NICE National Institute for Health and Care Excellence

NICE guidance

Eliglustat for treating type 1 Gaucher disease

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

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

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1 Recommendations

1.1 Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers. Eliglustat is only recommended when the company provides it with the discount agreed in the patient access scheme.

2 The condition

2.1 Gaucher disease is an inherited lysosomal storage disorder. It is caused by deficiency of the enzyme glucocerebrosidase. This deficiency leads to the inappropriate storage of complex lipids in some types of cell. This creates Gaucher cells, which occur throughout the liver, spleen, bone marrow and occasionally the lungs. There are 3 subtypes of Gaucher disease, of which type 1 (non-neuronopathic) is the most prevalent. All types of Gaucher disease are associated with a variety of symptoms, including pain, fatigue, anaemia, thrombocytopenia, jaundice, bone damage, and liver and spleen enlargement.

2.2 There are limited data available on the epidemiology of Gaucher disease. The overall frequency of all types of Gaucher disease is about 1 in 50,000 to 1 in 100,000 live births. Over 90% of people affected have type 1 Gaucher disease. The prevalence of type 1 Gaucher disease is estimated to be 1 in 200,000 in non-Ashkenazi Europeans, which equates to about 250 people in England and Wales. It is more common in people of Ashkenazi family origin, with a frequency of about 1 in 500 to 1 in 1,000 live births. Clinical experts estimate that there are 350 to 400 patients with Gaucher disease (types 1, 2 and 3) in England, and 50 to 100 patients could be eligible for treatment with eliglustat.

2.3 The company submission states that the natural history of untreated disease before the availability of enzyme replacement therapy is poorly documented, and there is limited information on life expectancy for people with Gaucher disease. People who present below the median age of onset of about 14 years with massive splenomegaly and hypersplenism have a particularly poor prognosis. These patients usually develop bone disease and immobility in the third or fourth decade of life, with a high early mortality.

3 The technology

3.1 Eliglustat (Cerdelga, Sanofi Genzyme) is a substrate reduction therapy that partially inhibits the enzyme glucosylceramide synthase. This action results in reduced production of glucosylceramide and so fewer Gaucher cells. It is given orally.

3.2 Eliglustat has a marketing authorisation in the UK for the long-term treatment of type 1 Gaucher disease in adults who are cytochrome P450 2D6 (CYP2D6) poor, intermediate or extensive metabolisers. The recommended dosage stated in the summary of product characteristics is 84 mg eliglustat (equivalent to the 100 mg eliglustat tartrate dose used in the clinical trials) twice daily in CYP2D6 intermediate and extensive metabolisers, and 84 mg eliglustat once daily in CYP2D6 poor metabolisers.

3.3 The summary of product characteristics lists the following adverse reactions for eliglustat: headache, nausea, diarrhoea, abdominal pain, flatulence, joint pain and fatigue. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 The list price of eliglustat is £342.23 per capsule. People who are intermediate or extensive metabolisers would be expected to have an average of 730.5 capsules a year, so the total annual drug cost per person would be approximately £250,000. People who are poor metabolisers would be expected to have an average of 365.25 capsules per year per person, so the total annual drug cost would be approximately £125,000. The company has agreed a patient access scheme, in which eliglustat would be provided with a discount. The discount is commercial in confidence and cannot be reported here. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

4 Evidence submissions

The evaluation committee (section 8) considered evidence submitted by the company for eliglustat, a review of this submission by the evidence review group (ERG) and evidence submitted by clinical experts, patient experts and NHS England.

Nature of the condition

4.1 Patient experts described how:

- Type 1 Gaucher disease can have a profound impact on health-related quality of life.
- Symptoms of Gaucher disease are not easily recognised and diagnosis can take a long time.
- The disease is rare, so there is little information about it, which can lead to frustration and anxiety for people who have it.
- The disease has an immediate impact on family life, social interactions and work.
- There is social stigma associated with Gaucher disease because of a lack of understanding about it, and an unmet need for mental health and psychosocial support.
- Haematological, bone and visceral symptoms are key factors affecting the health-related quality of life of people with type 1 Gaucher disease. As the disease progresses, it can cause anaemia and thrombocytopenia, which lead to fatigue, joint pain and reduced mobility. Severe disease is associated with bone damage, with an increased incidence of fragility fractures, pain and loss of self-reliance.

4.2 The patient experts reported that people with Gaucher disease face the challenge that they usually have no visible disability, except for a few older people who use a wheelchair or walking aids. This can make it difficult for them to access the care, support and services they need, such as benefits and employment support (for example, rest breaks, reduced working hours, time off for appointments and treatment).

4.3 The main treatment option is enzyme replacement therapy (ERT – imiglucerase or velaglucerase). This is given by regular intravenous infusion, which is time consuming and burdensome for patients and caregivers. Miglustat is an oral therapy, which provides an alternative for people for whom ERT is not suitable. Supportive therapy may include blood products, bisphosphonates or analgesics. NHS England and clinical experts stated that current clinical practice in England is to titrate the dose of ERT and use the lowest effective dose. The company stated that miglustat is used in a very small number of people. The clinical and patient experts noted that people with type 1 Gaucher disease choose ERT whenever possible because miglustat is associated with tolerability and safety issues, and modest efficacy. The company submission outlined that the management of Gaucher disease needs an individualised approach to treatment that takes into consideration disease manifestations, disease burden and quality-of-life needs.

Clinical evidence

4.4 The company conducted a systematic literature review and identified the following key phase 3 randomised controlled trials of eliglustat for type 1 Gaucher disease:

- ENCORE was an open-label trial comparing eliglustat (n=106) with imiglucerase (n=54) in patients whose disease was stable with ERT. Patients had 50 mg, 100 mg or 150 mg eliglustat twice daily titrated according to trough plasma concentration, or 30–130 U/kg/month of imiglucerase. The statistical design of the ENCORE trial was to test non-inferiority in the primary composite outcome, that is, the percentage of patients who remained stable for 52 weeks in the following parameters: haemoglobin levels decreased by 1.5 g/dL or less from baseline, platelet counts decreased 25% or less from baseline, spleen volume increased 25% or less from baseline and liver volume increased 20% or less from baseline. The non-inferiority margin was 25%. The analysis was stratified by ERT dose (see table 1 for further details).
- ENGAGE was a double-blind placebo-controlled trial comparing eliglustat (n=20) with placebo (n=20). The company submission referred to the population as being treatment naive. However, inclusion criteria allowed for patients who had previously had treatment with ERT as long as they had not had it within 9 months of recruitment to the trial. Patients in the eliglustat arm were given 50 mg on day 1; 50 mg twice daily from day 2 to week 4; and 50 mg or 100 mg twice daily from week 4 to week 39.

4.5 The company submission also included supportive information from a phase 3 trial (EDGE) and a phase 2 trial (NCT00358150)

- EDGE was a double-blind trial that compared once daily (100 mg or 200 mg) eliglustat with twice daily (50 mg or 100 mg) eliglustat in 170 patients with type 1 Gaucher disease. The trial started with a lead-in of up to 18 months, during which time patients had eliglustat 50 mg or 100 mg twice daily for at least 4 months, until therapeutic goals were achieved. Data were only provided for the open-label lead-in phase.
- The phase 2 trial (NCT00358150) included 26 patients who had not had ERT in the 12-months before the study. Eliglustat was administered at 50 mg twice daily from day 1 to day 20, after which the dosage could be increased to 100 mg twice daily if trough plasma concentrations were less than 5 ng/ml. The primary outcome measure was a composite requiring improvement from baseline to week 52 in at least 2 of the 3 main efficacy parameters, which were spleen volume, haemoglobin level and platelet count.

