would affect long-term clinical outcomes and was unconvinced that the evidence showed that sebelipase alfa fully addressed LAL deficiency and that the treatment effect would be maintained.

5.7 The committee discussed the potential of sebelipase alfa as a 'bridging therapy' in the treatment pathway for LAL deficiency. The committee noted that a clinical expert's evidence submission raised the possibility of using sebelipase alfa to stabilise LAL deficiency presenting in babies under 6 months before offering a haematopoietic stem cell transplant (HSCT). The committee noted that HSCT has the potential to treat

conditions in which people have an enzyme deficiency, and avoids the lifelong need for regular infusions, but that the procedure is associated with morbidity and mortality. The committee understood that before the availability of sebelipase alfa, HSCT had been tried in babies with LAL deficiency, but had limited success. Early death was not prevented, perhaps because the babies were too unwell at diagnosis. A committee member with relevant expertise commented that survival after HSCT for other conditions affecting babies has increased in recent years. However, the committee agreed that the effectiveness of HSCT for babies with LAL deficiency who had been stabilised on sebelipase alfa was unknown. The committee proposed a research recommendation to compare the benefits of long-term treatment with sebelipase alfa with shorter-term treatment with sebelipase alfa ('bridging therapy') followed by HSCT with curative intent for people with rapidly progressive LAL deficiency which presented when they were babies. Responses to consultation emphasised the practical difficulties of studying this mode of treatment. The committee heard that patients, carers and clinicians would be unwilling to stop an effective treatment to switch to a treatment which has not been shown to be effective and carries a high risk of morbidity and mortality. This would make recruiting to a trial to assess HSCT after sebelipase alfa difficult, even if this was the sole route to access the treatment under NICE recommendations. The committee concluded that it was not possible to make a recommendation for research into the use of sebelipase alfa as a bridging therapy before HSCT.

5.8 The committee noted that the marketing authorisation for sebelipase alfa states that the dosage for babies under 6 months with rapidly progressive LAL deficiency is 1 mg/kg once weekly with dose escalation up to 3 mg/kg considered based on clinical response. However, the committee noted that in LAL-CL03 dose escalation to 5 mg/kg was permitted when there was an inadequate response and neutralising antibodies were present. The committee heard from clinical experts in their submission that they felt strongly that the initial starting dosage of sebelipase alfa for babies

presenting with rapidly progressive LAL deficiency should be 3 mg/kg weekly, with escalation to 5 mg/kg if there is inadequate response. The committee heard from a clinical expert that in his experience, approximately 50% of babies were on a 3 mg/kg dose of sebelipase alfa and 50% were on a 5 mg/kg dose. The committee heard from the company that it is carrying out a clinical trial of the 5 mg/kg dose, but data from this trial are not yet available. The company stated in its submission to NICE that it only included clinical data from babies receiving the dosage stated in the marketing authorisation. The company also noted that it took into account that babies in LAL-CL03 had their dose escalated to 3 mg/kg over the trial period when estimating costs in its economic analyses. The committee further heard that the clinical experts would also consider, in some instances, dose escalation up to 3 mg/kg in some children whose symptoms presented after 6 months and whose LAL deficiency did not respond to the lower dose. The committee reaffirmed that its recommendations could only apply to the dosage covered by the marketing authorisation for sebelipase alfa unless it was directed by the Department of Health to make recommendations for the technology outside the terms of its marketing authorisation. However, the committee stated that it could consider evidence on the use of sebelipase alfa outside the terms of its marketing authorisation to inform discussions about its licensed use.

Proposed managed access agreement

5.9 The committee noted that, alongside its consultation responses, the company had submitted a revised proposal for a managed access agreement that had been updated after feedback from the committee in the second evaluation consultation document. The committee recognised that the managed access agreement was developed together with clinical and patient expert organisations. The committee discussed the content of the managed access agreement, given its advice to the company on what it would expect of a complete managed access agreement for sebelipase alfa. It recalled that the typical elements of a managed access agreement

would include starting and stopping criteria, mechanisms to manage the financial risk to the NHS, alongside collecting meaningful data to support a review of the technology at the end of the managed access agreement. The committee noted the company's financial proposals (the per-patient cost cap, per-mg price discount and total budget impact cap), and discussed these as part of its considerations on the cost to the NHS and personal social services and value for money (see sections 5.12, 5.15 and 5.16). It also noted the fixed duration of the agreement. The committee considered the proposals about who would start and stop treatment with sebelipase alfa and the proposed registry data to be collected to address uncertainties in the long-term clinical effectiveness of sebelipase alfa (see section 4.37).

