Cost-effectiveness of eliglustat (Cerdelga®) for the for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs)

The NCPE has issued a recommendation regarding the cost-effectiveness of eliglustat (Cerdelga®). The NCPE recommends that eliglustat (Cerdelga ®) should not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria as specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Genzyme) economic dossier on the cost effectiveness of eliglustat (Cerdelga®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **April 2018**

Summary

In May 2017, Sanofi Genzyme submitted a pharmacoeconomic assessment to the National Centre for Pharmacoeconomics (NCPE) to support the use of eliglustat (Cerdelga ®) for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6 poor metabolisers (PM), intermediate metabolisers (IM) or extensive metabolisers (EM). Eliglustat (Cerdelga ®) which is available as an oral hard-capsule formulation, containing 84mg eliglustat (equivalent to 100mg eliglustat tartrate). The recommended daily dose of eliglustat is 84 mg twice daily in CYP2D6 IM and EM, and 84 mg eliglustat once daily in CYP2D6 PMs. Eliglustat is not recommended in patients who are CYP2D6 indeterminate metabolisers or ultra-rapid metabolisers (URMs), as the accelerated metabolism of the drug may make it difficult to achieve therapeutic serum levels.

The comparator for the purpose of the pharmacoeconomic evaluation is the current first line standard of care for patients with GD1 in Ireland. Two enzyme replacement therapies (ERT) are considered first line therapy, imiglucerase (Cerezyme ®) and velaglucerase alfa (VPRIV ®). Both therapies require intravenous infusion every 2 weeks in either a home or outpatient hospital setting. The comparators were considered appropriate by the NCPE. Eliglustat offers eligible patients a daily oral alternative to biweekly ERT infusions. Should eliglustat (Cerdelga ®) be reimbursed, it is anticipated that it would be utilised first line in patients with GD1, either in treatment naïve patients or in patients whose disease is stable on ERT.

1. Comparative effectiveness of eliglustat

The efficacy data from clinical development programme supporting marketing authorisation for eliglustat was derived from two studies in the treatment naïve patient population with GD1 (ENGAGE and GZGD00304), and in one study in ERT treatment experienced patient population (ENCORE).

GZGD00304 was a phase 2 open label single-arm study to assess efficacy of eliglustat in 26 treatment naïve patients with GD1. The composite primary endpoint, requiring improvement from baseline to week 52 in at least 2 of the 3 main efficacy parameters (spleen volume, haemoglobin level, and platelet count), was met by 77% (95% CI: 58%, 89%) of the intention to treat (ITT) population and 91% (95% CI = 72%, 98%) of the 22 (85%) patients who completed week 52 assessments.

ENGAGE was a randomised, double-blind, placebo-controlled Phase 3 study evaluating the efficacy and safety of eliglustat compared to placebo in treatment naïve patients with GD1 over a 39-week primary analysis period (n=40). The ENGAGE study provides evidence of the potential clinical effectiveness of eliglustat compared with placebo in the treatment naïve patient population, however the RG note that patients recruited to the trial were not strictly treatment naïve as trial inclusion/exclusion criteria allowed for patients who had previously been treated with miglustat or ERT up to 6 or 9 months prior to randomisation. The primary efficacy endpoint in the ENGAGE study was the percentage change in spleen volume from baseline to week 39 with eliglustat compared to placebo. Spleen volume was significantly reduced for patients in the eliglustat arm (-28%) compared with a +2% increase for the placebo arm, resulting in a statistically significant treatment difference of 30.03% ($p>0.0001$).

The **ENCORE** study was an open-label, active comparator, non-inferiority, phase 3 randomised control trial designed to assess if eliglustat was non-inferior to imiglucerase at 52 weeks in patients with GD1 (n=160). The aim of the study was to establish whether patients with GD1 whose disease was considered stable having reached pre-specified therapeutic goals as defined by Pastores et. al 2004 while receiving ERT for at least 3 years would remain stable after switching to eliglustat therapy. The ENCORE study provides evidence of the potential clinical effectiveness of eliglustat compared with imiglucerase in the treatment experienced patient population. The primary objective of ENCORE study was to determine whether eliglustat would be deemed not clinically inferior to imiglucerase therapy by more than acceptable amount which was demonstrated at a -25% non-inferiority margin. In total 85% of patients who switched to eliglustat therapy from imiglucerase therapy in the ENCORE study met hematologic and organ volume disease stability criteria at 52 weeks compared with 94% of patients who were maintained on imiglucerase therapy. Therefore, the results demonstrate that patients who are stable on ERT and are switched to eliglustat from imiglucerase can do so without loss of efficacy in the majority of cases, however a minority of patients (~15%) will not remain stable on eliglustat and will be required to switch back to ERT therapy.