Clinical results – ENCORE

4.6 The ENCORE study showed that 84.8% of patients on eliglustat and 93.6% on imiglucerase met the primary composite endpoint of stability at 52 weeks. Stability was maintained for 104 weeks in 87.8% of patients (n=95) having eliglustat. Further details of the primary outcome results are presented in table 1. In both treatment groups, more than 92.0% of patients had stable disease in each component of the composite endpoint.

Table 1 ENCORE study results (per protocol set*)

Outcome	**Eliglustat (n=99)**	**Imiglucerase (n=47)**
Composite primary endpoint	84.8% (95% CI 76.2 to 91.3)	93.6% (95% CI 82.5 to 98.7)
Difference in percentage stable for 52 weeks	−8.8% (95% CI −17.6 to 4.2)	
Patients whose disease met stable criteria of primary endpoint (exact 95% CI)		

Haemoglobin criteria	94.9% (0.89 to 0.98)	100%
Platelet criteria	92.9% (0.86 to 0.97)	100%
Spleen volume criteria	95.8% (0.88 to 0.99)	100%
Liver volume criteria	96.0% (0.90 to 0.99)	93.6% (0.83 to 0.99)
Percentage whose disease was stable for 104 weeks (95% CI): eliglustat (n=95)		
Composite endpoint	87.4% (0.79 to 0.93)	
Patients whose disease met the stable criteria of primary endpoint (95% CI): eliglustat (n=99)		
Haemoglobin criteria	96.8% (0.91 to 0.99)	
Platelet criteria	93.7% (0.87 to 0.98)	
Spleen volume criteria	95.8% (0.88 to 0.99)	
Liver volume criteria	96.0% (0.90 to 0.99)	
*Per protocol set: patients in the full analysis set who adhered to treatment at least 80% of the time during the primary analysis period, had no major protocol deviations expected to interfere with the assessment of efficacy as defined in the statistical analysis plan and did not have haematological decline because of medically determined aetiologies other than Gaucher disease. Abbreviations: CI, confidence interval; n, number.		

4.7 Of the secondary outcomes (absolute and percentage changes in haemoglobin, platelet count and organ volumes at week 52 and week 104), the difference was statistically significant between treatment groups only for absolute and percentage changes in haemoglobin levels, for which there was a larger reduction for eliglustat (−0.28, 95% CI −0.52 to −0.03, p=0.03). The company stated that this difference was not clinically meaningful because it remained within the normal range. There were small or no differences in bone-related outcomes: spine bone mineral density (0.06), lumbar spine T-score (0.01) and Z-score (0.0), total femur bone mineral density (0.19), and total femur T-score (0.03) and Z-score (0.02). Data on the Gaucher Disease Type 1 Severity Scoring System (GD-DS3) were collected. This is the main measure used to score the severity of type 1 Gaucher disease in clinical practice in England. The range of GD-DS3 scoring is from 0 to 19 (0 to 3 indicates borderline to mild disease; 3 to 6, moderate disease; 6 to 9, marked disease; above 9, severe disease). Scores were all below 3 indicating mild disease, and they showed no clinically important improvements, with little change from baseline to week 52.

4.8 The company also presented a post-hoc subgroup analysis according to pre-treatment with either velaglucerase alfa or imiglucerase. The company stated that the results showed that:

- eliglustat had similar efficacy, both post-imiglucerase and post-velaglucerase alfa, with continued stability
- haemoglobin levels showed a similar change from baseline to week 52 in both groups
- spleen and liver volume outcomes also showed no statistically significant change from baseline in both groups.

Clinical results – ENGAGE

4.9 Eliglustat was associated with a 27.77% reduction in spleen volume from baseline, which translated to a statistically significant mean difference of 30.03% in spleen volume (the primary outcome measure) compared with the placebo group ($p<0.001$). This reduction in spleen volume continued through to week 78, with a mean reduction of 44.60% in the eliglustat group. Additionally, by week 78, disease in patients who started eliglustat at week 39 showed a similar response to that at week 39 in patients randomised to eliglustat at week 0.

4.10 The company submission stated that eliglustat showed efficacy compared with placebo on all secondary endpoints. At 39 weeks, there were statistically significant differences in liver volume (−6.64%, 95% CI −11.37 to −1.91; $p=0.0072$), haemoglobin levels (1.22 g/dL, 95% CI 0.57 to 1.88; $p=0.0006$) and platelet count (41.06%, 95% CI 23.95 to 58.17; $p<0.0001$). These results were maintained at week 78.

4.11 The GD-DS3 scores showed no clinically important improvements at 39 weeks. The company reported that there was a clinically significant decrease in bone marrow burden scores for 5 patients in the trial, with 3 shifting from marked/severe to moderate bone marrow infiltration.

Clinical results – EDGE

4.12 The company submission presented the interim analysis for the 18-month lead-in period only. The primary composite outcome was the proportion of patients in whom therapeutic goals were maintained or reached. It was based on measures of bone crisis, haemoglobin levels, platelet counts, and spleen and liver volumes. All 5 therapeutic goals were reached in 137 (83%) patients. The company stated that the analysis of the randomised part of the study had not been completed at the time of submission.

Clinical results – NCT00358150

4.13 For the composite primary outcome, statistically significant improvements in haemoglobin, platelet counts, and liver and spleen volumes were maintained throughout 4 years of treatment, showing long-term change from baseline with eliglustat.

Adverse events

4.14 The company presented a safety analysis that pooled data from 393 patients with type 1 Gaucher disease who had eliglustat in the clinical trial programme. The overall results of the pooled safety analysis showed that eliglustat was generally well tolerated, with few patients (3%) stopping treatment because of adverse events. Adverse events were mostly mild (78%) or moderate (44%), and were not thought to be related to eliglustat in 79% of patients. The most common events were headache (17%), joint pain (14%), nasopharyngitis (13%), upper respiratory tract infection (11%), diarrhoea (10%) and dizziness (10%).

Health-related quality of life

4.15 The company stated that eliglustat maintained health-related quality of life in patients whose disease was stable with ERT in the ENCORE study (see table 2). The company also highlighted that, because eliglustat is an oral therapy, it is easier to use compared with enzyme replacement infusions, which take an average of 2 hours every 2 weeks and need some clinical oversight.

Table 2 Health-related quality-of-life outcomes – ENCORE

Health-related quality-of-life measure	Treatment group	Baseline	Week 52
Fatigue Severity Score*	Eliglustat (n=97)	3.06 (1.55)	3.13 (1.63)
	Imiglucerase (n=45)	3.01 (1.54)	2.92 (1.54)

Brief Pain Inventory**, average pain	Eliglustat (n=95)	1.67 (2.05)	1.55 (1.97)
	Imiglucerase (n=46)	1.17 (1.44)	0.85 (1.19)
SF-36 – general health	Eliglustat (n=96)	70.50 (19.56)	71.21 (19.03)
	Imiglucerase (n=46)	75.15 (18.67)	78.91 (15.28)
SF-36 – physical component score	Eliglustat (n=95)	49.59 (9.16)	51.22 (8.37)
	Imiglucerase (n=46)	53.38 (7.17)	55.07 (5.20)
SF-36 – mental component score	Eliglustat (n=95)	51.97 (9.85)	50.97 (10.30)
	Imiglucerase (n=46)	51.99 (8.87)	51.34 (10.09)
* Higher score indicates higher level of fatigue. ** Higher number indicates greater pain or interference. Abbreviation: n, number.			