5.10 The committee agreed that the population who would be eligible to start and stop treatment with sebelipase alfa in the revised managed access agreement was covered by the sebelipase alfa marketing authorisation. It further considered whether the managed access proposal reflected the population expected to receive treatment in clinical practice based on its discussions of the clinical effectiveness, value for money and budget impact evidence for sebelipase alfa. The committee considered that the statement in the managed access agreement that all babies under 1 year presenting with LAL deficiency and people over 18 years with LAL deficiency and liver fibrosis (with an Ishak score equal to or higher than 3) would start treatment with sebelipase alfa reflected the clinical experts' preferences. It noted that the criteria for starting treatment in people presenting between 1 and 18 years were based on whether the person had malabsorption, hepatomegaly, liver fibrosis or liver dysfunction. The committee noted that the revised managed access proposal did not allow people to restart treatment with sebelipase alfa. It concluded that the population for whom sebelipase alfa would be considered within the revised managed access agreement was identified more objectively than in the initial proposals. The committee acknowledged that the starting and stopping criteria would restrict the number of eligible patients and

therefore limit the overall budget impact. However, it still had some concerns that it had not been provided with sufficient justification as to how the criteria would ensure that, in light of the heterogeneous patient population with LAL deficiency and the weak evidence base, the population would be restricted to only people who would gain most benefit from sebelipase alfa treatment, and that none of those who would gain most benefit would be excluded from treatment.

5.11 The committee discussed the proposed follow-up, monitoring and data collection criteria in the proposed managed access agreement. It noted that the outcomes to be measured included clinical outcomes, surrogate measures for clinical outcomes and quality-of-life measurements. The committee noted that in children under 18 years there were no direct measures of liver damage in the outcomes listed. The committee stated that non-invasive measures of liver damage (which do not involve a biopsy) are available and that measuring definite clinical outcomes rather than surrogate markers was preferable. The committee explored the measures of quality of life that were included in the data collection proposal. It heard from the company that currently there is no quality-of-life measure available which has been specifically designed to capture the experiences of people with LAL deficiency. Therefore the company included generic quality-of-life questionnaires in the revised proposed managed access agreement; the SF-36 for the adult population and paediatric-specific measures for babies and children. The committee expressed concern that the quality-of-life measures would not fully capture the quality of life and experiences of people with LAL deficiency. It also said that it would have preferred the company to submit a detailed data collection protocol and analysis plan, to more fully explore the long-term effects of sebelipase alfa treatment. The committee considered that although the quality-of-life measures included in the managed access proposal were appropriate, the clinical outcome measures chosen were not the most relevant for capturing the clinical effectiveness of sebelipase alfa in preventing long-term complications of LAL deficiency across the

whole population. It concluded that the data collection and monitoring plan proposed in the managed access agreement was not sufficiently detailed and had a number of important limitations.

Cost to the NHS and personal social services

5.12 The committee discussed the costs of treatment with sebelipase alfa in the company's submission. It noted that the company estimated an annual cost of treatment, based on the list price, of £491,992 for an 11 year old. The company proposed a cap on the annual cost per patient and a discount to the price per mg; the level of discount and cap are commercial-in-confidence and cannot be reported here. The committee highlighted that the dosage of sebelipase alfa was based on a person's weight. Therefore, the treatment costs would be significantly higher for young people and adults with LAL deficiency than for children, and would increase with time for those diagnosed in childhood. The committee noted that for the population presenting with rapidly progressive LAL deficiency as babies, the company had estimated the costs based on the dosage used for this population in the clinical trial (that is 3 mg/kg, following a period of dose escalation from 1 mg/kg). The committee recalled that it had heard from the clinical experts that they would be likely to use even higher doses in clinical practice, which would increase the costs of sebelipase alfa in that group (see section 5.8). The committee was aware that if some people needed dose escalation above the licensed dose in clinical practice then the annual cost of treatment would be higher than for people receiving the licensed dose. However, it heard from the company that if the dose were escalated above the licensed dose, the annual cost cap would limit the additional costs to the NHS. The committee concluded that the average annual cost of treatment calculated by the company for the population likely to receive sebelipase alfa may underestimate the actual cost in clinical practice, although this may be offset by the proposed cost cap. The committee welcomed the additional discount to the price per mg of sebelipase alfa proposed by the company, but concluded that, because of the annual cost cap, the effect of this discount was small.

5.13 The committee considered the assumptions in the company's budget impact analysis for diagnosis, treatment rates and adherence. It was aware that several of the parameters were the same as those in the company's cost–consequence model, and therefore the same limitations applied (see 'Value for money' section).