The evidence from the clinical trial programme which directly compares eliglustat therapy with an ERT is the ENCORE non-inferiority trial which compares eliglustat and imiglucerase in the ERT treatment stable population. No direct head to head evidence is available which

compares eliglustat with either ERTs in the treatment naïve population while no studies were undertaken which compare eliglustat with velaglucerase alfa in the treatment stable population rendering it difficult for the RG to indicate the performance of eliglustat in the treatment naïve patient population relative to either ERT therapy and in the treatment stable population relative to velaglucerase alfa.

2. Safety of eliglustat

The applicant provided a pooled safety analysis set included a descriptive summary of adverse events from the phase II study GZGD0030426 (n=26), ENGAGE (n=40), ENCORE (n=157), the lead in period of the EDGE (n=170) study. The Eliglustat Safety Set contained 393 patients who had received at least one dose of eliglustat, representing 535 patient-years of eliglustat exposure, with 14 patients receiving eliglustat for over 5 years and was conducted as part of the evaluation by the regulatory authorities. An analysis of the frequency of adverse events was undertaken along with a comparative analysis of adverse events associated with miglustat was undertaken because of concerns of a class effect associated with SRT. Of 393 patients, 334 experienced one or more adverse events. Most patients (92%) continued taking eliglustat; 8% (n=33) withdrew from one of the trials due to an adverse event, however only adverse events in 5 of these patients (1.3%) were considered related to eliglustat therapy. The following adverse events were reported in 10% or more of patients, regardless of relationship to eliglustat: headache (17%), arthralgia (14%), nasopharyngitis (13%), diarrhoea (10%), and dizziness (10%). Two adverse events considered related to eliglustat were reported in 5% or more of patients (headache and dizziness, both 5%). No relationship was observed between incidence of adverse events and dose of eliglustat. The RG note that rates of diarrhoea (10%), weight decrease (2%), tremor (1%), or peripheral neuropathy (2%) associated with eliglustat were markedly lower than noted for miglustat, suggesting that these are not class effects of glucosylceramide inhibition.

3. Cost effectiveness of eliglustat

The applicant submitted a cost utility model, based on a model reported by Ganz et al 2017, to consider the decision problem. The model was constructed in Microsoft Excel as a 10-health state Semi-Markov cohort state transition model which allows for the evaluation of the impact of costs and health benefits (QALYs) associated with the introduction of eliglustat therapy in two patient populations; the ERT treatment naïve patient population and ERT treatment experienced, disease stable adult patient population with GD1 in Ireland. The

analysis supports the comparison of eliglustat therapy with both first line standard of care ERT therapies; imiglucerase and velaglucerase alfa, in treatment of adult patients with GD1 which is also stratified by CYP2D6 metaboliser status.

In the base case analysis of the submitted HTA dossier and the various preferred scenarios, eliglustat was associated with an incremental QALY gain of 0.84 QALYs when compared with velaglucerase alfa and imiglucerase in a ERT-stable population. As there is no survival advantage between active treatments, there were no incremental life-years (LYs) associated with eliglustat treatment. The cost of treatment informs the largest proportion of total costs and subsequently the incremental costs. However incremental costs vary depending on the population treated (treatment naïve/ treatment stable), the metaboliser status of the patient group (IM/ EM or PM), the choice of comparator, the presence or absence of a PAS discount (velaglucerase alfa), and the average comparator dose of ERT employed in the model (the applicant presented doses of 29 units/33 units/ 42.4 units/kg/Q2W). The results of the incremental cost effectiveness analysis and budget impact analysis associated with the ERT treatment stable population are presented below. This patient population is expected to reflect the majority of GD1 patients in Ireland as the likelihood of being a PM is low (~5-10% of patients with GD1 in Ireland) and the IM and EM population are expected to comprise up to an estimated 90% of the GD1 population.

