

5.05 ELIGLUSTAT, oral capsule, 100 mg, Cerdelga[®], Genzyme.

1 Purpose of Application

- 1.1 Section 100 listing for eliglustat for treatment of Gaucher Disease type 1 (GD1) patients over the age of 18. Given that other drugs subsidised for treatment of GD1 are not PBS-listed but are listed on the Life Saving Drugs Program (LSDP), the sponsor did not anticipate listing on the PBS and requested that eliglustat be considered for inclusion on the LSDP as per its main comparator.

2 Requested listing

- 2.1 The submission requested listing for the treatment of patients aged ≥18 years who have a confirmed diagnosis of GD1 and have at least one GD1 related disease manifestation including skeletal disease, haematological complications or gastrointestinal complications due to enlarged liver or spleen.
- 2.2 The basis for the proposed listing was cost minimisation against enzyme replacement therapy (ERT) currently listed on the LSDP (i.e. imiglucerase or velaglucerase-alfa).
- 2.3 Suggestions and additions proposed by the Secretariat to the requested listing below are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ELIGLUSTAT Tablet 100 mg	56	5	\$ [REDACTED]	Cerdelga Genzyme

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Gaucher disease type 1
PBS Indication:	Gaucher disease type 1
Treatment phase:	Initial
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	<i>Must be treated by a specialist physician with experience in the management of patients with Gaucher disease type 1.</i>

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<p>Clinical criteria:</p>	<p>Patient must have a confirmed diagnosis of Gaucher disease type 1.</p> <p>AND</p> <p>The condition must include one or more of splenomegaly, hepatomegaly, anaemia, thrombocytopenia, or skeletal disease.</p> <p>AND</p> <p><i>The treatment must not be administered concomitantly with enzyme replacement therapy for Gaucher disease type 1.</i></p>
<p>Population criteria:</p>	<p>Patient must be aged 18 years or older.</p> <p>AND</p> <p>Patient must have evidence of a CYP2D6 genotype that is classified as either a poor, intermediate or extensive metaboliser.</p>
<p>Prescriber Instructions</p>	<p><i>Clinical criteria are defined as:</i></p> <ul style="list-style-type: none"> - <i>Haemoglobin ≤ 105 g/L for females and ≤ 115 g/L for males on at least 2 occasions more than 1 month apart</i> - <i>Platelet count ≤ 120 x 10⁹/L on at least 2 occasions more than 1 month apart</i> - <i>Liver volume 1.25 times normal (CT or MRI); or spleen volume 5 times normal (CT or MRI)</i> - <i>Skeletal disease must be beyond mild osteopenia or Erlenmeyer flask deformity (symptoms, skeletal survey or MRI).</i> <p>The following dosing levels are recommended according to metaboliser status:</p> <ol style="list-style-type: none"> (1) patients classified as poor CYP2D6 metabolisers are to be prescribed 100 mg of eliglustat once daily; (2) patients classified as intermediate or extensive CYP2D6 metabolisers are to be prescribed 100 mg of eliglustat twice daily; (3) eliglustat should not be used in patients who are ultra-rapid or indeterminate CYP2D6 metabolisers. <p><i>Eliglustat is contraindicated in intermediate or extensive metabolisers taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor. Eliglustat is also contraindicated in poor metabolisers taking a strong CYP3A inhibitor. Co-administration with a strong CYP3A inducer is also not recommended.</i></p>
<p>Administrative advice</p>	<p>Confirmed diagnosis of GT1 can be established by either the specific deficiency of glucocerebrosidase enzyme activity in leukocytes or cultured skin fibroblasts, or by the presence of mutations in the glucocerebrosidase gene in tissue or peripheral blood leukocytes.</p> <p><i>For a list of CYP3A inhibitors and CYP2D6 inhibitors that may result in drug-drug interactions with eliglustat refer to the Product Information for eliglustat.</i></p>