- It noted the company's assumption that not all patients with LAL deficiency would be diagnosed in clinical practice. It was aware that the clinical experts agreed with this assumption.
- The committee heard from the clinical experts that all babies diagnosed with LAL deficiency before 6 months would have sebelipase alfa because it is the only active treatment available, and so considered this assumption reasonable. The committee also considered it was reasonable to assume that not all people with less severe symptoms of LAL deficiency would have sebelipase alfa and that treatment would only likely be started in clinical practice for people with liver fibrosis. It noted that the proportion of people with liver fibrosis was estimated by the clinical experts to be around 80%, although this figure may be an overestimate (see section 5.3).
- The committee accepted that it would be likely that all parents or carers of babies with LAL deficiency would adhere to the treatment regimen for their child. It considered that the assumption that 100% of people presenting with LAL deficiency after 1 year of age would adhere to treatment was appropriate.

The committee noted that the budget impact of sebelipase alfa was very sensitive to rates of diagnosis, uptake and treatment continuation.

5.14 In light of its consideration of the assumptions in the budget impact model, the committee discussed the estimated number of people who would have sebelipase alfa. The clinical expert at the second committee meeting stated that experience in recruiting for sebelipase alfa clinical trials suggested that the number of people diagnosed and offered sebelipase alfa over the next 5 years was likely to be closer to the current number of

people diagnosed with LAL deficiency than the number of people predicted by gene mutation studies. The committee accepted that in the next 5 years the number of people receiving sebelipase alfa was not expected to increase greatly, but it noted the potential for genetic screening for lysosomal storage disorders to identify a greater number in the future. The committee was aware that the patient group had identified 25 people with LAL deficiency in specialised care in England (see section 4.36), and that the company had revised its population estimates based on surveys of specialist centres with input from the patient group. It noted that the revised estimates also took into account the criteria in the managed access agreement. The committee accepted that the number of patients in England was more objectively estimated in the revised budget impact analysis than it was in the previous version. It noted that although the eligibility criteria for the revised managed access agreement were more restrictive than the previous proposal, and fewer patients were included, the estimated budget impact was greater. It understood that this was because it was predicted that more babies would have treatment, and the cost of treatment is higher because of the higher dosage permitted in this group. The committee concluded that the 5-year net budget impact, as presented by the company in its revised analysis and including the proposed cost cap and price per mg discount, is likely to be an accurate estimate.

5.15 The committee discussed the total budget impact cap proposed by the company; the level of this cap was confidential and cannot be reported here. The committee noted that the proposed cap provided greater certainty of the budget impact for sebelipase alfa and removed the risk that the NHS would incur unexpected additional costs; the committee welcomed this. The committee was aware that the benefits of the cap in providing certainty would be substantially reduced if it were to consider making recommendations for only a subgroup of the managed access agreement population.

Value for money

5.16 The committee discussed the structure of the cost–consequence model, noting that it was based on an economic model for non-alcoholic steatohepatitis (NASH). It heard from the clinical experts that both LAL deficiency and NASH were associated with progressive liver fibrosis and cirrhosis and some patients would need a liver transplant. The committee asked whether the rate of liver disease progression would be the same for the 2 diseases. The committee heard from the company that it expected liver disease progression to be more rapid in LAL deficiency, but no data were available to validate this. The clinical experts stated that in LAL deficiency there is much greater variability in the rate of liver disease progression compared with NASH. The committee noted that in the model some people could develop hepatocellular carcinoma. The clinical experts stated that they were unaware of any cases of hepatocellular carcinoma in people with LAL deficiency but this could be because the condition is rare. The committee noted that costs after a liver transplant and the impact of a liver transplant on quality of life had not been included in the model. It heard from the company that this was a conservative assumption in its modelling because the company considered that more people on best supportive care would need a liver transplant than with sebelipase alfa. The committee concluded that the structure of the model was broadly appropriate, but it was unclear whether the modelling captured the variability of liver disease progression in LAL deficiency.

5.17 The committee noted that without long-term data on clinical outcomes, the company had assumed in its modelling that sebelipase alfa would prevent further liver disease progression. It further noted the ERG's view that there were no data from the trials supporting a difference in liver disease progression between people having best supportive care or sebelipase alfa and that the transition probabilities used in the model should be the same for sebelipase alfa and best supportive care. The committee considered the ERG scenario to be extremely conservative. The committee considered that the evidence from the trials (including the

longer-term results after 52–76 weeks of treatment; see sections 4.10 and 4.11) and statements from the patient experts showed that sebelipase alfa has a treatment effect, and the ERG scenario was not plausible. The committee heard from clinical experts that if a person's disease progression was stabilised at the point they had cirrhosis but without significant loss of liver function then the person would be expected to have near-normal quality of life and a good prognosis. It equally considered that there was limited evidence to validate the company's initial assumption that sebelipase alfa would completely stop further disease progression; it considered that the longer-term results reduced some of the uncertainty around this assumption, but it was still not convinced that the assumption made by the company was reasonable.