In the applicant's base case analysis, eliglustat is associated with an incremental cost of €495,882 and an incremental QALY gain of 0.84 giving a calculated base case incremental cost effectiveness ratio of €588,146/QALY relative to imiglucerase therapy. Relative to velaglucerase alfa, eliglustat is associated with an incremental cost of €44,718 and an incremental QALY gain of 0.84 giving a calculated base case incremental cost effectiveness ratio of €53,038/QALY.

The NCPE implemented a number of changes to the model, resulting in a final ICER of €2,388,466/QALY (incremental costs €2,013,782; incremental QALYs 0.84) comparing eliglustat to imiglucerase and a final ICER of 2,009,852/QALY (incremental costs €1,694,562; incremental QALYs 0.84) for the comparison of eliglustat relative to velaglucerase alfa.

Under the NCPE preferred scenario, the probability of cost-effectiveness of eliglustat relative to imiglucerase and velaglucerase alfa at the willingness-to-pay thresholds of €20,000 and €45,000/QALY was 0% and 0% respectively.

4. Budget impact of eliglustat

The list price per pack of 56 capsules of eliglustat is €24,785. As the applicant is seeking reimbursement for eliglustat under the High-Tech Drugs Scheme, the list price of eliglustat is further subject to rebate, high tech fee or wholesale mark-up fee which increases the cost per pack of 56 capsules of eliglustat to €25,529. The total annual cost of eliglustat per patient is dependent on a patient's CYP2D6 status. Patients who are intermediate or extensive metabolisers receive 100mg twice daily while poor metabolisers receive 100mg once daily. Less than 10% of all eligible patients are expected to be PM with an annual cost per patient of €166,392. Approximately 90% of all eligible patients are expected to be IM or EM with an annual cost per patient is expected to be €332,784.

The applicant estimates the gross budget impact of eliglustat to be approximately €18,094,095 over 5 years. The costs included in the applicant's budget impact analysis were linked with the cost utility model. These costs included the drug acquisition costs, administration costs (which relate to the cost associated with discontinuation and switching from ERT), medical resource use costs and social services resource use costs. CYP2D6 testing costs were not included and are assumed to be zero as the applicant proposes to absorb the costs of genotype testing. The applicant estimates that assumes a market share uptake of 56% in year 1 which translates as 5 patients being eligible for eliglustat therapy in year 1, increasing to 7 patients by year 5. The applicant also included direct medical and social service costs offsets from the introduction of eliglustat. However, the RG could not validate the direct medical and social service costs offsets from the introduction of eliglustat in the Irish clinical setting, which were excluded from the RG's revised budget impact analysis. The RG considered the patient and clinician preference to derive revised estimates of market share. This included the outputs from a survey undertaken in the ENCORE trial which indicated that patients overwhelmingly (94%) prefer an oral based therapy over an infusion therapy in GD1. In addition, the RG contacted a leading treating physician in Ireland who indicated that should eliglustat be reimbursed, all patients will be offered eliglustat therapy. Therefore, the RG consider a 100% market share to be more reflective of the patient and clinical perspective in year 1 (n=8) increasing by an additional 2 patients from year 2 to year

5 (n=10). A revised gross budget impact based on the RG's preferred assumption that all eligible patients would receive eliglustat treatment i.e. 100% market share and which excluded direct medical and social services costs yielded a revised 5-year cumulative projected gross budget impact of €15,308,053.

The applicant estimates the 5-year net drug budget impact following the introduction of eliglustat to result in a cumulative cost saving of - €1,083,205 while the NCPE estimates a 5-year cumulative net budget impact results in an increase in spending of €4,012,793 (excluding costs of ERT administration) or €3,387,791 (including costs of ERT administration).

5. Patient Submissions

No patient submissions were received during the course of this appraisal.

6. Conclusion

Following the NCPE assessment of the company's submission, the NCPE recommends that eliglustat (Cerdelga ®) should not be considered for reimbursement unless cost effectiveness can be improved relative to existing therapies. This recommendation should be considered in addition to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.