

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Evaluation consultation document

Eliglustat for treating type 1 Gaucher disease

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using eliglustat in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of eliglustat in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation determination (FED).
- Subject to any appeal by consultees, the FED may be used as the basis for NICE's guidance on using eliglustat in the context of national commissioning by NHS England.

For further details, see the [Interim Process and Methods of the Highly Specialised Technologies Programme](#).

The key dates for this evaluation are:

Closing date for comments: 4 April 2017

Second evaluation committee meeting: 19 April 2017

Details of membership of the evaluation committee are given in section 7.

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

1 Recommendations

- 1.1 Eliglustat is not 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.
- 1.2 This guidance is not intended to affect the position of patients whose treatment with eliglustat 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.

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, Genzyme Therapeutics) 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 £249,999.02. 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 £124,999.51. 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 7) 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 units per kilogram per month of imiglucerase. The statistical design of the ENCORE trial was to test non-inferiority and 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 were not having treatment at time 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 patients time 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 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% 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 , $p=0.03$). There were small or no differences in bone-related outcomes: spine bone mass density (0.06), lumbar spine T-score (0.01) and Z-score (0.0), total femur bone mass 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 ($p<0.0001$). 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 – NCT00358150

- 4.12 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.

Clinical results – EDGE

- 4.13 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.

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) | 70.5 (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 | | | |

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, 81% of 93 patients who had switched from ERT to eliglustat said they preferred oral therapy because of the convenience it offered.

4.17 In the ENGAGE trial, eliglustat was associated with an improvement in disease-specific quality of life (fatigue severity score 0.7, 95% CI 0.02 to 1.33) compared with placebo at week 39. 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 company submission did not clearly explain how the pre-specified non-inferiority margin was derived for the ENCORE trial. It 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 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 not included in the marketing authorisation for eliglustat.
- 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 noted that, although few patients withdrew from ENCORE because of adverse events, only 44 of the 159 patients who started the trial were in the analysis at 4 years. The ERG highlighted that this unexplained loss of patients from follow-up brings uncertainty when interpreting the long-term results.

- 4.23 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.
- 4.24 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. The ERG noted the trial had a small sample size (n=26) and there was an unexplained loss of patients from later time points in the study. The ERG highlighted that, because of this, the treatment effects seen over the 4-year follow-up were uncertain.
- 4.25 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.
- 4.26 The ERG noted that the summary of product characteristics for imiglucerase and velaglucerase alfa recommend higher starting doses 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.

- 4.27 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.
- 4.28 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 these benefits 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

- 4.29 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.

- 4.30 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 (6.5-9.5), and severe (more than 9.5) disease. People could move between any of the living states in each cycle, or 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.
- 4.31 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.
- 4.32 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.
- 4.33 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. (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.

- 4.34 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.
- 4.35 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.

4.36 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 | £199,976 | £263,203 |
| | PM: £124,999.51 | | |
| Cost of infusing in hospital plus cost of nurse support at home | - | £1,751 | £1,751 |
| Management cost (for example, delivery, homecare services) | £480 | £12,587 | £12,587 |
| 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

4.37 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.

4.38 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.

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. | |

4.39 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

4.40 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).

4.41 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.

4.42 The company estimated that using eliglustat would result in 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

4.43 The ERG highlighted 2 main concerns about the structure of the model developed by the company: the use of long-term transitions in the model 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.

- 4.44 The ERG stated that assuming long-term equivalence of eliglustat and ERT underpinned the calculation of long-term benefits, and had a considerable 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.
- 4.45 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.
- 4.46 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.
- 4.47 The ERG considered that the company's assumptions about stopping treatment were reasonable given the lack of data available. However, it highlighted that the results from the model were very sensitive to stopping rates and the duration over which they were applied.
- 4.48 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.
- 4.49 The ERG identified the Wyatt et al. study (2012), which showed that the mean age at which treatment was started was 35.2 years in the treatment-naive population and was 46.4 years in those who were stable on treatment with ERT. The ERG considered that the starting age in the model was underestimated, therefore overestimating lifetime differences. The ERG explored this in its analyses

- 4.50 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. The ERG highlighted that this was a key driver in the model.
- 4.51 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.
- 4.52 The ERG noted concerns with the costs for ERT in the model. The ERG was concerned 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.
- 4.53 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

4.54 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.

4.55 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.

- 4.56 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.

4.57 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, 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.