4.16 In the ENCORE trial, a questionnaire (at screening) exploring treatment preference between oral or intravenous administration showed that 94% of patients in the eliglustat group and 94% in the imiglucerase group had a preference for oral treatment. After 12 months of treatment, all 93 patients who had switched from ERT to eliglustat said they preferred oral therapy, with 81% stating that this was because of the convenience it offered.

4.17 In the ENGAGE trial, placebo was associated with an improvement in fatigue severity score at week 39 (absolute change -0.6) compared with eliglustat (absolute change 0.1) but the difference was not statistically significant. There was no statistically significant difference in brief pain inventory (average pain; −0.2, 95% CI −0.81 to 0.36) between the treatment and placebo groups. In terms of the SF-36 measures, there were no statistically significant differences between the 2 groups for general health score, physical component score, and mental component score.

Evidence review group comments

4.18 The ERG commented that the non-inferiority margin of 25% was wider than would normally be accepted, and suggested that a margin of 15% would have been more robust. A 25% non-inferiority margin assumes that a 10% reduction in efficacy is clinically insignificant, an assumption that was not justified clinically by the company. The ERG acknowledged that the European Medicines Agency accepted the broader margin because of the rare nature of the disease and that conducting a larger trial (as would be necessary with a 15% margin) would not be feasible.

4.19 The ERG stated that the trials were of reasonable quality and well conducted, but at the time of their review highlighted that long-term data for eliglustat were limited, especially in the context of a lifelong condition. Additionally, only 66 patients across the studies had untreated disease.

4.20 The ERG noted that most patients in the trials were intermediate metabolisers and extensive metabolisers. About 3% of patients were ultra-rapid metabolisers and would not have been eligible for treatment with eliglustat under the marketing authorisation.

4.21 The ERG commented that, because of the open-label nature of the trial, there was a high risk of bias for any subjective outcomes.

4.22 The ERG highlighted that the sample size in the ENGAGE trial was very small (n=40), and the randomised phase of the trial was too short (39 weeks) to measure improvements in bone outcomes for people with type 1 Gaucher disease.

4.23 The ERG noted that the phase 2 single-arm trial, which included patients who were not having treatment with ERT, provided supporting data for 1, 2 and 4 years of treatment with eliglustat, although not all patients remained in the analysis beyond 1 year and not all outcomes were reported at 4 years. Additionally, the ERG noted the trial had a small sample size (n=26).

4.24 The ERG highlighted that no data comparing eliglustat with ERT were presented from patients who had not previously had treatment. Additionally, a direct comparison of eliglustat with velaglucerase alfa was not available for patients whose disease was stable with ERT.

4.25 The ERG noted that the summary of product characteristics for imiglucerase and velaglucerase alfa recommend higher starting dosages of 60 U/kg every 2 weeks. However, the standard operating procedure developed by expert consensus in England reports that a maintenance dose of 15–30 U/kg is appropriate for most patients on either imiglucerase or velaglucerase alfa, although this may be increased to 60 U/kg. Expert advice to the ERG suggested typical doses were around 25 U/kg (range: 15–28 U/kg), and the expert submission reported doses of 20–40 U/kg. The ERG highlighted that lower doses of ERT would have affected the long-term costs in the model. NHS England commented that current clinical practice in England is to titrate the dose of ERT and use the lowest effective dose, stating that an economic evaluation should take account of this.

4.26 The ERG commented that the evidence from ENCORE showed a higher number of patients experienced treatment-related adverse events with eliglustat than with imiglucerase. However, the ERG commented that this difference in tolerability may have been because patients had stable disease with ERT when recruited to the trial. The ERG noted that the evidence was mostly limited to the short-term data although some longer-term data up to 4 years showed that eliglustat was generally well tolerated.

4.27 The ERG highlighted that the health-related quality-of-life data for eliglustat did not show a benefit compared with ERT, even though people expressed a preference for oral treatment in a patient survey. The ERG acknowledged that there may be some health-related quality-of-life benefits resulting from having oral therapy rather than an intravenous infusion. However, it considered that the magnitude of benefit assumed by the company was unreasonably large when compared with quality-adjusted life year (QALY) decrements from adverse events and QALY benefits of other oral therapies estimated in previous NICE submissions.

Economic evidence

4.28 The company developed a cost–consequence analysis using a 10 health state semi-Markov model (that is, the transition probabilities used in the model depended on a patient's initial health state). The model, comparing eliglustat with imiglucerase and with velaglucerase alfa, included 2 patient groups: those who were treatment naive and those who were taking ERT and whose disease was considered clinically stable. Within each of these populations, the model also considered subgroups based on metaboliser status. The company did not present a comparison with miglustat, stating that it is used in less than 2% of patients, and is associated with issues around tolerability and efficacy. The company also stated that eliglustat is not expected to be used in place of miglustat in this small population.

4.29 The starting age of people in the treatment-naive population was assumed to be 32 years based on the mean age in the ENGAGE trial. The starting age of people in the population whose disease was stable with ERT who switched to eliglustat was assumed to be 38 years. Health states were defined by a patients' scores on the GD-DS3 severity scoring system. In the model, people were grouped by: mild (GD-DS3 score 0 to 3.5), moderate (3.5 to 6.5), marked (6.5 to 9.5), and severe (more than 9.5) disease. People could move between any of the living states in each cycle, remain in their current state, or move to the absorbing death state. All people with moderate, marked and severe disease were assumed to have at least 1 instance of bone or joint pain or bone crisis, based on the contribution of this domain to the overall GD-DS3 score.

4.30 For people whose disease was stable with ERT, transition probabilities in the first year were based on the ENCORE trial and thereafter based on data from the GD-DS3 score study, a registry validating the GD-DS3 scoring system. The model assumed differential clinical effectiveness in the first year and then equal effectiveness in subsequent years. For the treatment-naive population, treatment effectiveness was assumed equal and based on the eliglustat arm of the ENGAGE study.

4.31 The model used a time horizon of 70 years and a cycle length of 1 year. The company stated that this was appropriate given the limited data available. The analysis was conducted from the perspective of the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

4.32 Some of the assumptions used in the company's model were:

- The treatment efficacy of eliglustat and the comparators is equal in the treatment-naive population.
- After the trial period, the state transitions derived from GD-DS3 Score Study data are the same for eliglustat and all the comparators.
- After their disease becomes stable on the selected treatment, people might stop treatment for up to 3 years and switch to a different therapy. (A stopping rate of 1.9% was applied for the treatment-naive population for both eliglustat and ERT. For the population whose disease was stable with ERT, a 1.9% stopping rate was applied for eliglustat but it was assumed that patients having ERT would not stop treatment.)
- Mortality is the same for eliglustat and ERT across all health states, and mortality rate does not increase with disease severity.

  The outcomes at 39 weeks from the ENGAGE trial were used for people at 1 year in the model.