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Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Gaucher disease type 1
PBS Indication:	Gaucher disease type 1
Treatment phase:	Continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	<i>Must be treated by a specialist physician with experience in the management of patients with Gaucher disease type 1.</i>
Clinical criteria:	Patient must have previously received PBS-subsidised therapy with this drug for this condition. AND <i>Patient must have demonstrated clinical improvement or stabilisation of Gaucher disease type 1 symptoms.</i> AND <i>The treatment must not be administered concomitantly with enzyme replacement therapy for Gaucher disease type 1.</i>
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions	Eliglustat is used in patients who are poor, intermediate or extensive CYP2D6 metabolisers, as determined by genotyping. The following dosing levels according to metaboliser status are to be adhered to: (1) patients classified as poor CYP2D6 metabolisers are to be prescribed 100 mg of eliglustat once daily; (2) patients classified as intermediate or extensive CYP2D6 metabolisers are to be prescribed 100 mg of eliglustat twice daily; (3) eliglustat should not be used in patients who are ultra-rapid or indeterminate CYP2D6 metabolisers, as determined by genotyping. <i>Eliglustat is contraindicated in intermediate or extensive metabolisers taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor. Eliglustat is also contraindicated in poor metabolisers taking a strong CYP3A inhibitor. Co-administration with a strong CYP3A inducer is also not recommended.</i>
Administrative advice	<i>For a list of CYP3A inhibitors and CYP2D6 inhibitors that may result in drug-drug interactions with eliglustat refer to the Product Information for eliglustat.</i>

2.4 The ESC noted that CYP2D6 and CYP3A inhibitors affect the metabolism of eliglustat and considered whether monitoring would be required. With reference to the relevant contraindications and precautions in the eliglustat Product Information, it

was agreed, however, that prescribers would likely minimise or avoid the co-administration of these interacting drugs when prescribing eliglustat.

3 Background

- 3.1 Eliglustat was approved by the TGA for “the long term treatment of adult patients with Gaucher disease type 1 (GD1)”, effective 17 February 2015.
- 3.2 The PBAC has not previously considered eliglustat for the treatment of GD1.

4 Clinical place for the proposed therapy

- 4.1 Gaucher disease is an autosomal recessive lysosomal storage disorder caused by acid beta-glucosidase (glucocerebrosidase or glucosylceramidase) deficiency, which results in the accumulation of its major natural substrate, glucosylceramide (GL-1), especially in cells of the liver, spleen, and bone marrow. Three clinical subtypes of Gaucher disease are recognised: type 1 (non-neuropathic), type 2 (acute neuropathic), and type 3 (subacute/chronic neuropathic). Gaucher disease type 1 (GD1) is the most common subtype in the US, Canada, and Europe, representing approximately 94% of the Gaucher disease population.
- 4.2 Eliglustat was nominated as a first-line oral therapy (alongside intravenous imiglucerase and velaglucerase-alfa) for GD1 patients with at least one GD1-related symptom.

5 Comparator

- 5.1 Imiglucerase and velaglucerase-alfa were nominated as the comparators. The ESC accepted the nominated comparators, however questioned whether miglustat, despite currently not being used in Australia, could also be an appropriate comparator.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission was based on one head-to-head trial (ENCORE) comparing eliglustat to imiglucerase (n=159). One supplementary trial (ENGAGE) comparing eliglustat to placebo (n=40) in a predominantly treatment naïve (87.5%) population was also presented.
- 6.4 Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
ENCORE (GZGD02607)	Primary Analysis Period Clinical Study Report. A Phase 3, Randomized, Multi-Center, Multi-National, Open-Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 who have Reached Therapeutic Goals with Enzyme Replacement Therapy (ENCORE).	Clinical study report 52 week primary analysis period [18 April 2014]
	104-WEEK RESULTS MEMO REPORT. Phase 3, Randomized, Multi-Center, Multi-National, Open-Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 who have Reached Therapeutic Goals with Enzyme Replacement Therapy.	104-Week Results Memo Report
Supplementary randomised trial		
ENGAGE (GZGD02507)	Double-Blind Primary Analysis Period Clinical Study Report. Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 (ENGAGE).	Clinical study report 39 week primary analysis period [28 March 2013]
	78-Week Results Memo Report. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1. (ENGAGE).	C78 week results memo [07 May 2014]
	Turkia et al. Engage: A phase 3, randomized, double blind, placebo controlled, multi center study to investigate the efficacy and safety of eliglustat in adults with Gaucher disease type 1: 9 month results.	J Inherit Metab Dis 2013;36:S268
	Mistry et al. Effect of Oral Eliglustat on Splenomegaly in Patients With Gaucher Disease Type 1. The ENGAGE Randomized Clinical Trial.	JAMA. 2015;313(7):695-706

Source: Table 11, pp50-54 of the submission

- 6.5 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Eliglustat versus imiglucerase					
ENCORE	159	R, OL 52 weeks	Low*	At least 3 years treatment with ERT	Maintenance of response in composite outcome of haemoglobin level, platelet count, spleen volume and liver volume
Eliglustat versus placebo					
ENGAGE	40	R, DB 39 weeks	Low	No SRT within last 6 months or ERT within last 9 months	Change from baseline in: spleen volume (primary outcome), haemoglobin level, platelet count and liver volume

DB=double blind; ERT = Enzyme replacement therapy; MC=multi-centre; OL=open label; R=randomised.