- 4.58 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. 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. The committee discussed its main concerns with the evidence base:

- The ERG noted that the non-inferiority margin of 25% for the ENCORE trial was wider than normal. 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 placebo-controlled ENGAGE study, which included a treatment-naive population, also allowed inclusion of people who had previously had ERT provided they were not having treatment at the time of entry into the trial. Additionally, there were no comparative data with ERT for patients who had not had previous treatment.
- 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 7% of the Gaucher population are poor metabolisers, while 3% of people had poor metaboliser status in the ENGAGE trial.
- About 48% of patients in the ENCORE trial had a higher dosage of eliglustat (150 mg twice daily) than the recommended dosage stated 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 use of a higher dosage than in the marketing authorisation for eliglustat. The company stated that their modelling suggested only minor differences in plasma levels with the higher dose, and that it would be associated with a negligible gain. The committee understood, however, that the basis for this modelling were the blood concentration data from the trials in which dose adjustments had been made in response blood concentration measurements. Therefore, it concluded that the predictions were subject to bias.

The committee was mindful of the challenges in developing a clinical trial programme for a rare condition, but concluded that it would need to take these uncertainties into account in its decision-making.

- 5.4 The committee discussed the appropriate dose for the ERT. It was aware that the doses specified in the summary of product characteristics for imiglucerase and velaglucerase alfa (starting doses 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 doses 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 Gaucher disease occasionally have very severe disease and may need a higher starting dose. The committee also heard that there were no differences in the effect of eliglustat in the ENCORE trial when stratified according to ERT dose. The committee concluded that the dose recommended in the standard operating procedure was reflective of clinical practice.

- 5.5 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). However, it also noted the view of the European Medicines Agency's Committee for Medicinal Products for Human Use that the trial did not comprehensively show that the usual regulatory standard of -20% had been achieved. 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. The committee concluded that eliglustat could potentially be an effective treatment for type 1 Gaucher disease, but

remained concerned about the uncertainty about effectiveness in comparison with ERT, particularly in the long term.

- 5.6 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

- 5.7 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 concluded that this would add to any uncertainty around the value for money of eliglustat.
- 5.8 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:

- The company assumed that eliglustat and ERT have equal efficacy in patients who had not previously had treatment. The committee was aware that there was no direct evidence comparing eliglustat with ERT in this population. It agreed with the ERG that evidence from the ENCORE trial would have been more appropriate.
- 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. Moreover, the committee was aware that 48% of patients in ENCORE had a higher dose of eliglustat and these data were used in the model. The committee considered that there was uncertainty around the assumption of equivalence, especially in the long term.
- The dose of ERT used in the model was 42.4 U/kg, every 2 weeks, based on the mean dose of imiglucerase patients had in the ENCORE study. The committee recalled (see section 5.4) that a dose of between 15–30 U/kg was considered most reflective of clinical practice. The committee was aware that the dose of ERT was a key driver of results and that the ERG had explored the impact of including a dose of 25 U/kg. The committee considered that the ERG exploratory analysis that included a dose of 25 U/kg was appropriate, especially because the results of the ENCORE trial showed no difference in the response to eliglustat in terms of the dose of the comparator ERT.
- The company assumed that the mortality risk does not increase with disease severity. The committee considered that this was an unrealistic assumption. It noted that the ERG explored the impact of increased mortality risk for patients in the 'marked' and 'severe' health states.
- The company assumed that there are no administration costs associated with eliglustat because it is an oral therapy. The committee considered that the ERG's exploration including a monthly dispensary

cost for eliglustat was appropriate, noting that this had a minor impact on the results.

- The ERG highlighted that the administration costs for ERT were likely to be overestimated in the company's model because they were higher than the costs of hospital administration. The committee agreed that this was implausible and noted that the ERG had explored this assumption.

The committee considered that these reflected important uncertainties in the model, but was satisfied that the ERG had presented results based on assumptions preferred by the committee.

5.9 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.

5.10 The committee discussed the results of the company's cost–consequence model in the intermediate and extensive metabolisers. It understood that the company's model estimated the lifetime incremental benefit associated with eliglustat to be 2.44 QALYs for people who had not had

previous treatment and 2.28 QALYs for people whose disease was stable with ERT. The committee was aware that confidential discounts are available for eliglustat and ERT; the ERG incorporated these discounts as part of confidential analyses presented to the committee. Based on list prices, the company's results indicated that eliglustat was associated with an additional cost of £687,837 per patient compared with imiglucerase and a cost saving of £519,226 per patient compared with velaglucerase alfa for intermediate and extensive metabolisers whose disease was stable with ERT. The company's results for the treatment-naive population were similar to those in the population whose disease was stable with ERT (see table 4). The committee agreed that there was considerable uncertainty around these estimates because of the assumptions discussed in sections 5.8 and 5.9. The committee considered the ERG's exploratory analysis around these assumptions (see section 4.55) represented more plausible incremental costs and benefits associated with eliglustat. For people whose disease was stable with ERT with intermediate and extensive metaboliser status, it resulted in an incremental cost of £2,638,293 per patient compared with imiglucerase and a cost of £1,849,412 per patient compared with velaglucerase alfa. The committee noted that similar results were seen for the treatment-naive population with intermediate and extensive metaboliser status. 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. The committee noted that, for people with intermediate and extensive metaboliser status, eliglustat was associated with a substantial cost compared with ERT. The committee appreciated the important advantages of an oral treatment but considered that this alone did not justify the additional price charged by the company. The committee concluded that eliglustat did not offer value for money for people with intermediate and extensive metaboliser status, even when taking into account the cost–consequence results incorporating the confidential discounts for ERT and eliglustat.