4.33 Quality-of-life data were derived from the GD-DS3 score study, which also collected SF-36 data. The SF-36 scores were mapped to EQ-5D utilities using a published algorithm. Utility decrements were applied to patients having treatment to reflect the impact of adverse events. The ERG agreed that the GD-DS3 score study provided the most complete set of utility values. The model also incorporated preference for oral therapy over infusion therapy in the base-case analysis via a utility increment of 0.12, which was applied in every cycle. This value was taken from a vignette study that was commissioned by the company.

4.34 Costs for drug acquisition, administration, and monitoring and management were included in the model. Differential monitoring and management costs were applied to each health state, broadly increasing with severity of disease. No costs associated with adverse events were included in the model, and the company assumed that additional training of healthcare staff was not needed for administration of eliglustat or the comparators. No administration costs were included in the model for eliglustat. Table 3 presents the costs included in the model. Additionally, direct medical and social service costs were included, ranging from £2,583.05 per year for the mild health state with no clinical symptoms of bone disease to £6,411.63 for the severe health state with severe skeletal complications.

4.35 Confidential discounts were available for eliglustat, imiglucerase and velaglucerase alfa, and results incorporating the confidential prices were explored by the ERG for all analyses in a confidential appendix.

Table 3 Costs per treatment per patient per year based on the list prices

Items	Eliglustat	Imiglucerase	Velaglucerase alfa
List price of the technology per treatment per patient	IM and EM: £249,999.02 PM: £124,999.51	£199,976.00	£263,203.00
Cost of infusing in hospital plus cost of nurse support at home	–	£1,751.00	£1,751.00
Management cost (for example, delivery, homecare services)	£480.00	£12,587.00	£12,587.00
Training cost	£0.00	£0.00	£0.00
Other costs (for example, monitoring, tests)	£0.00	£0.00	£0.00
Abbreviations: EM, extensive metabolisers; IM, intermediate metabolisers; PM, poor metabolisers.			

Model results

4.36 The company estimated that the lifetime benefit associated with using eliglustat in place of ERTs (driven almost entirely by the quality-of-life improvement associated with mode of administration) was 2.44 QALYs for people who had not had treatment before and 2.28 QALYs for people whose disease was stable with ERT.

4.37 The results of the incremental costs for eliglustat compared with imiglucerase and velaglucerase alfa in people whose disease was stable with ERT and those who were not having treatment at time of starting eliglustat are presented in table 4. The results are based on list prices; confidential discounts are available for eliglustat and ERT.

Table 4 Summary of incremental costs in company's base-case cost-effectiveness model

Comparison	Incremental cost
'ERT-stable' population, IM and EM	
People switching from imiglucerase	£687,837
People switching from velaglucerase alfa	−£519,226
'ERT-stable' population, PM	
People switching from imiglucerase	−£1,698,539
People switching from velaglucerase alfa	−£2,905,602
Treatment-naive population, IM and EM	
People who would otherwise start on imiglucerase	£672,251
People who would otherwise start on velaglucerase alfa	−£467,818
Treatment-naive population, PM	
People who would otherwise start on imiglucerase	−£1,855,035
People who would otherwise start on velaglucerase alfa	−£2,995,104
Abbreviations: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser.	

4.38 The company presented one-way sensitivity analyses to explore uncertainty. Incremental costs were most heavily influenced by patient weight because this determined the dosing and costs of the ERT comparators. Other influential parameters were those used to model overall survival of patients, the number of doses of ERT patients were assumed to have per month and the duration over which patients could stop eliglustat. Varying the utility increment assigned to eliglustat for its more favourable administration method was the biggest driver of the difference in QALYs.

Budget impact analysis

4.39 The company presented a 5-year budget impact model to estimate the costs of eliglustat to the NHS. It was based on estimates of total costs generated by the cost–consequence model. Some other key assumptions made by the company were:

- Newly diagnosed patients were assumed to start treatment on eliglustat rather than imiglucerase/velaglucerase alfa.
- Costs were based on the licensed dose of eliglustat and the dosing of ERTs used in the ENCORE clinical trial.
- Effects of mortality and stopping treatment were included in the estimated total costs.
- Model results for intermediate or extensive metabolisers were used (most patients in the trials).

4.40 The company stated that there was uncertainty over uptake rates, which would be driven both by clinician and patient preference, and by NHS purchasing decisions.

4.41 The budget impact calculations estimated the difference in costs over 5 years if eliglustat were to be introduced as a treatment option. The company estimated that using eliglustat would result in additional costs of £84,559 in year 1 after launch, leading to a total cost of £571,487 in year 5 (a cumulative total of £1,623,219). These results are based on the list prices for eliglustat and ERT.

Evidence review group review

4.42 The ERG highlighted 2 main concerns about the structure of the model developed by the company: the use of long-term transitions and the use of the GD-DS3 score system to define health states. The ERG considered the company's approach to generating long-term transition probabilities to be complicated, stating that it reduced the transparency of the model, so making validation difficult. The ERG stated that, because the same transition probabilities were applied to both treatment and comparator groups, it was unclear why a simpler approach was not used. Additionally, the ERG stated that the GD-DS3 score appeared to be insensitive to changes in disease status, so did not reflect differences between the treatments seen in the ENCORE trial. This meant that differences between the treatment and comparators were not accounted for in the model. This resulted in a bias towards equivalence in clinical benefits, so underestimating the differences between eliglustat and imiglucerase seen in the ENCORE study.

4.43 The ERG stated that assuming long-term equivalence of eliglustat and ERT underpinned the calculation of long-term benefits, and had the potential to impact on estimated incremental QALYs. The ERG considered that this assumption had not been adequately justified in the company's submission. It stated that short-term non-inferiority results in the ENCORE trial did not imply non-inferiority in the long term.

4.44 The ERG questioned whether the inclusion of a large number of health states was necessary. The ERG acknowledged that more health states can improve the accuracy of a model. However, the advantage of this approach is offset when the model has a greater complexity and reduced transparency as a result. The ERG commented that this was particularly important because data for type 1 Gaucher disease are limited.

4.45 The ERG questioned the company's assumption that eliglustat and ERT were equivalent in people who had not had previous treatment. It considered that the evidence from the ENCORE trial should have been incorporated instead.

4.46 The ERG considered that the company's assumptions about stopping treatment were reasonable given the lack of data available.

4.47 The ERG stated that mortality risk would increase with severity of disease, so disagreed with the company's assumption on mortality. The ERG explored this assumption in its analyses.

4.48 The ERG considered that the dose of eliglustat in the model was in line with practice. However, the ERG noted that the efficacy data were taken from ENCORE, in which 48% of patients had a higher dosage of eliglustat (150 mg twice daily) for most of the trial.

4.49 The ERG disagreed that there will be no administration costs associated with eliglustat because it is an oral therapy, and explored incorporating a minimum pharmacy dispensary cost. Additionally, the ERG considered that the company overestimated the administrative costs for ERT delivered at home because it was implausible that it would be higher than the cost of hospital administration.

