Record of the Rare Disorders Advisory Committee Ad-Hoc Meeting held on 8 July 2024

Rare Disorders Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Rare Disorders Advisory Committee meeting; only the relevant portions of the meeting record relating to Rare Disorders Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Rare Disorders Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present
Rhiannon Braund (Chair)
Emma Glamuzina
Helen Evans
James Cleland
Tim Stokes

Apologies
Adibah Khan
Carlo Marra
Katherine Neas

2. Summary of recommendations

	Pharmaceutical and Indication	Recommendation
•	Eliglustat for type 1 Gaucher disease within the context of treatments for rare disorders, subject to Special Authority criteria	Cost Neutral

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Rare Disorders Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021.Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Rare Disorders Advisory Committee is a Specialist Advisory Committee of Pharmac. The Rare Disorders Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Rare Disorders Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Rare Disorders that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Rare Disorders that differ from the Rare Disorders Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Rare Disorders Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Rare Disorders.

4. Welcome and introduction

4.1. The Chair welcomed the Committee with a karakia followed by whakawhanaungatanga.

4.2. Members noted this meeting was to consider an application deferred from the Committee's May 2024 meeting due to unforeseen circumstances.

5. Eliglustat for Gaucher disease

Application

5.1. The Advisory Committee reviewed the application for eliglustat for the treatment of Gaucher disease.

5.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

5.3. The Advisory Committee **recommended** that eliglustat be listed for Gaucher disease **only if cost neutral** to the health system cost of currently funded treatment with taliglucerase alfa, within the context of treatments for rare disorders, subject to the following Special Authority criteria:

> **Initial application** only from a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. The patient has a diagnosis of symptomatic Gaucher disease confirmed by the demonstration of specific deficiency of glucocerebrosidase in leukocytes or cultured skin fibroblasts, and genotypic analysis; and
> 2. Patient does not have another life-threatening or severe disease where the prognosis is unlikely to be influenced by eliglustat or the disease might be reasonably expected to compromise a response to eliglustat; and
> 3. Any of the following:
> 3.1 Patient has haematological complications of Gaucher disease; or

3.2 Patient has skeletal complications of Gaucher disease; or
3.3 Patient has significant liver dysfunction or hepatomegaly attributable to Gaucher disease; or
3.4 Patient has reduced vital capacity from clinically significant or progressive pulmonary disease due to Gaucher disease; or
3.5 Patient is a child and has experienced growth failure with significant decrease in percentile linear growth over a 6 to12 month period; and

Renewal only from a metabolic physician or any relevant practitioner on the recommendation of a metabolic physician. Approvals valid for 3 years for applications meeting the following criteria:
All of the following:

1. Patient has experienced a symptomatic improvement and improvements in the main symptom or symptoms for which therapy was started have been maintained; and
2. Patient has experienced a clinically objective improvement or no deterioration in haemoglobin levels, platelet counts and liver and spleen size; and
3. Radiological (MRI) signs of bone activity performed at two years since initiation of treatment, and five yearly thereafter, demonstrate no deterioration shown by the MRI, compared with MRI undertaken immediately prior to commencement of therapy or adjusted dose; and
4. Patient has not developed another medical condition that might reasonably be expected to compromise a response to eliglustat.

5.4. In making this recommendation, the Advisory Committee considered:

- Current treatment with fortnightly infusions affects the quality of life for people with health need from Gaucher disease as well as their whānau and the people who care for them.
- Good quality data shows that disease stability can be achieved with eliglustat for type 1 Gaucher disease, and outcomes (including spleen and liver volumes, and haematological and bone parameters) have been enduring for up to approximately 8 years.
- Eliglustat has the potential to relieve pressure on infusion services, if it is used for people who would otherwise receive enzyme replacement therapy (ERT) treatments ie imiglucerase and taliglucerase alfa, administered via intravenous infusion services.
- There may be cost savings to the person, and to the health system associated with eliglustat due to the oral administration of the treatment (ie not needing IV infusion time and/or resource).
- There is uncertainty regarding the safety and efficacy of eliglustat in type 3 Gaucher disease, however it is unlikely that evidence of this will be become available given the rarity of the condition and it would be reasonable to consider Gaucher disease as spectrum of disease and include this very small group in the recommended population.

Discussion

Māori impact

5.5. The Committee discussed the impact of funding eliglustat for Gaucher disease on Māori health outcomes. The Committee noted Gaucher disease is not one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus. The Committee considered that although there is no evidence to suggest Gaucher disease is more prevalent in Māori, this does not exclude the possibility that Māori with Gaucher disease experience inequitable access to specialist services and/or inequitable health outcomes.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

5.6. The Committee discussed the impact of funding eliglustat for Gaucher disease on people who have been underserved by the health system. The Committee did not identify any group with known inequitable health outcomes associated with Gaucher disease, but noted that the lack of available evidence did not exclude the possible presence of these inequities. The Committee considered that the time required travelling to, and receiving fortnightly currently funded treatment may inequitably affect people living rurally/at further distance from an infusion centre, or people who cannot afford the time away off paid work.