5.18 The committee noted that the utility values used by the company for liver disease health states in the cost–consequence model were not calculated from quality-of-life data collected from people with LAL deficiency, but were those that had been used by Mahady et al. in modelling NASH and were mostly based on data collected from people with chronic liver disease (cirrhosis, decompensated liver disease and hepatocellular carcinoma). The committee agreed with the ERG that some of the utility values used by the company for children and adults with LAL deficiency were higher than the age-dependent UK population values for people without a chronic health condition, and as such were implausible. The utility values also did not reflect patients' accounts of how LAL deficiency negatively affected their quality of life. The committee noted that the ERG had suggested using utility values from Crossan et al., in which quality-of-life data from people with hepatitis C were collected. The Crossan et al. utility values were lower than those in the company base case. The committee heard the company's concerns that some of the people in the Crossan study had become infected with hepatitis C because of intravenous drug use and may have physical or psychological comorbidities which could affect their quality of life. It heard that the company considered that the ERG's suggested utility values were

inconsistent and were underestimates for the model population, and noted the company's example that the highest utility value used in the ERG's analysis (0.66) was the same as the quality of life of a 100-year-old person in the general UK population. The committee was aware that some EQ-5D data were presented in the company submission from the European LAL deficiency patient and carer survey, although they were not suitable to estimate reliable utility values. The committee concluded that there were issues with the utility values identified by both the company and ERG because they had not been derived from people with LAL deficiency. It also considered that the company's utility values might be overestimates of the true utility values, and the ERG's values might be underestimates. It concluded that the true utility values were likely to be closer to the ERG's values because it was unlikely that people with LAL deficiency had a better quality of life than age-matched people without a chronic condition.

5.19 The committee discussed 2 of the assumptions about the future costs of sebelipase alfa in the company's original analysis:

- The price of sebelipase alfa would drop by 30% after 10 years because of the potential availability of generic or biosimilar versions of sebelipase alfa after expiry of the sebelipase alfa patent.
- There would be a reduction in drug wastage and associated costs after 2017 because of the availability of 5 mg vials of sebelipase alfa.

The committee stated that it had not previously considered price reductions resulting from the potential introduction of generics or biosimilars because this is speculative and the impact of their introduction is unknown. Similarly, the committee considered that although it acknowledged 5 mg vials were in development, it had to make its decisions based on the costs of sebelipase alfa available now. The committee noted that the company removed these assumptions in the revised cost–consequence model. The committee concluded that the price reduction after 10 years and the use of 5 mg vials were both

inappropriate assumptions, and therefore that the company's revised analysis was appropriate.

5.20 The committee discussed the most appropriate discount rate used for costs and health effects. The committee understood from the company's sensitivity analyses that the results of the company's cost–consequence analysis were sensitive to the discount rate. The committee was aware from NICE's guide to the methods of technology appraisal (2013) that a non-reference case discount rate of 1.5% for costs and benefits may be considered by the committee if, based on the evidence presented, the long-term health benefits are very likely to be achieved. Further, the committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs. The committee noted that although sebelipase alfa did extend life expectancy for babies presenting with rapidly progressive LAL deficiency, it was unclear whether their life expectancy would be restored to near normal. The committee recognised that some people presenting with LAL deficiency later in life would also have reduced life expectancy because of the complications of LAL deficiency. Also, the committee emphasised that the long-term benefits of sebelipase alfa were highly uncertain. It recalled that it was unable to determine the variability in response, whether the treatment effect was maintained and how sebelipase alfa affected long-term clinical outcomes including complications of LAL deficiency and life expectancy (see sections 5.5 and 5.6). The committee considered that it was not convinced that the long-term health benefits of sebelipase alfa treatment were likely to be achieved. Therefore the committee did not consider that there was a strong case for using a 1.5% discount rate. It concluded that it was more appropriate for the company to include the standard 3.5% discount rate in its base case.

5.21 The committee noted that its preferred modelling assumptions (see sections 5.16–5.21) were:

- including the ERG's adjustment of health-related quality of life to UK population values and the ERG's preferred utility values
- including the company's treatment effect for sebelipase alfa in its transition probabilities (noting its concerns about whether this represented the true treatment effect for sebelipase alfa)
- no price reduction of sebelipase alfa after 10 years
- continued use of 20 mg vials
- a 3.5% discount rate applied to costs and health benefits.