5.11 The committee discussed the results of the company's cost-consequence model in the people with poor metaboliser status. For people with poor metaboliser status whose disease was stable with ERT, the cost savings associated with using eliglustat were estimated by the company at £1,698,539 and £2,905,602 per patient compared with imiglucerase and velaglucerase. 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. The results indicated that eliglustat remained cost saving but the extent of expected savings was substantially lower than the company's estimates. The expected savings were £6,825 per patient compared with imiglucerase and £795,706 per patient compared with velaglucerase alfa in the population whose disease was stable with ERT. The expected savings were £49,688 per patient compared with imiglucerase and £755,340 per patient compared with velaglucerase alfa in the treatment-naive population. The committee was also 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. Additionally, the committee noted that ERT for treatment of Gaucher disease (imiglucerase and velaglucerase alfa) had not been formally evaluated by NICE, so its value for money was also uncertain irrespective of metaboliser status (see section 5.7). This, together with the uncertainties in the evidence base for eliglustat, meant that the committee was not convinced that eliglustat offered value for money in people with poor metaboliser status.

5.12 Having noted that the ERG's exploratory analyses generally reflected the committee's preferred assumptions, the committee considered any substantial uncertainties around these results. The committee noted that the key driver of the difference between the ERG's and the company's results was the assumption around the dose of ERT. Recalling its discussion in sections 5.4 and 5.8, the committee was satisfied that the ERG's analyses reflected the dose of ERT used in clinical practice in

England and therefore concluded that the results were sufficiently robust for decision-making.

- 5.13 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

- 5.14 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.
- 5.15 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 costs of eliglustat. 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.

5.16 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. The committee understood that this increased the costs in year 5 from £571,487 to £11,123,765 and increasing the cumulative cost over 5 years from £1,623,219 to £34,701,740 based on list prices for all technologies. The committee noted that, taking into account the confidential discounts available for eliglustat and ERT, the budget impact associated with eliglustat compared with ERT decreased. However, the committee considered that the budget impact remained considerable, especially in the context that benefits of eliglustat over ERT related solely to the benefits of it being an oral treatment.

5.17 The committee considered the cost of eliglustat in the context of costs incurred by the company for research, development and manufacturing. It

heard from the company that this technology was not particularly different from other treatments in terms of development costs and, because of a much smaller eligible population than with other disease areas, this meant the costs for eliglustat were higher. The committee was not convinced that the high costs could be justified given the likely costs of development and the overall population eligible for treatment. The committee concluded that it had not been given enough justification for the high cost per person of eliglustat, or for the overall cost of eliglustat in terms of what could be expected to be reasonable in the context of a highly specialised service.

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

- 5.18 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.
- 5.19 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. The committee concluded that the impact of eliglustat on the delivery of specialised services is likely to be relatively negligible.

Conclusion

- 5.20 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. 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. The committee was mindful, however, of the substantial additional costs of eliglustat compared with ERT in people with intermediate and extensive metaboliser status. The committee was not convinced that these could be justified solely based on the benefits of an oral treatment. The committee recognised that eliglustat potentially offered cost savings in people with poor metaboliser status, but was mindful of the very limited evidence base for this population. The committee had concerns about the true value for money provided by eliglustat in this population, particularly when considering that the value for money of ERT itself was not established. The committee concluded that it could not recommend eliglustat, within its marketing authorisation, for treating type 1 Gaucher disease.