4.50 The ERG was concerned with the costs for ERT in the model, noting that the company did not include any vial wastage. The ERG reiterated that there was considerable evidence to suggest that substantially lower doses of ERT are used in practice (see section 4.26), so the higher dose of ERT treatment assumed in the model overestimated the ERT acquisition cost. The ERG also noted that patients who had not had previous treatment in the model were assumed to have had the same dose of ERT as patients whose disease was stable. However, the clinical adviser to the ERG suggested that newly diagnosed patients are typically less severely affected than patients who start treatment in childhood and so do not need such intensive dosing.

4.51 The ERG stated that the budget impact model was linked directly to the cost–consequence model, so its concerns around the company's model were also applicable to the company's budget impact analysis. The ERG noted a number of issues with the budget impact analysis beyond those identified in the cost–consequence model. These related to:

- The costs incorporated in the budget impact model, which were taken from the cost–consequence model, represented the average lifetime costs when allowing for mortality rather than the costs of treating the disease in 1 patient for 5 years. The ERG stated that the latter was relevant to the budget impact analysis and the company's approach underestimated total costs. With regard to stopping treatment, the ERG stated that the effects of switching were double counted because both the cost–consequence model and the budget impact analysis accounted for switching.
- The choice of treatment for the incident population in the absence of eliglustat: the ERG suggested that it is plausible that all patients are offered velaglucerase alfa rather than some patients having imiglucerase.
- The composition of the Gaucher population (the budget impact model excluded poor metabolisers): the ERG stated that this may have overestimated the costs of treatment with eliglustat.

ERG exploratory analyses

4.52 The ERG conducted exploratory analyses to address the uncertainties it had identified in the company's cost–consequence model. It presented its own base-case analysis with its preferred assumptions, including:

- additional administration costs for eliglustat (£14.40 monthly dispensary cost)
- revised administration costs for ERT treatments (home therapy cost equal to hospital cost)
- revised estimate of the QALY benefits of oral therapy (estimate of 0.05)
- revised modelling of mortality to allow for increased mortality risk for people with marked and severe disease
- reduction in dose of ERT to bring it in line with UK practice (25 U/kg)
- using ENCORE effectiveness data in the treatment-naive population during the first cycle.

4.53 The impact of the ERG's analyses, based on list prices for ERT treatments, was to reverse the company's results for intermediate and extensive metabolisers for the comparison with velaglucerase: eliglustat was no longer cost saving (see table 5). For the comparison with imiglucerase, the incremental costs estimated by the ERG were substantially higher than those estimated by the company (see table 6). The cost savings with eliglustat for poor metabolisers, based on the ERG's analyses, were substantially lower compared with imiglucerase and velaglucerase. The key driver of the change in results was the dose of ERT treatment used.

4.54 The ERG also highlighted that the QALY benefits of eliglustat compared with imiglucerase and velaglucerase alfa were reduced to around 1.05, driven by alternative assumptions about the size of the incremental benefit for oral therapy.

Table 5 ERG base-case analysis – incremental QALYs and costs (eliglustat versus velaglucerase alfa) – based on list prices of eliglustat and ERT

Patient group	Incremental QALYs	Incremental cost
'ERT stable' IM/EM (total)	1.05	£1,849,412
'ERT stable' PM (total)	1.05	−£795,706
ERT naive IM/EM (total)	1.06	£1,900,060
ERT naive PM (total)	1.06	−£755,340
Abbreviations: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser; QALY, quality-adjusted life year.		

Table 6 ERG base-case analysis – incremental QALYs and costs (eliglustat versus imiglucerase) – based on list prices of eliglustat and ERT

Patient group	Incremental QALYs	Incremental cost
'ERT stable' IM/EM (total)	1.05	£2,638,293
'ERT stable' PM (total)	1.05	−£6,825
ERT naive IM/EM (total)	1.04	£2,605,712
ERT naive PM (total)	1.04	−£49,688
Abbreviations: EM, extensive metaboliser; ERT, enzyme replacement therapy; IM, intermediate metaboliser; PM, poor metaboliser; QALY, quality-adjusted life year.		

4.55 The ERG presented an exploratory analysis for the budget impact analysis. This included the assumptions in section 4.54 but also assumed zero mortality and no treatment stopping. Based on these revised cost assumptions, and using list prices, the budget impact of eliglustat was estimated by the ERG at an additional cost of £11,677,472 in year 5 and £36,428,402 over 5 years. Additionally, the ERG explored the impact of assuming that 4% of eliglustat patients would be poor metabolisers, based on the proportion in the ENGAGE trial. This reduced the budget impact to £11,123,765 in year 5 and £34,701,740 over 5 years.

Additional evidence

4.56 Following consultation on the evaluation consultation document, the company provided 4-year data from ENCORE. Data for mean haemoglobin concentration, platelet count, and spleen and liver volumes remained stable for up to 4 years. Year to year, all 4 measures remained collectively stable in 85% or more of patients, as well as individually in 92% or more. Mean bone mineral density Z-scores (lumbar spine and femur) remained stable and were in the healthy reference range.

4.57 The company provided results from Ibrahim et al. (2016), based on an indirect comparison of eliglustat with imiglucerase. Data for eliglustat was from a phase 2 study and ENGAGE. Data for imiglucerase was from a cohort of patients who had not had treatment, with comparable baseline haematological and visceral parameters from the International Collaborative Gaucher Group Registry. The company stated that results for spleen and liver volumes, haemoglobin and platelet count showed that no clinically meaningful differences in efficacy were found.

4.58 The company agreed that it was appropriate to use real world dose data for ERT but it stated that real world weight data must also be used when estimating the total administered dose. The company stated that using the ENCORE weight of 67.5 kg resulted in a mean total dose of 4 vials of ERT, but using real world weights of between 71.8 kg and 75.0 kg resulted in a mean total dose of 5 vials.

4.59 The ERG stated that the dose of ERT in the ERG base case came from English prescribing data that reported average units per month independent of weight, so the average weight in the model was not relevant. However, the ERG presented exploratory analyses using estimates of ERT use based on real world weight and the weight-dependent ERT dosing rate. This had the impact of increasing the costs of ERT in the model.

4.60 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 eliglustat, having considered evidence on the nature of type 1 Gaucher disease, its control by enzyme replacement therapy (ERT), and the value placed on the benefits of eliglustat by people with the condition, those who represent them and clinical experts. It also took into account the value for money that eliglustat represents, and the effective use of resources for specialised commissioning.

Nature of the condition

5.1 The committee understood that type 1 Gaucher disease is chronic, and that it needs lifelong treatment and causes symptoms such as fatigue, bone pain and reduced mobility. The committee noted comments from the patient experts that there is considerable impact on bones. This leads to varying forms of disability and, even with current treatments, people can experience symptoms such as fatigue, bruising, bone pain and, in those with severe disease, fractures. The committee heard from the patient experts about the profound impact the disease has on patients' and carers' quality of life and emotional wellbeing. The committee concluded that type 1 Gaucher disease is a debilitating condition that has a significant impact on quality of life.