Therefore, in the committee's preferred analysis, sebelipase alfa was associated with a total quality-adjusted life year (QALY) gain of 17.15, compared with 10.52 QALYs for best supportive care (incremental QALY gain of 6.64; probabilistic result). The total and incremental costs associated with sebelipase alfa were considered commercial in confidence by the company, and cannot be reported here. The committee emphasised that the incremental QALY gain strongly depended on the assumption that sebelipase alfa completely halted disease progression, and this assumption was uncertain (see section 5.17). The committee concluded that there was the potential for an incremental QALY gain of up to 6.64 associated with sebelipase alfa treatment, but that this was very uncertain.

5.22 The committee considered the overall value for money provided by sebelipase alfa. It was aware that NHS England has a single budget for specialised services of £13 billion, which includes a budget of £156 million for high-cost drugs. It then discussed the overall value of sebelipase alfa, taking into account both its health benefits (the range of estimates presented by the company and ERG was between 0 and 21.4 additional QALYs, and the committee's preferred estimate was up to 6.64 additional QALYs) and associated costs, in the context of other highly specialised technologies:

- It recalled that NICE's highly specialised technology guidance on eculizumab for treating atypical haemolytic uraemic syndrome stated

that eculizumab produced incremental QALY gains when compared with standard care (estimated to be 25.22 by the company and 10.14 by the ERG). The committee also recalled that the incremental costs for eculizumab compared with standard care were considerable; these are commercial in confidence and cannot be reported here. NICE estimated an annual cost per patient for eculizumab of £211,000 to £340,000 using the list price for eculizumab.

- It recalled that NICE's highly specialised technology guidance on elosulfase alfa for treating mucopolysaccharidosis type IVa stated that elosulfase alfa produced incremental QALY gains when compared with standard care (estimated to be 18.18 by the company and 10.03 by the ERG). NICE estimated an annual cost of £394,680 per patient using the list price for elosulfase alfa (the annual cost per patient to the NHS for elosulfase alfa is lower than that estimated by NICE because elosulfase alfa has a patient access scheme, which provides it at a discounted cost; this patient access scheme and the associated incremental costs are commercial in confidence and cannot be reported here). Elosulfase alfa also has a managed access agreement, which contains additional confidential commercial arrangements that further reduce the cost to NHS England.

After considering the company's revised model, the committee noted that the incremental costs for sebelipase alfa were higher than those for eculizumab and elosulfase alfa. Furthermore, although the company's estimated incremental QALY gains (21.4) for sebelipase alfa were similar to those for the other technologies, the committee considered that the actual incremental QALY gain would be lower (6.64 according to the committee's preferred assumptions). In addition, there was an extremely high degree of uncertainty surrounding the QALY estimates for sebelipase alfa depending on the extent and duration of the treatment effect on liver pathology and its influence on long-term clinical outcomes. The committee noted that the long-term benefits of sebelipase alfa were uncertain because of the limited data available. It heard from clinical and patient

experts that this was common to most highly specialised technologies because of the rarity of the conditions and the difficulties in carrying out clinical trials and analyses in small populations. The committee considered that, even based on more optimistic assumptions of long-term treatment effect, the cost of sebelipase alfa would be very high, and that it would be higher relative to treatment benefits than the committee had previously regarded as acceptable. The committee was unconvinced that sebelipase alfa represented overall good value for money to the NHS.

5.23 The committee discussed whether there were any subgroups of people for whom sebelipase alfa could be considered to offer greater value for money to the NHS than the population eligible under the managed access agreement. It noted in particular the comments received from the patient experts and from consultation, which stated that, for babies with rapidly progressive LAL deficiency, sebelipase alfa is the only treatment option that may allow them to live beyond 1 year. The committee noted that the company had presented an analysis in which it assessed the costs and benefits for babies with rapidly progressive LAL deficiency only (see section 4.22). The committee noted that this group had greater incremental QALYs than the whole population, but the incremental costs were also higher. It considered that when the proposed cost cap and price discount were included, the balance between the QALYs gained with sebelipase alfa and the additional cost for this subgroup improved. However, the committee was aware that costs for sebelipase alfa in this group were still very high, and was not convinced that the benefits of treatment were sufficient to justify these very high costs, especially considering that there was limited information about the benefits of sebelipase alfa in this population over the longer term of the lifelong treatment period. The committee therefore concluded that although sebelipase alfa is a potentially life-saving treatment for babies with rapidly progressive LAL deficiency and there is a compelling clinical need for these patients, the benefits of treatment were uncertain and the cost was too high for these benefits.

5.24 The committee was also aware that in the rest of the population covered by the company's economic model (that is, children and adults without rapidly progressive disease), the clinical need for sebelipase alfa was more variable, and the balance between costs and QALYs gained was not better than for the whole population combined. Therefore, consistent with its conclusion for the whole population (see section 5.22), the committee further concluded that sebelipase alfa could not be considered good value for money in this group.