* Although ENCORE was open-label, the risk of bias is partially mitigated as some efficacy and safety outcomes (organ volume and bone imaging data, ECG and holter monitor data and nerve conduction data) were assessed by blinded central evaluators

Source: compiled during the evaluation

- 6.6 Whilst the outcomes measured in ENGAGE were similar to those in ENCORE (spleen volume, liver volume, platelet count and haemoglobin level), the interpretation within the trials was different. Patients in ENCORE (a non-inferiority trial) had already achieved a predefined therapeutic goal in all four measures prior to enrolment, and ENCORE was designed to compare the proportion of patients in which the therapeutic goals were maintained within a predefined margin after 52 weeks of treatment with eliglustat or imiglucerase. Whereas ENGAGE (a superiority trial) compared the absolute and relative changes in the four outcomes from baseline at 39 weeks of treatment with eliglustat and placebo.
- 6.7 Eliglustat was considered to be non-inferior to imiglucerase if the lower bound of the 95% confidence interval for the difference in the percentage of patients who remained stable at 52 weeks between eliglustat and imiglucerase was above -25% from the null. From the ENCORE Clinical Study Report (CSR (p34)), the non-inferiority margin was determined to be about halfway between the expected 95% for imiglucerase and the observed 51% for matched patients who had responded to imiglucerase and then discontinued treatment for 1 year. Although neither the CSR nor the sponsor provided a clear rationale for this approach, the ESC noted that setting an MCID halfway between an expected treatment effect outcome and an expected non-treated outcome has been used by regulatory agencies to provide indirect assurance of intrinsic efficacy when active-controlled trials are necessary rather than placebo-controlled trials. If applied here, this prespecified minimal clinically important difference (MCID) of 25% does not have a clinical basis. The CSR further stated that this accounts for a 10% difference between the active-comparator (imiglucerase, expected to have a response rate of 95%) and test treatment (eliglustat, expected to have a numerically inferior response rate of 85%) arms plus an additional 15% for the inherent variability in estimating the difference between these two treatments. The submission also claimed that the European Medicines Agency (EMA) suggested a non-inferiority margin of 20%. The submission's assumption that eliglustat could be considered non-inferior to imiglucerase even though it has a 10% lower expected response rate implied that a 10% lower response rate would not be clinically significant i.e. that the MCID for the proportion of GD1 patient who remain stable on treatment would be 10%. However, no evidence has been provided to support this claim. The PSCR contended that

“[t]he assumed 10% difference between eliglustat and imiglucerase was considered clinically acceptable in light of the variability of individual assessments and the nature of the composite endpoint that required stability in all four domains”.

- 6.8 The ESC did not find the arguments provided in the PSCR to be sufficient clinical justification for the stated non-inferiority margin between eliglustat and imiglucerase.
- 6.9 Although the submission stated that the criteria for stability in the composite outcome was based on Kishnani et al 2009, the criteria used in ENCORE was broader than that in Kishnani et al 2009, a randomised trial that compared the efficacy and safety of imiglucerase infusion given every 4 weeks versus every 2 weeks in GD1 patients. No explanation was provided as to why the margins for stability in ENCORE are greater than that in Kishnani et al 2009.

Comparative effectiveness

- 6.10 Table 3 summarises the results in ENCORE.