Summary of evaluation committee’s key conclusions

| | Evaluation title: | Section |
|---|--------------------------|----------------|
| Key conclusion | | |
| Eliglustat is not 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. | | 1.1 |
| The committee concluded that eliglustat could potentially be an effective treatment for type 1 Gaucher disease but remained concerned about the robustness of the results. It agreed that there was uncertainty about the equivalence of eliglustat compared with enzyme replacement therapy (ERT). However, the committee acknowledged eliglustat could provide valuable quality-of-life benefits for people because it was an oral treatment. The committee noted the substantial additional costs of eliglustat compared with ERT in people with intermediate and extensive metaboliser status. The committee was not convinced that these could be justified solely based on the benefits of an oral treatment. | | 5.20 |
| The committee recognised that eliglustat potentially offered cost savings in people with poor metaboliser status, but was mindful of the very limited evidence base for this population. The committee had concerns about the true value for money provided by eliglustat in this population, particularly when considering that the value for money of ERT itself was not established. | | |

| 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. 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. | 5.1 |
| | | 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. | 5.18 |
| 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. | 5.6 |
| 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. 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. | 4.4 |
| | | 5.3 |

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| <p>Uncertainties generated by the evidence</p> | <p>The committee had the following concerns:</p> <ul style="list-style-type: none"> • the non-inferiority margin of 25% for the ENCORE trial was wider than normal • there were no comparative data with ERT for patients who had not had previous treatment • there were few data on patients with poor metaboliser status • 48% of people in the ENCORE trial had a higher dosage of eliglustat than is specified in the marketing authorisation. <p>The committee was mindful of the challenges in developing a clinical trial programme for a rare condition, but concluded that it would need to take these uncertainties into account in its decision-making.</p> | <p>5.3</p> |
| <p>Impact of the technology</p> | <p>The committee concluded that eliglustat could potentially be an effective treatment for type 1 Gaucher disease, but remained concerned about the robustness of the results.</p> | <p>5.5</p> |
| <p>Cost evidence</p> | | |
| <p>Availability and nature of evidence</p> | <p>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.</p> <p>The company presented a 5-year budget impact analysis to estimate the costs of eliglustat to the NHS.</p> | <p>4.29</p> <p>4.40</p> |

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| <p>Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis</p> | <p><u>Cost–consequence analysis</u></p> <p>The committee considered that there was uncertainty around the assumption of equivalence of eliglustat with ERT, especially in the long term. There was uncertainty around the dosage of ERT used in the ENCORE trial, which was thought to be 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.</p> <p>The utility increment (0.12) assumed for oral treatment was considered to be too high. The true value was uncertain, but the alternative value (0.05) used by the ERG was more appropriate.</p> <p><u>Budget impact model</u></p> <p>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:</p> <ul style="list-style-type: none"> • 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. <p>The committee considered the ERG’s exploratory analyses around the assumptions made by the company to be more plausible.</p> | <p>5.8</p> <p>5.9</p> <p>5.15</p> <p>5.16</p> |
| <p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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?</p> | <p>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</p> <p>The committee concluded that, although the true value was uncertain, the alternative value (0.05) used by the ERG was more appropriate.</p> | <p>5.9</p> |

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| <p>Cost to the NHS and PSS</p> | <p>The committee considered that its preferred assumptions were reflected in the results of the ERG's exploratory analyses of the budget impact analysis. It understood that this increased the costs in year 5 from £571,487 to £11,123,765 and increased the cumulative cost over 5 years from £1,623,219 to £34,701,740 based on list prices for all technologies. The committee noted that, taking into account the confidential discounts available for eliglustat and ERT, the budget impact associated with eliglustat compared with ERT decreased. However, the committee considered that the budget impact remained considerable, especially in the context that benefits of eliglustat over ERT related solely to the benefits of an oral treatment.</p> | <p>5.16</p> |
| <p>Value for money</p> | <p>The committee had concerns about the true value for money provided by eliglustat, particularly when considering that the value for money of ERT itself was not established.</p> <p>The committee noted that, for people with intermediate and extensive metaboliser status, eliglustat was associated with a substantial cost compared with ERT. The committee appreciated the important advantages of an oral treatment but considered that this alone did not justify the additional price charged by the company. The committee concluded that eliglustat did not offer value for money for people with intermediate and extensive metaboliser status.</p> <p>The committee recognised that eliglustat potentially offered cost savings in people with poor metaboliser status, but was mindful of the very limited evidence base for this population. The committee was not convinced that eliglustat offered value for money in people with poor metaboliser status.</p> | <p>5.7</p> <p>5.10</p> <p>5.11</p> |
| <p>Impact beyond direct health benefits and on the delivery of the specialised service</p> | <p>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.</p> | <p>5.8</p> |
| <p>Additional factors taken into account</p> | | |
| <p>Access schemes</p> | <p>Not applicable</p> | <p>-</p> |
| <p>Equalities considerations and social value judgements</p> | <p>No equality issues that needed to be taken into consideration by the Committee were identified.</p> | <p>-</p> |

6 Proposed date for review of guidance

- 6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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

March 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 appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser, a project manager and an associate director.

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Technical Lead

Raisa Sidhu

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Associate Director

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