5.25 The committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when evaluating sebelipase alfa. The committee noted NICE's position statement about this, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this evaluation of sebelipase alfa. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the value for money offered by sebelipase alfa.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

5.26 The committee considered the potential wider societal benefits of sebelipase alfa treatment proposed by the company and the patient experts. It understood from the patient experts that sebelipase alfa improves the general health and functioning of people with LAL deficiency. Because it extends life in babies with the rapidly progressive form of the condition, it would enable children with the condition to be educated. For adults with the condition and carers of people with the condition, it would enable them to work or perhaps work for longer and take part in social activities. The committee also appreciated that

sebelipase alfa may reduce the need for parents and carers to visit their child in intensive care and may remove the need for a liver transplant. The committee recognised that patients need to travel to receive their infusions with sebelipase alfa and this has an effect on costs and time. However, these are expected to be lower if sebelipase alfa is available within a homecare arrangement. On balance, the committee agreed that there would be cost savings and benefits with sebelipase alfa incurred outside the NHS and personal social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies.

Conclusion

5.27 The committee recognised that LAL deficiency is a serious and rare condition, which has a major impact on some people with the condition, and that currently there are no options available for the treatment of LAL deficiency. It considered that sebelipase alfa provided clinical benefits for people with LAL deficiency compared with best supportive care, and was potentially life-saving for babies with rapidly progressive disease. However, in the population as a whole there was a lack of evidence on the variability in response, whether the treatment effect was maintained and how sebelipase alfa affected long-term clinical outcomes including complications of LAL deficiency and life expectancy. Because of this, the modelled survival estimates and long-term clinical benefits of sebelipase alfa were highly uncertain. The committee considered that, even with the proposed price per mg discount and annual per patient cost cap, the cost of sebelipase alfa was very high, and it did not consider that the benefits of sebelipase alfa in people with LAL deficiency were sufficient to justify the high cost. The committee considered that, although it had some concerns about the criteria and evidence collection proposed in the managed access agreement, the proposal that was developed together with patient organisations and clinical experts, had attempted to define the patients who would benefit the most from sebelipase alfa treatment and would reduce the budget impact. The committee also welcomed the

budget certainty provided by the total budget impact cap. However, it considered that the costs of sebelipase alfa still remained too high given the nature and size of the overall benefits and the important clinical uncertainties. The committee concluded that sebelipase alfa should not be recommended for all people with LAL deficiency.

5.28 The committee considered whether there were any groups of people for whom sebelipase alfa could be considered to offer greater value for money to the NHS than the whole population covered by the managed access agreement. It recalled that the severity of symptoms in people with LAL deficiency varies widely and that some people with LAL deficiency may not need sebelipase alfa treatment. It therefore considered whether it could make separate recommendations for babies with rapidly progressive disease, and children and adults.

5.29 **Babies with rapidly progressive disease:** The clinical experts stated that all babies presenting with symptoms before 1 year needed sebelipase alfa because it is the only treatment that can prevent early death. The committee considered that sebelipase alfa is potentially life-saving in this group, and that there is an important clinical need for this treatment. Sebelipase alfa could potentially offer considerable benefits, in terms of QALYs gained. However, despite the clinical uncertainties being smaller than in other population groups and reduced further by the recent longer-term evidence, the benefits remained highly uncertain particularly for lifelong treatment. In addition, sebelipase alfa is associated with very high costs, although the size of this population is small and so the budget impact and financial risk to NHS might be more manageable than in other groups. On balance, the committee considered that the benefits of treatment were too uncertain and were not great enough to justify the very high cost. It considered that sebelipase alfa did not represent appropriate value for the NHS even in this population group. The committee concluded that the conditions of the proposed managed access agreement and the proposed price per mg discount and cost cap were not

sufficient for it to recommend sebelipase alfa as an appropriate use of NHS resources in babies with rapidly progressive LAL deficiency.

5.30 **Children and adults:** The committee recognised that children and adults with LAL deficiency are clinically different to babies with rapidly progressive disease, both in terms of their clinical need and the size of the potential treatment benefit. It noted that this population is very heterogeneous, and had some concerns that the proposed managed access agreement may not fully identify the people with the greatest clinical need or those who would benefit most. It welcomed the longer-term results presented by the company, which reduced some of the uncertainty around the original assumptions about the effectiveness of sebelipase alfa, although it considered that the long-term benefits of treatment remain uncertain. The committee noted that the overall benefits of treatment with sebelipase alfa are much less in this population than in babies and are also highly uncertain, but the costs of treatment remain very high. The committee therefore considered that sebelipase alfa does not offer appropriate value for this group. The committee concluded that sebelipase alfa was not recommended for national commissioning in children and adults with LAL deficiency.