5.2 The committee discussed the current treatment options and management of type 1 Gaucher disease. The committee heard that the main treatment options available are imiglucerase and velaglucerase alfa, both of which are recommended by the Lysosomal Storage Disorder Expert Advisory Group and nationally commissioned. The committee heard that the 2 treatments are considered equivalent in terms of efficacy, but velaglucerase alfa is preferred because it has a lower cost. The committee heard that miglustat, a substrate reduction therapy, may be offered to people for whom ERT is not suitable. However, the clinical experts highlighted that its efficacy is modest and that it is not well tolerated. Supportive therapy (for example, blood products, bisphosphonates, analgesics) may be offered to patients not having ERT or miglustat, or alongside these treatments in patients with complications. The committee understood from the clinical experts that, for this reason, the most relevant comparators for eliglustat are velaglucerase alfa and imiglucerase. The committee heard that ERT was an established and effective treatment option that had changed the treatment landscape for type 1 Gaucher disease. However, patient experts highlighted that they were administered intravenously and that this could be burdensome for patients, resulting in poor quality of life and mental wellbeing. The advantages of an oral treatment were emphasised, that is, more freedom to travel and attend university, and to live a more normal life without regular transfusions. The committee concluded that intravenous ERT, such as velaglucerase alfa and imiglucerase, were established treatments in the NHS, but that an oral treatment option would be of significant value to patients.

Impact of the new technology

5.3 The committee considered the clinical-effectiveness evidence presented by the company. It noted the evidence review group's (ERG's) comments that the trials were of reasonable quality. It heard from the clinical experts that the populations were generalisable to patients in clinical practice in England. However, the ERG highlighted that the non-inferiority margin of 25% for the ENCORE trial primary composite outcome was wider than normal. The committee was aware that the European Medicines Agency's Committee for Medicinal Products for Human Use noted that the trial did not comprehensively show that the usual regulatory standard of −20% had been achieved. The committee noted the company's explanation that the European Medicines Agency accepted a broader margin because of the rare nature of the disease, meaning that a larger trial could not feasibly be conducted. The committee understood the challenges in developing a clinical trial programme for a rare condition, and concluded that the ENCORE trial was sufficiently robust for its decision-making.

5.4 The committee discussed the appropriate dose for the ERT. It was aware that the dosages specified in the summary of product characteristics for imiglucerase and velaglucerase alfa (starting dosages of 60 U/kg every 2 weeks) were higher than those recommended in the NHS England standard operating procedure (maintenance dose of 15–30 U/kg). In the ENCORE trial, 58% of people had dosages of imiglucerase of at least 35 U/kg every 2 weeks. The committee questioned which dose reflects clinical practice in England. It heard from clinical experts that the approach in practice is to titrate the dose of ERT and use the lowest effective dose. It heard that patients generally start on 30 U/kg, followed by close monitoring for the first 12 months, with further dose reductions depending on response. The clinical experts stated that some people with newly diagnosed type 1 Gaucher disease occasionally have very severe disease and may need a higher starting dose. The committee concluded that the dose recommended in the standard operating procedure was reflective of clinical practice.

5.5 The committee discussed the dose of imiglucerase in the ENCORE trial. The committee noted that the dosage in ENCORE was between 30 U/kg and 130 U/kg every month and these efficacy data were used in the model. However, the dose in practice is lower (see section 5.4) and the company questioned if the efficacy data would need to be adjusted accordingly. The committee heard from the ERG that that the data showed that, in people having lower doses of ERT, their condition continues to respond to treatment. The clinical expert confirmed that, because treatment is individualised, the dose is titrated to the lowest effective dose. Higher doses of ERT might result in a more rapid response, but longer-term individualised therapy results in similar levels of response. The committee was satisfied that using the efficacy data for ERT from ENCORE was appropriate.

5.6 The committee discussed the dose of eliglustat in the ENCORE trial. About 48% of patients in this trial had a dosage of eliglustat (150 mg twice daily) higher than that recommended in the summary of product characteristics. The committee was aware that efficacy data from ENCORE were used in the model, and was concerned that this reflected response to a higher dosage than in the marketing authorisation for eliglustat. The company stated that their pharmacokinetic/pharmacodynamic modelling suggested only minor differences in plasma levels with the higher dosage, and that it would be associated with a negligible difference in clinical response. The committee understood, however, that the basis for this modelling was the blood concentration data from the trials in which dose adjustments had been made in response to blood concentration measurements. Therefore, the predictions from the model could be subject to bias. However, the clinical expert confirmed that experience in practice has shown the continued efficacy of eliglustat at a dosage of 100 mg twice daily. The committee was satisfied that using the efficacy data for eliglustat from the ENCORE trial would not introduce major bias to the results.

5.7 The committee discussed the remaining uncertainties within the evidence base. It noted that the placebo-controlled ENGAGE study, which included a treatment-naive population, also allowed inclusion of people who had previously had ERT provided they had not had ERT within 9 months of recruitment to the trial. Additionally, there were no comparative data with ERT for patients who had not had previous treatment. The committee also noted that there were few data on patients with poor metaboliser status; most patients in the trials were intermediate and extensive metabolisers. The company submission stated that up to 7% of the Gaucher population are poor metabolisers. Following consultation, the company stated that its pharmacokinetic/pharmacodynamic modelling suggested that similar clinical outcomes are expected for poor metabolisers having the lower dose of eliglustat. The committee concluded that it would need to take these uncertainties into account in its decision-making.

5.8 The committee discussed the results from the key clinical trials. It noted that the ENCORE trial achieved the pre-specified non-inferiority measure for eliglustat compared with imiglucerase based on the composite primary endpoint (encompassing haemoglobin levels, platelet counts, spleen volume and liver volume). The committee noted that there was no direct comparison of eliglustat with velaglucerase alfa but recalled that it was considered to be equivalent to imiglucerase (see section 5.2). Also, the results from the ENGAGE study showed a statistically significant and clinically meaningful improvement in spleen volume with eliglustat. The committee heard from the clinical experts that they considered eliglustat to be equivalent, or very nearly equivalent, to ERT based on clinical measures such as haemoglobin levels and platelet counts, as well as in terms of how patients felt while having eliglustat. The patient experts stated that the option of an oral treatment with eliglustat was invaluable and most patients would consider treatment with eliglustat if it was available. Following consultation, the company presented 4-year data from ENCORE showing that the outcomes remained stable. The clinical expert stated that this showed that the efficacy of eliglustat was independent of the residual effects of prior long-term ERT. The committee noted that eliglustat is a lifelong treatment and long-term benefits remained uncertain because these data are not based on a comparison with ERT. However, the committee accepted that the data were consistent with the possibility of long-term benefit. The committee concluded that eliglustat is an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty of effectiveness in comparison with ERT in the long term.

5.9 The committee considered the adverse effects associated with eliglustat. It noted that headache, nausea, diarrhoea, flatulence and fatigue were common adverse reactions highlighted in the summary of product characteristics. The committee heard from the clinical experts that the stopping rate of about 2 to 3% seen in the trials was similar to that seen in clinical practice. It highlighted that stopping treatment was generally in response to lifestyle changes such as wanting to start a family. The committee understood that the adverse effects associated with eliglustat were acceptable to patients, especially in the context of the advantages of oral administration.

Value for money

5.10 The committee noted that the main comparator for this evaluation was ERT. It also noted that, because NICE has not evaluated ERT, there was uncertainty about its benefits and value for money and, by extension, the benefits and value for money of eliglustat. The committee noted the statement from NHS England that the risks around value for money offered by ERT were lower for Gaucher disease compared with the risks for conditions such as Fabry disease. This is because it believed, in Gaucher disease, the effectiveness of ERT is well established and because the dose of ERT can be titrated to the lowest effective dose and the number of patients is lower. However, the committee was mindful that the benefits and value for money of ERT has not been formally considered. The committee noted that its considerations on the value for money of eliglustat were based on the current evidence and clinical practice, but that they would need to be reconsidered if ERT was no longer available in routine practice. The committee also encouraged the company, NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits of eliglustat and ERT for treating type 1 Gaucher disease.