Table 3: Proportion of patients who remained stable in ENCORE based on the primary composite outcome and individual components of the composite outcome in per protocol set

	Eliglustat N=99, n(%)	Imiglucerase N=47, n(%)	Difference (95%CI)	OR (95% CI)	RR (95% CI)
Proportion of patients stable at week 52	84 (84.8)	44 (93.6)	-8.8% (-17.6, 4.2)	0.38 (0.10, 1.39)	0.91 (0.81, 1.01)
Patients whose haemoglobin did not decrease > 1.5 g/dL from baseline	94 (94.9)	47 (100)	-5.1% (-11.3, 2.7)	0.18 (0.01, 3.34)	0.95 (0.90, 1.01)
Patients whose platelet count did not decrease > 25% from baseline	92 (92.9)	47 (100)	-7.1% (-13.9, 0.7)	0.13 (0.01, 2.32)	0.93 (0.87, 1.03)
Spleen volume (in MN) did not increase > 25% from baseline*	68 (95.8)	39 (100)	-4.2% (-11.7, 5.0)	0.25 (0.01, 4.92)	0.96 (0.90, 1.03)
Liver volume (in MN) did not increase > 20% from baseline	95 (96.0)	44 (93.6)	2.4% (-4.9, 13.5)	1.62 (0.35, 7.55)	1.03 (0.94, 1.12)

* Not applicable for splenectomised patients, so eliglustat N=71, imiglucerase N=39

Text in italics indicate values calculated using StatsDirect during evaluation

Text in bold indicates statistically significant difference at 5%

Source: Table 26, p75 and table 27, p76 of the submission

- 6.11 The lower bound of the 95% CI for the primary outcome was -17.6%, thus the prespecified non-inferiority margin of -25% was met. Consideration was given as to whether the magnitude of change from baseline in the composite outcome are reasonably indicative of a “stable” patient AND the acceptance of the non-inferiority margin proposed by the submission. In the request for ACPM advice (p20) the TGA delegate commented that, “although non-inferiority was established at 52 weeks based on pre-defined criterion (composite outcome for stability) which was appropriate, the numerical results were in favour of CEREZYME (imiglucerase) for all outcomes (spleen volume, platelet count, haemoglobin) except liver volume. It is not clear whether this may be clinically significant over the long-term for any patients switching to eliglustat from ERT.” and had requested that the sponsor to comment on this issue in its pre-ACPM response.
- 6.12 There was no statistically significant difference in any of the measures for skeletal or bone disease or disability or in quality of life data reported with the SF-36 between eliglustat and imiglucerase treated patients.

- 6.13 The proposed dosing of eliglustat in Australia was noted to be markedly different to that used in ENCORE. In ENCORE, all patients were started on 50 mg twice daily, irrespective of CYP2D6 metaboliser status, and increased every fortnightly if the plasma trough level of eliglustat is < 5 ng/mL, up to a maximum of 150 mg twice daily. Whereas the proposed dose in the product information for eliglustat is 100 mg once daily for CYP2D6 poor metabolisers and 100 mg twice daily for CYP2D6 intermediate or extensive metabolisers (patients who are ultra-rapid or indeterminate metabolisers are contraindicated) with no regards to plasma trough levels. The submission argued that population pharmacokinetic analysis using data from healthy subjects and GD1 patients show that similar efficacy results would be achieved if patients used 100 mg twice daily instead of 150 mg twice daily, with an estimated 4% maximum increase for individual patient spleen volume with the higher dose. This claim could not be independently verified. The population pharmacokinetic (PopPK) simulation model provided with the submission only reported bioavailability (C_{max}, AUC) as the outcome, with no clinical outcomes reported.
- 6.14 The PSCR presented the results of a comparison of the observed change from baseline in spleen volume of six patients in ENCORE who received eliglustat 150 mg twice daily compared to the predicted change from baseline in spleen volume if the patient was to have received eliglustat 100 mg instead. The PSCR claimed that these six patients would have received 100 mg twice daily based on phenotype dosing rather than 150 mg twice daily based on the ENCORE trial dosing. The ESC noted the PSCR's claim, however considered that since there were 42 intermediate or extensive CYP2D6 metabolisers on 150 mg twice daily in the ENCORE trial, a post-hoc simulation of just six patients may not be adequately representative of all patients in ENCORE who received 150 mg twice daily. In addition, given the simulation only presented change in spleen volume (a secondary outcome), the results may not be representative of the proportion of patients who remain stable (the primary composite outcome including haemoglobin level, platelet count, change in liver volume and change in spleen volume).
- 6.15 The ESC considered that, given eliglustat would be dosed according to the TGA-approved dosing regimen, it was unclear whether a claim of non-inferiority with imiglucerase could be supported, given:
- patients who received 150 mg BD in ENCORE would receive 100 mg BD on the PBS;
 - there is some evidence that the lower dose of eliglustat will lead to a lower plasma concentration which may lead to worse clinical outcomes;
 - the additional pharmacokinetic modelling presented in the PSCR (as discussed above) is for one secondary outcome only and may not be representative of other relevant outcomes; and
 - the primary outcome of ENCORE is sensitive – if treatment with 100 mg BD instead of 150 mg BD resulted in 2 fewer eliglustat patients remaining 'stable' (i.e. 82/99), the results would not support non-inferiority at the 20% margin proposed by EMA (risk difference -10.8%; 95% CI: -20.8, 1.5).
- 6.16 In ENGAGE, treatment with eliglustat resulted in statistically significantly increased haemoglobin and platelet counts and statistically significant reductions in spleen and liver volumes compared with placebo, in a population of predominantly (87.5%) treatment-naïve patients. Patients treated with eliglustat did not perceive a change in