Summary of evaluation committee's key conclusions

	Evaluation title: Sebelipase alfa for treating lysosomal acid lipase deficiency	**Section**
Key conclusion		
Sebelipase alfa is not recommended for long-term enzyme replacement therapy for treating lysosomal acid lipase (LAL) deficiency in babies with rapidly progressive disease. The committee recognised that sebelipase alfa is a potentially life-saving treatment in this population, and there is a compelling clinical need. It was concerned that, even with the company's proposed discount and cost cap, the cost of sebelipase alfa is exceptionally high and is too high to be considered value for money in the context of uncertainties about the potential long-term benefits of treatment. Sebelipase alfa is not recommended for treating LAL deficiency in children or adults.		1.1, 1.2

The committee considered that sebelipase alfa provided clinical benefits for people with LAL deficiency compared with best supportive care, and was potentially life-saving for babies with rapidly progressive disease. However, in the population as a whole there was a lack of evidence on the variability in response, whether the treatment effect was maintained and how sebelipase alfa affected long-term clinical outcomes including complications of LAL deficiency and life expectancy. Because of this, the modelled survival estimates and long-term clinical benefits of sebelipase alfa were highly uncertain. The committee considered that, even with the proposed price per mg discount and cost caps, the cost of sebelipase alfa was very high, and it considered that the benefits of sebelipase alfa in people with LAL deficiency were not sufficient and were too uncertain to justify the high cost. For babies, even in light of additional longer term results, the benefits of sebelipase alfa remained uncertain. Although the clinical uncertainties were smaller than in other population groups and were reduced by the longer-term evidence, the benefits remained uncertain particularly in the longer term of the lifelong treatment. In addition, sebelipase alfa is associated with very high costs. For children and adults, the committee considered that the benefits were much less than in babies and were highly uncertain, but the costs of treatment remain very high.		5.28–5.30
Current practice		
Nature of the condition, including availability of other treatment options	Babies with rapidly progressive LAL deficiency have pain, poor feeding, growth failure and severe hepatic disease, and a very short life expectancy of less than a year. Best supportive care does not prevent early death. People presenting with symptoms later in life typically have less rapidly progressive disease and the natural history, and particularly the rate of symptom progression, was highly variable in people presenting with symptoms of LAL deficiency later in childhood or adulthood. The possible long-term effects of LAL deficiency include liver cirrhosis and liver failure. The committee concluded that LAL deficiency had a very large impact on some patients with the condition, but it was unclear about the quality-of-life impact of symptoms of less severe forms of LAL deficiency. The committee heard from clinical experts that in clinical practice, all babies with LAL deficiency would have treatment, but it would not routinely be offered to older patients whose symptoms are less severe and whose condition is less rapidly progressive. The presence of fibrosis would indicate a need for treatment.	5.1–5.3
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from the clinical experts that because sebelipase alfa is the first therapy that specifically targets the underlying cause of LAL deficiency, they considered it to be a step change in managing the condition.	5.4
Adverse reactions	The summary of product characteristics lists the most serious adverse reactions with sebelipase alfa (seen in around 3 in 100 patients) as being signs and symptoms of severe allergic reactions.	3.2
Clinical evidence		
Availability, nature and quality of evidence	The committee discussed the evidence for the efficacy of sebelipase alfa for babies presenting before 6 months with rapidly progressive LAL deficiency. It noted that the company had compared 12-month death rates in LAL-CL03, a single-arm open-label study, with those in LAL-1-NH01, a natural history cohort study. The committee discussed the evidence for the efficacy of sebelipase alfa for children and adults who did not present with rapidly progressive LAL deficiency before 6 months, focusing on LAL-CL02, a randomised controlled trial comparing sebelipase alfa with placebo in people presenting with symptoms of LAL deficiency in childhood or adulthood.	4.5, 5.5, 5.6
Uncertainties generated by the evidence	The committee was very uncertain about whether the effects seen in the clinical trials would be maintained over the long term, were sufficient to prevent long-term complications and would fully address LAL deficiency. It also considered the longer term results of the clinical trials, and was reassured that the evidence with longer term follow up reduced some of the uncertainty, although it was still only available for a relatively short period for a potentially lifelong treatment. For babies, the committee was unable to determine the variability in response to treatment, whether the response could be maintained and whether it was sufficient to prevent long-term complications of LAL deficiency and fully restore life expectancy, because numbers were small and because no robust comparative data were available.	5.5, 5.6