5.11 The committee discussed the company's cost–consequence model and the assumptions on which it was based. It noted that the model structure was complex but reflected the important health states. The committee discussed the key assumptions included in the company's economic model:

- In the absence of direct evidence comparing eliglustat with ERT in patients who had not previously had treatment, the company assumed that eliglustat and ERT have equal efficacy in such patients. The ERG stated that evidence from the ENCORE trial would have been more appropriate. Following consultation, the company stated that the mean treatment duration with ERT before entering ENCORE was about 10 years, so these data could not be generalised to people who had not previously had treatment. The company stated that its assumption of equivalence was supported by an indirect comparison (Ibrahim et al., 2016) on the basis of which the European Medicines Agency's Committee for Medicinal Products for Human Use stated that comparable results can be expected. The ERG agreed that using data from ENCORE was not ideal, but considered that it was superior to the company's approach. The company used data from ENGAGE to estimate transition probabilities for patients having eliglustat, and applied these to both treatment arms in the first cycle of the model. The ERG stated that this did not capture any potential differences between eliglustat and ERT. The committee agreed that both approaches had limitations. It heard that, because these transition probabilities were applied to the first cycle only, it had a very small impact on the results.

- The company assumed long-term equivalence of eliglustat and ERT, and the ERG highlighted that this had a considerable impact on estimated incremental quality-adjusted life years (QALYs). The committee agreed with the ERG that non-inferiority was not the same as equivalence, and that non-inferiority in the short term does not imply non-inferiority in the long term. The committee considered the 4-year data presented by the company following consultation (see section 5.8) and also noted that the company presented varied approaches to transition within the model, resulting in a negligible impact on total QALYs gained. The ERG, however, clarified that the assumption of long-term equivalence was not underpinned by how transition probabilities are calculated, but by using the same probabilities in the long term across both arms of the model. The committee maintained that there was uncertainty around the assumption of equivalence in the long term.

5.12 The committee discussed the utility increment used in the company's model for oral therapy, which it understood was the key driver of QALY benefits. It heard from the patient and clinical experts that the availability of an oral treatment would have a huge impact on health-related quality of life compared with an intravenous infusion. The committee took note of several patient testimonies describing the positive impact of an oral treatment and the potential this offered for them to return to a more normal life. The committee heard from the ERG that it agreed that oral therapy would provide a clear quality-of-life benefit but questioned the extent of the benefit assumed by the company, even though this was based on a vignette study. The ERG highlighted that an increment of 0.12 was substantial when compared with the decrements from significant adverse events and the benefits of other oral therapies estimated in previous NICE submissions. The committee was aware that the ERG explored an alternative utility increment of 0.05. The committee concluded that, although the true value was uncertain, the alternative value used by the ERG was more appropriate.

5.13 The committee noted the results of the company's cost–consequence model (see section 4.37). The committee agreed that there was considerable uncertainty around these estimates because of the assumptions discussed in sections 5.11 and 5.12. The committee considered the ERG's exploratory analysis around these assumptions (see section 4.52) represented more plausible incremental costs and benefits associated with eliglustat. The committee noted that incremental QALYs reduced from 2.28 to 1.06 for the treatment-experienced population and from 2.44 to 1.05 for the treatment-naive population when the ERG included all of its revised assumptions. When the ERG incorporated the confidential discounts available for eliglustat and ERT, eliglustat resulted in cost savings for both populations. Using real world weight in the estimation of the dose of ERT would increase the cost savings further. The committee was mindful of the uncertainty around the long-term impact of eliglustat but appreciated the important advantages of an oral treatment. The committee concluded that, taking into account the confidential discounts for ERT and eliglustat, eliglustat offered value for money compared with ERT for people with intermediate and extensive metaboliser status.

5.14 The committee noted the results of the company's cost–consequence model in the people with poor metaboliser status. The committee then discussed the results of the ERG's exploratory analysis for people with poor metaboliser status noting that these reflected the assumptions preferred by the committee. These ERG results indicated that eliglustat was cost saving and the cost savings increased further when the confidential discounts were included. The committee was concerned that the trials included very few people with poor metaboliser status, so questioned whether the results from the model could be generalised to this population. Following consultation, the company stated that its pharmacokinetic/ pharmacodynamic modelling indicated that no differences in clinical outcomes were expected at a dosage of 100 mg twice daily for eliglustat. The committee was mindful that very few patients had poor metaboliser status and that an oral treatment option was valued by patients. The committee concluded that eliglustat offered value for money in people with poor metaboliser status.

5.15 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 eliglustat. It 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 was any basis for taking a different view about the relevance of the PPRS to this evaluation of eliglustat. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the value for money offered by eliglustat.

Cost to the NHS and Personal Social Services

5.16 The committee discussed the estimated uptake of eliglustat over a 5-year period. It noted that the company had revised the estimates in its original submission based on its experiences in European countries. The company explained that the uptake was shown to be lower in the first year and the company had adjusted for this in its revised estimates. The estimates are deemed commercial in confidence by the company and cannot be reported here. However, the clinical experts confirmed that, while the uptake in England was expected to be higher in the first 2 years compared with the company's estimates, the overall 5-year estimated uptake was reasonable. The committee was satisfied that the company's revised estimates sufficiently reflected the expectations in clinical practice in England.

5.17 The committee discussed the company's budget impact analysis. It was aware that it was based on estimates of total costs generated by the cost–consequence model, but the company also made some additional assumptions (see section 4.40). The committee considered the assumptions in the company's budget impact analysis. It noted that the company assumed that patients with a new diagnosis would start treatment on eliglustat rather than ERT, and that dosing for ERT was based on the ENCORE trial (that is, 42.4 U/kg every 2 weeks), which was not reflective of clinical practice (see section 5.4). The committee also noted that the model was based on people who were intermediate and extensive metabolisers, so excluded poor metabolisers, which would have overestimated the total costs of eliglustat for patients eligible for treatment. The ERG also highlighted issues related to incorporation of mortality and stopping treatment from the cost–consequence model (see sections 4.47 and 4.48), which the committee agreed would have underestimated the budget impact of eliglustat. The committee concluded that the company's estimates of budget impact were too uncertain, and so it considered the ERG's exploratory budget impact analyses in its decision-making.

5.18 The committee discussed the ERG's exploratory analyses of the budget impact analysis. It noted that the ERG revised several assumptions that were the same as its exploratory analysis of the company's cost–consequence model, with the additional assumptions of zero mortality, no treatment stopping, and that 4% of eliglustat patients were poor metabolisers. The committee was satisfied that these explorations reflected the committee's preferences. Following consultation, the company stated that it was inappropriate to exclude mortality because any deaths would mean the NHS is no longer paying for treatment. The ERG, however, considered that the company's approach potentially double counted mortality and preferred to exclude mortality and stopping treatment from the cost–consequence model and only include it in the budget impact model. The committee considered that, while approaches could differ, it was important that the approach used was internally consistent and did not double count the impact of mortality on budget impact. The committee was also aware that this had a negligible impact in the model and was content to consider the ERG's results. The committee understood that taking into account the confidential discounts available for eliglustat and ERT, eliglustat resulted in cost savings compared with ERT.