their quality of life other than a modest improvement in physical functioning as measured by the SF-36 compared to those treated with placebo.

- 6.17 The PSCR also responded to issues raised in the Commentary regarding the reliability of using a genotype test to inform the appropriate dose of eliglustat, especially if this method differed from the type(s) of test used in the studies which contributed data to the pharmacokinetic analyses. The PSCR advised that the method used in these studies was the same as would be used for the assessment of Australian patients and that the highly reproducible genotyping test produces phenotypic categories that have been standardised in pharmacogenomics. It was highlighted that the use of the phenotypic categories is illustrated in the Clinical Pharmacogenetic Implementation Guidelines for drugs metabolised by CYP2D6 and the laboratory being used for Australian patient testing is accredited by the National Association of Testing Authorities (NATA) for pharmacogenomics (specifically, NATA-accredited laboratory 3427).
- 6.18 Advice on this testing issue was also sought from the Medicare Benefits Division of the Department, which advised that although advice could not be provided on the CYP2D6 test until a co-dependent application was submitted to MSAC, performing the testing in a NATA-accredited pathology laboratory provided some re-assurance that safety and quality standards relating to the test would be performed to Australian standards given that this is not necessarily the case for testing conducted outside the provisions of the Schedule of Medicare Benefits.
- 6.19 The ESC noted the advice from the PSCR and MBD regarding the CYP2D6 testing and was also reassured that the test processing used in Australia was the same as the test processing used to generate the evidence for the pharmacokinetic analyses, thus avoiding the need for an assessment of comparative test performance. The ESC therefore accepted that the test was a reasonable method of informing eliglustat dose in the Australian context.

Comparative harms

- 6.20 In ENCORE, there were statistically significantly more (RR=1.15; 95% CI: 1.01, 1.38) patients treated with eliglustat who experienced any adverse events (97/106, 92%) compared with those treated with imiglucerase (42/53, 79%). There was also a statistically significantly greater proportion (RR=3.33, 95% CI: 1.59, 7.37) of patients treated with eliglustat who experienced treatment-related adverse events (40/106, 38%) compared with those treated with imiglucerase (6/53, 11%). The most significant differences were in gastrointestinal (RR=10.0, 95% CI 1.82, 58.1) and nervous system (RR=14.64, 95% CI 1.93, infinite) disorders. The PSCR argued that as the ENCORE trial was not powered or designed to detect significant differences in adverse events, the safety results reported in ENCORE should be interpreted with caution. The ESC noted that this is best achieved with reference to the confidence intervals presented.
- 6.21 There were eight total medical events of interest reported in patients treated with eliglustat; four events of syncope in three patients and four events of cardiac arrhythmia in three patients. However, only three atrioventricular blocks were adjudicated (investigator considered whether adverse events were possibly, probably or definitely related to the study drug) to be possibly related to eliglustat and all of the

syncope events were considered to be unrelated or only remotely possibly related to eliglustat treatment in ENCORE.

Benefits/harms

6.22 A summary of the comparative harms for eliglustat versus imiglucerase is presented in the table below.

Table 4: Summary of comparative harms (adjudicated to be related to treatment) for eliglustat and imiglucerase in ENCORE, safety/full analysis set