Impact of the technology	The committee acknowledged the patient experts' view that sebelipase alfa offered a lifeline for babies presenting with rapidly progressive LAL deficiency. It also noted the views of patient experts with symptoms starting later in life; how sebelipase alfa had stopped their symptoms, enabled them to do day-to-day activities again and restored their quality of life.	5.4
Cost evidence		
Availability and nature of evidence	The committee discussed the structure of the company's cost–consequence model, noting that it was based on an economic model for non-alcoholic steatohepatitis (NASH). It heard that both LAL deficiency and NASH were associated with liver disease progression. The committee concluded that the structure of the model was broadly appropriate.	5.16
Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis	The committee concluded that the structure of the model was broadly appropriate, but it was unclear whether the modelling captured the variability of liver disease progression in LAL deficiency. The committee concluded that it was appropriate to model a long-term treatment effect for sebelipase alfa but because the longer term results only partly reduced the uncertainty around the company's assumption that the long-term consequences of LAL deficiency would be completely prevented by sebelipase alfa, the modelled survival benefit was highly uncertain.	5.16, 5.17
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee noted that the utility values used by the company for liver disease health states in the cost–consequence model were not calculated from quality-of-life data collected from people with LAL deficiency. It also considered that some of the utility values used for children and adults with LAL deficiency were not plausible because they were higher than the age-dependent UK population values for people without a chronic health condition. It concluded that the company's utility values might be overestimates of the true utility values, and the ERG's values might be underestimates. It concluded that the true utility values were likely to be closer to the ERG's values because it was unlikely that people with LAL deficiency had a better quality of life than age-matched people without a chronic condition.	5.18

Cost to the NHS and PSS	The committee accepted that the number of patients in England who would be likely to receive sebelipase alfa treatment in the first 5 years of use by the NHS was more objectively estimated in the revised budget impact analysis than it was in the previous version. It noted that although the eligibility criteria for the revised managed access agreement were more restrictive than the previous proposal, and fewer patients were included, the estimated budget impact was greater. It understood that this was because it was predicted that more babies would have treatment, and the cost of treatment is higher because of the higher dosage permitted in this group. The committee concluded that the 5-year net budget impact, as presented by the company in its revised analysis and including the proposed cost cap and price per mg discount, is likely to be an accurate estimate.	5.14
Value for money	The committee noted that the long-term benefits of sebelipase alfa were uncertain. The committee considered that, even based on more optimistic assumptions of long-term treatment effect, the cost of sebelipase alfa would be very high, and that it would be higher relative to treatment benefits than the committee had previously regarded as acceptable. The committee was unconvinced that sebelipase alfa represented overall good value for money to the NHS. The committee concluded that although sebelipase alfa is a life-saving treatment for babies with rapidly progressive LAL deficiency and there is a compelling clinical need for it to be made available for these patients, the benefits of treatment were very uncertain and the cost was too high for these benefits.	5.23, 5.24
Impact beyond direct health benefits and on the delivery of the specialised service	The committee agreed that there would be cost savings and benefits with sebelipase alfa incurred outside the NHS and personal and social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies.	5.28
Additional factors taken into account		

Access schemes	The committee considered the revised managed access proposal submitted by the company. It considered the proposals about who would start and stop treatment with sebelipase alfa and the proposed registry data to be collected. It concluded that the population for whom sebelipase alfa would be considered within the revised managed access agreement was identified more objectively than in the initial proposals. However, it still had some concerns that it had not been provided with sufficient justification as to how the criteria would ensure that in light of the heterogeneous patient population with LAL deficiency and the weak evidence base, the population would be restricted to only people who would gain most benefit from sebelipase alfa treatment and that none of those who would gain most benefit would be excluded from treatment. It also concluded that the data collection and monitoring plan proposed in the managed access agreement was not sufficiently detailed and had a number of limitations. The committee also discussed the proposed annual per patient cost cap, the discount to the price per mg and the budget impact cap. These are commercial in confidence. It welcomed the additional discount to the price per mg of sebelipase alfa proposed by the company, but concluded that, because of the annual cost cap, the effect of this discount was small. It also welcomed the budget certainty provided by the total budget impact cap.	5.9–5.12, 5.26
Equalities considerations and social value judgements	During consultation on the draft scope, a consultee asked whether a definition of early and late-onset LAL deficiency would be based on the person's age at diagnosis. The marketing authorisation for sebelipase alfa was granted after the scoping workshop. It stipulates different treatment regimens for LAL deficiency presenting in infancy (defined as before 6 months) according to the rate of disease progression. The evidence for 2 distinct populations based on the rate of progression was considered separately by the committee because of differences in their treatment needs, and on the high mortality in the group with rapidly progressive LAL deficiency. However, the committee did not consider sebelipase alfa at its list price to be good value for money and did not recommend sebelipase alfa within its marketing authorisation.	–

6 Review of guidance

6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
January 2017

7 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 to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

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.

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more technical personnel, a project manager and the Associate Director for the highly specialised technologies programme.

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