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

5.19 The committee noted that, because eliglustat is an oral therapy, it would give people the freedom to travel and attend university, and remove the need for people to take time off work for intravenous infusion appointments. It heard that the drug would be associated with important indirect mental health benefits because it allows people to live a more normal life. The committee concluded that eliglustat is likely to have a significant impact on people's lives beyond its direct health benefits.

5.20 The committee noted that, although eliglustat is an oral therapy, it will be important for people to have the drug started and to be monitored in expert centres. The committee understood from the company submission that no additional development or staff training above what is already in place for the provision of care will be needed in relation to eliglustat. The committee heard from the clinical experts that the availability of eliglustat will reduce the need for the nursing support that is often needed for home infusions of ERT, and patient experts highlighted the burden on specialist centres of running homecare services. The committee concluded that the impact of eliglustat on the delivery of specialised services is likely to be relatively negligible.

Conclusion

5.21 The committee understood that type 1 Gaucher disease can be a debilitating condition that has severe effects on the lives of people with the condition, and their families and carers. It agreed that there was uncertainty about the equivalence of eliglustat compared with ERT in the long term. However, the committee considered that, because it is an oral treatment, it could potentially provide important quality-of-life benefits for people currently having intravenous ERT, as well as for people who have not previously had treatment. Together with its consideration that eliglustat was cost saving compared with ERT, the committee concluded that it could recommend eliglustat, within its marketing authorisation, for treating type 1 Gaucher disease when ERT would otherwise be offered.

Summary of evaluation committee's key conclusions

HST5	Evaluation title: Eliglustat for treating type 1 Gaucher disease	Section
Key conclusion		

Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers. Eliglustat is only recommended when the company provides it with the discount agreed in the patient access scheme.		1.1
The committee concluded that eliglustat is an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty of effectiveness in comparison with enzyme replacement therapy (ERT) in the long term.		5.8
The committee appreciated the important advantages of an oral treatment and, together with its consideration that eliglustat was cost saving compared with ERT, the committee concluded that it could recommend eliglustat.		5.21
The committee noted that its considerations on the value for money of eliglustat were based on the current evidence and clinical practice, but that they would need to be reconsidered if ERT was no longer available in routine practice.		5.10
Current practice		
Nature of the condition, including availability of other treatment options	The committee understood that type 1 Gaucher disease is a debilitating condition with symptoms such as fatigue, bone pain and reduced mobility, which have a significant impact on quality of life.	5.1
	ERTs such as velaglucerase alfa and imiglucerase are established and effective treatments available in the NHS, but can be burdensome because they are administered intravenously.	5.2
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 noted that, because eliglustat is an oral therapy, it would give people the freedom to travel and attend university, and remove the need for people to take time off work for intravenous infusion appointments. The committee concluded that eliglustat is likely to have a significant impact on people's lives beyond its direct health benefits.	5.19

Adverse reactions	The committee understood that the adverse effects associated with eliglustat were acceptable to patients, especially in the context of the advantages of oral administration.	5.9
Clinical evidence		
Availability, nature and quality of evidence	The main evidence for eliglustat came from the ENCORE and ENGAGE trials. The statistical design of the ENCORE trial was to test non-inferiority. There were no trials comparing eliglustat with velaglucerase alfa.	4.4
	The committee noted the evidence review group's (ERG's) comments that the trials were of reasonable quality. It heard from the clinical experts that the populations were generalisable to patients in clinical practice in England.	5.3
Uncertainties generated by the evidence	The committee discussed the following areas of uncertainty: • dosages of eliglustat and ERT in the trials compared with dosage in practice • the lack of comparative data with ERT for patients who had not had previous treatment • the scarce data on patients with poor metaboliser status.	5.5, 5.6, 5.7
Impact of the technology	The committee concluded that eliglustat is an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty of effectiveness in comparison with ERT in the long term.	5.8
Cost evidence		

Availability and nature of evidence	The company submitted a cost–consequence model comparing eliglustat with imiglucerase and with velaglucerase alfa in 2 patient populations: those who were treatment naive and those who were taking ERT and whose disease was considered clinically stable. The semi-Markov model included 10 health states.	4.28
	The company presented a 5-year budget impact analysis to estimate the costs of eliglustat to the NHS.	4.39
Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis	**Cost–consequence analysis** The committee considered that there was uncertainty around the assumption of equivalence of eliglustat with ERT in the long term. The dose of ERT in the company's analysis was higher than that used in clinical practice. The committee considered that: • the company's assumption that mortality risk does not increase with disease severity was unrealistic • administration costs for ERT were likely to be overestimated in the company's model because they were higher than the costs of hospital administration • assuming no administration costs for eliglustat was unrealistic • the utility increment (0.12) assumed for oral treatment was too high and the true value was uncertain, but the alternative value (0.05) used by the ERG was more appropriate.	5.10, 5.11

	Budget impact model The company's analysis was based on estimates of total costs generated by the cost–consequence model, so uncertainties in the model carried through. The committee concluded that company's estimates of budget impact were additionally uncertain because: • the model excluded poor metabolisers • the dosage of ERT was assumed to be higher than in clinical practice • of incorporation of mortality and stopping treatment in estimated total costs. The committee considered the ERG's exploratory analyses around the assumptions made by the company to be more plausible.	5.17, 5.18
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 the ERG's comments that a utility increment of 0.12 (assumed by the company) was substantial when compared with the decrements from significant adverse events and the benefits of other oral therapies estimated in previous NICE submissions The committee concluded that, although the true value was uncertain, the alternative value (0.05) used by the ERG was more appropriate.	5.11
Cost to the NHS and PSS	Based on the ERG's exploratory analyses, and taking into account the confidential discounts available for eliglustat and ERT, eliglustat resulted in cost savings compared with ERT.	5.18

Value for money	Based on the ERG's exploratory analyses, and taking into account the confidential discounts available for eliglustat and ERT, eliglustat resulted in cost savings compared with ERT across the populations.	5.7
	The committee was mindful of the uncertainty around the long-term impact of eliglustat but appreciated the important advantages of an oral treatment. The committee concluded that, taking into the confidential discounts for ERT and eliglustat, eliglustat offered value for money compared with ERT.	5.13, 5.14
Impact beyond direct health benefits and on the delivery of the specialised service	The committee concluded that eliglustat is likely to have a significant impact on people's lives beyond its direct health benefits because it is an oral therapy.	5.19
Additional factors taken into account		
Equalities considerations and social value judgements	No equality issues that needed to be taken into consideration by the committee were identified.	–

6 Implementation

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

6.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has type 1 Gaucher disease and the doctor responsible for their care thinks that eliglustat is the right treatment, it should be available for use, in line with NICE's recommendations.

6.3 The Department of Health and the company have agreed that eliglustat will be available to the NHS with a patient access scheme which makes eliglustat available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Sanofi on GB-PatientAccess@Sanofi.com or 0800 854 430.

7 Recommendations for further research

7.1 The committee encourages the company, NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits and costs of eliglustat and enzyme replacement therapy for treating type 1 Gaucher disease.

8 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 appraisal is assigned to a team consisting of 1 or more health technology analysts, technical advisers, a project manager and an associate director.

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