	Eliglustat N=106, n (%)	Imiglucerase N=53, n (%)	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Eliglustat	Imiglucerase	
Gastrointestinal	20 (19)	1 (2)	10.0 (1.82, 58.1)	19	2	17 (7.5,25.9)
Diarrhoea	5 (5)	0 (0)	<i>5.55 (0.68, inf)</i>	5	0	4.7 (-2.2,10.6)
Dyspepsia	3 (3)	1 (2)	<i>1.50 (0.22, 10.4)</i>	3	2	0.9 (-7.3, 6.5)
Nausea	3 (3)	0 (0)	<i>3.53 (0.40, inf)</i>	3	0	2.8 (-4.0,8.0)
GORD	3 (3)	0 (0)	<i>3.53 (0.40, inf)</i>	3	0	2.8 (-4.0,8.0)
Nervous system	14 (13)	0 (0)	14.64 (1.93, inf)	13	0	13.2 (6.1, 21)
Headache	4 (4)	0 (0)	<i>4.54 (0.54,inf)</i>	4	0	3.8 (-3.1, 9.3)
Somnolence	3 (3)	0 (0)	<i>3.53 (0.40, inf)</i>	3	0	2.8 (-4.8,8.0)

* Mean (SD) duration of follow-up was 421.4 (35.23) days for eliglustat and 404.4 (33.29) days for imiglucerase

Abbreviations RD = risk difference; RR = risk ratio

Text in italics indicate values calculated during evaluation using StatsDirect v2.7.8

Text in bold indicates statistically significant differences

Source: Table 37, p90 of the submission and Table 11-5, pp130-132 of ENCORE CSR

6.23 On the basis of direct evidence presented by the submission in ENCORE, for every 100 patients treated with eliglustat in comparison to imiglucerase:

- Approximately 9 fewer patients would be stable at week 52;
- Approximately 5 fewer patients would have haemoglobin levels that had not decreased from > 1.5 g/dL from baseline by week 52;
- Approximately 7 fewer patients would have platelet counts that had not decreased from > 25% from baseline by week 52;
- Approximately 4 fewer non-splenectomised patients would have a spleen volume that had not increased > 25% from baseline by week 52;
- Approximately 2 more patients would have a liver volume that would not increase > 20% from baseline by week 52;
- Approximately 17 additional patients would have gastrointestinal disorders over a mean duration of follow-up of 404.4 days to 421.4 days; and
- Approximately 13 additional patients would have nervous system disorders over a mean duration of follow-up of 404.4 days to 421.4 days.

Clinical claim

- 6.24 The submission described eliglustat as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over imiglucerase. These claims were not adequately supported as:
- The definition of a “stable” response in ENCORE was broader and more relaxed compared to Kishnani et al 2009 and the non-inferiority margin of 25% assumed that eliglustat is 10% worse than imiglucerase, which may not be reasonable for a non-inferiority claim as no reasonable justification for a MCID was provided in either the submission or the PSCR.
 - Whilst ENCORE, the pivotal clinical trial, did demonstrate that eliglustat is likely to be non-inferior to imiglucerase in the ability to maintain therapeutic goals in GD1, the dose of eliglustat used in ENCORE is greater than that proposed by the submission for the PBS population and therefore it is unclear if the efficacy from ENCORE is applicable to the PBS population.
 - ENCORE demonstrated that patients treated with eliglustat had statistically significantly more treatment-related adverse events than patients treated with imiglucerase, including severe events such as syncope, arrhythmias and cardiac conduction disorders.
- 6.25 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.
- 6.26 The PBAC considered that the claim of non-inferior safety was not adequately supported by the data.

Economic analysis

- 6.27 A cost-minimisation analysis against imiglucerase (as a representative for ERT) was presented by the submission.
- 6.28 The equi-effective doses were estimated as ERT (imiglucerase or velaglucerase-alfa) 42.4 U/kg/fortnight being equi-effective to eliglustat 196.81 mg daily (2755.34 mg per fortnight). The dose of ERT was taken from the 52-week mean dose of imiglucerase in ENCORE and the dose of eliglustat was taken from a weighted mean dose based on the estimated proportion of patients with poor versus intermediate/extensive metaboliser status based on the patients enrolled in ENCORE and ENGAGE with the recommended dose in the product information. The dose equivalence may not be appropriate as the approach to estimating the dose for each drug is inconsistent. The mean dose of eliglustat in ENCORE was calculated to be 228.3 mg daily, whilst the weighted mean Australian dose for imiglucerase (from years 1-10 post initiation of treatment) according to the ICGG registry was 32.4 U/kg/fortnight. The ESC noted that the submission’s approach of adjusting the eliglustat dose from the trial to reflect likely Australian usage, but not adjusting the imiglucerase dose was considered to be inconsistent. Alternative approaches would be to compare the likely Australian doses of eliglustat (196.8 mg daily) with imiglucerase (32.4 U/kg/fortnight), which would no longer provide assurance of equi-effectiveness, OR to rely on the mean doses used in ENCORE, which were 228.3 mg daily of eliglustat compared to 42.4 U/kg/fortnight of imiglucerase (which more directly reflect the evidentiary basis for any PBAC conclusion of non-inferiority).

- 6.29 The PSCR claimed that the dose equivalence of 196.81 mg eliglustat daily to 42.4 U/kg imiglucerase twice weekly was a “trial based relativity” based on ENCORE. The ESC considered this to be inaccurate as the mean dose of eliglustat in ENCORE was 228.3 mg daily; 196.81 mg was an ‘adjusted’ mean dose based on patient CYP2D6 metaboliser status and the TGA approved dosing regimen (100 mg BD for intermediate/high metabolisers; 100 mg D for poor metabolisers). ENCORE did not directly provide evidence that 196.81 mg eliglustat daily is equivalent to 42.4 U/kg imiglucerase twice weekly.
- 6.30 The ESC thus considered that the equi-effective dose should be based on the ENCORE trial as this was the highest standard of evidence available, whereby the equi-effective doses would be 228.3 mg daily of eliglustat compared to 42.4 U/kg imiglucerase twice weekly. The ESC noted, however, that these equi-effective doses were higher than the TGA-recommended doses. Given the uncertainty of the applicability of these doses to Australia and the low clinical need for a potentially inferior alternative, there is little basis to give benefit of the doubt to the sponsor.

Drug cost/patient/year

- 6.31 \$ [REDACTED] (assuming 100 mg BD and 13 scripts per year) compared with \$ [REDACTED] for imiglucerase (assuming [REDACTED] vials used per fortnightly infusion, for 26 infusions a year).
- 6.32 The submission’s estimate was based on an assumption of an average dose of 42.4 U/kg of imiglucerase in an average patient of 69.7 kg, resulting in [REDACTED] vials (at \$ [REDACTED] per vial) used per fortnightly infusion, for 26 infusions a year. Each infusion would also be associated with a MBS item cost for \$97.95.
- 6.33 The submission estimated that each eliglustat 100 mg capsule would cost \$ [REDACTED], based on a dose equivalence of eliglustat 196.8 mg daily and imiglucerase 42.4 U/kg fortnightly. If using the dose equivalence from the mean dose in ENCORE (i.e. eliglustat 228.3 mg daily and imiglucerase 42.4 U/kg fortnightly assuming a mean patient weight of 69.7 kg) was used, a cost of \$ [REDACTED] per eliglustat 100 mg capsule would be estimated, a 13% decrease from the submission’s estimate.
- 6.34 As the ESC considered that the equi-effective doses were more appropriately derived from the mean doses in the ENCORE trial, the estimated cost of \$ [REDACTED] per eliglustat 100 mg capsule was considered more acceptable.

Estimated PBS usage & financial implications

- 6.35 This submission was not considered by DUSC. The submission used a combination of epidemiological and market share approach to estimate the financial implications for the listing of eliglustat on the LSDP, relying on information from the ICGG registry and the LSDP for inputs. There were no adjustments for patient co-payments. The submission’s financial estimates are shown in Table 5.

Table 5: Submission’s financial estimates for listing of eliglustat on the LSDP

	2016	2017	2018	2019	2020
Number of patients					
Eliglustat					
Velaglycerase-alfa					
Imiglycerase					
Total					
ERT patients substituted for					
Total dispensed packs/vials on LSDP^A					
Eliglustat					
Velaglycerase-alfa					
Imiglycerase					
Vials of ERT substituted for					
Total cost of eliglustat	\$	\$	\$	\$	\$
Total cost of ERT substituted for	\$	\$	\$	\$	\$
Net cost to LSDP	\$	\$	\$	\$	\$
Cost savings from MBS*	-\$	-\$	-\$	-\$	-\$
Net cost to the budget	\$	\$	\$	\$	\$

^AAssumes each patient will use [redacted] packs of eliglustat per year or [redacted] vials of imiglycerase per infusion

*Based on assumption of reduced ERT administration costs.

Source: Attachment 9, Eliglustat_Section E_March 2015 PBAC.xlsx

- 6.36 The financial estimates may be an underestimate as the submission did not include costs for management of additional adverse events associated with eliglustat; and there was likely double counting involved in the inclusion of MBS savings (as this was included in the cost-minimisation analysis for deriving the price of eliglustat).
- 6.37 The redacted table above shows that in year 5, the submission’s estimated number of patients would be less than 10,000 and the estimated net cost to the LSDP would be less than \$10 million per year.

Quality Use of Medicines

- 6.38 The submission stated that risk minimisation material to support the quality use of eliglustat had been developed to guide patients and prescribers on the appropriate use of eliglustat. The sponsor also expressed a willingness to replace up to one box of eliglustat per year to any patient whose therapy has been lost or damaged. It was unknown if this was a calendar year or per year of treatment. The submission also discussed how eliglustat addresses the criteria for listing on the LSDP.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

7 PBAC Outcome

- 7.1 The PBAC rejected the request to list eliglustat on the PBS for the treatment of Gaucher Disease type 1 on the basis that the results of the direct randomised trial (ENCORE) suggested inferiority, and that clinically important inferiority could not be excluded with confidence.

- 7.2 The PBAC accepted that the nominated comparators, imiglucerase and velaglucerase-alfa, were appropriate.
- 7.3 The PBAC noted that on the basis of direct evidence presented by the submission in ENCORE, for every 100 patients treated with eliglustat in comparison to imiglucerase:
- Approximately 9 fewer patients would be stable at week 52;
 - Approximately 5 fewer patients would have haemoglobin levels that had not decreased from > 1.5 g/dL from baseline by week 52;
 - Approximately 7 fewer patients would have platelet counts that had not decreased from > 25% from baseline by week 52;
 - Approximately 4 fewer non-splenectomised patients would have a spleen volume that had not increased > 25% from baseline by week 52;
 - Approximately 2 more patients would have a liver volume that would not increase > 20% from baseline by week 52;
 - Approximately 17 additional patients would have gastrointestinal disorders over a mean duration of follow-up of 404.4 days to 421.4 days; and
 - Approximately 13 additional patients would have nervous system disorders over a mean duration of follow-up of 404.4 days to 421.4 days.
- The PBAC noted that these results were based on the per protocol analysis. The PBAC considered that this comparison might more clearly show inferiority of eliglustat compared with imiglucerase if it were based on the intention to treat analysis.
- 7.4 The PBAC noted that the lower bound of the 95% confidence interval for the primary outcome from ENCORE (% stabilised at week 52) was -17.6%, which fell within the pre-specified non-inferiority margin of -25%. The PBAC agreed with ESC, however, that the submission did not provide sufficient clinical justification for the 25% non-inferiority margin between eliglustat and imiglucerase.
- 7.5 The PBAC also noted that the lower bound for the primary outcome would also fall within the EMA suggested non-inferiority margin of 20%, however this was considered unreliable due to the high sensitivity of the primary outcome and the differences in dosing in the trial compared with that proposed for the PBS population. The PBAC noted that the dose of eliglustat used in the ENCORE trial (150 mg BD) was greater than that proposed by the submission for the PBS population (100 mg BD) and that if treatment with 100 mg BD instead of 150 mg BD resulted in 2 fewer eliglustat patients remaining 'stable' (i.e. 82/99), the results would not support non-inferiority at the 20% margin suggested by the EMA. The PBAC thus determined that the primary outcome measure did not conclusively demonstrate non-inferiority.
- 7.6 The PBAC also noted that in the ENCORE trial patients treated with eliglustat had statistically significantly more treatment-related adverse events than patients treated with imiglucerase, including severe events such as syncope, arrhythmias and cardiac conduction disorders.
- 7.7 Given that the PBAC did not consider that the submission had conclusively demonstrated non-inferiority, it also did not accept the cost-minimisation analysis. The PBAC further noted that the financial estimates presented may be

underestimated as the submission likely double counted the inclusion of MBS savings.

7.8 The PBAC noted that this submission is eligible for an independent review.

Outcome:

Rejected.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Genzyme firmly believes that Cerdelga provides significant clinical benefits through proven efficacy and safety for patients with Gaucher disease. This is the result of the largest Gaucher program ever developed and regulatory and health authorities in the US, Europe, Japan and Australia have approved Cerdelga as first-line therapy for adults with Gaucher disease type 1. Cerdelga is the only first-line oral therapy indicated for the treatment of Gaucher disease type 1. Genzyme is committed to bringing Cerdelga to patients around the world, and will explore ways to work with the Department of Health to make this important therapy available to Australian patients.