Background

5.7. The Committee noted the enzyme replacement therapy (ERT) imiglucerase was first funded in 1999 for people with type 1 Gaucher disease (GD1) via an application to the (now disestablished) Gaucher Panel, and in 2013 this listing was expanded to include people with type 3 Gaucher disease (GD3). The Committee noted in 2017, the Gaucher Panel reviewed funding applications for taliglucerase and velaglucerase and considered either agent would be a suitable alternative ERT for all people with Gaucher disease currently on treatment in New Zealand; Pharmac opened a competitive funding process (Request For Proposals (RFP)) for the supply of a first line ERT for the treatment of all people (GD1 and GD3) with Gaucher disease, and taliglucerase was awarded sole supply.

5.8. The Committee noted that taliglucerase is currently available on the Pharmaceutical Schedule for people who meet Special Authority Criteria, and people who have exceptional clinical circumstances meaning taliglucerase or IV infusions in general cannot be tolerated can apply for funded imiglucerase or (oral) miglustat via the Named Patient Pharmaceutical Assessment (NPPA) process.

5.9. The Committee noted in 2010 PTAC recommended that miglustat be funded for people with Gaucher disease who are intolerant to imiglucerase, but this proposal was not progressed as Pharmac was unable to negotiate a provisional listing agreement with the supplier. The Committee noted in 2016 the Gaucher Panel considered miglustat had a poor side effect profile and was clinically inferior to ERT. The Committee noted in November 2018, the Rare Disorders Subcommittee (now Advisory Committee) recommended that a new application for miglustat for Gaucher disease be declined based on low quality evidence of benefit and the adverse effect profile, and in February 2019, PTAC accepted the Subcommittee's recommendation.

5.10. The Committee noted in December 2023, Pharmac proposed to decline the applications for miglustat, and at the time of writing, Pharmac is reviewing consultation feedback on this proposal.

5.11. The Committee noted Pharmac has not previously considered an application for eliglustat.

Health need

5.12. The Committee noted Gaucher disease is an autosomal recessive lipid storage disease characterised by the deposition of glucocerebroside in cells of the macrophage-monocyte system (the liver, spleen, and bone marrow). The Committee noted that an increase in fat deposits over time can cause a range of symptoms relating to spleen and liver enlargement, anaemia, and bone involvement; symptoms include fatigue, easy bruising and a tendency to bleed, bone pain, degeneration and fractures. The Committee noted that in rare cases, the brain and nervous system are affected.

5.13. The Committee noted that the severity of Gaucher disease varies widely; some people present in childhood with virtually all the complications of Gaucher disease, whereas others remain asymptomatic into the eighth decade of life. The Committee noted that symptomatic patients may experience premature mortality from the consequences of splenectomy, severe bone disease, bleeding, infection, liver failure, or severe pulmonary disease.

5.14. The Committee noted that Gaucher disease has traditionally been divided into 3 clinical subtypes: GD1 being the most common, which accounts for 95% of cases, with no neurological involvement and occurs primarily in adults; Type 2 (GD2), which occurs in infants and results in mortality by 2 years of age; and GD3, which affects children and characterised by sub-acute neuropathological symptoms such as seizures, cognitive impairment and progressive encephalopathy. However, the Committee considered that some cases do not fit precisely into one of these categories, and the overall disease could instead be considered as a spectrum rather than comprising discrete groups.

5.15. The Committee noted GD1 affects between 1:50,000 and 1:100,000 people, and while it can affect anyone, it is reported to be the most common genetic disorder in Jewish people and with 1 in 450 people of Ashkenazi Jewish decent having some form of the disease. The Committee considered it difficult to estimate the prevalence of GD3 in New Zealand, but noted that internationally it is estimated to be about 1 in 200,000 people.

5.16. The Committee noted in 2018, there were 20 people receiving funded ERT for GD in New Zealand; 18 people with GD1 and two people with GD3. The Committee noted in 2023, 15 people were dispensed funded taliglucerase alfa, and 6 people were dispensed funded imiglucerase. This totals to 21 people, one more than those receiving funded therapy for Gaucher disease in New Zealand in 2018 (as per the Rare Disorders Subcommittee meeting record). The Committee noted that NPPA applications for miglustat have been considered for people with exceptional circumstances that prevent them from receiving ERT treatment.

5.17. The Committee noted is no data available regarding the incidence or severity of Gaucher disease in Māori to be able to assess inequities in Māori health outcomes, due to the rarity of Gaucher disease in New Zealand.

5.18. The Committee was not aware of any other population groups experiencing health inequities who are disproportionately affected by Gaucher disease, although people on low incomes would be disadvantaged by the current treatment as these people are less likely to be able to get time off work and attend for infusion. The Committee considered there was no data suggesting over-representation of Jewish people in the population with Gaucher disease in New Zealand.

5.19. The Committee noted that current treatment with ERT for Gaucher disease in New Zealand requires people to receive fortnightly intravenous (IV) infusions in hospital for a duration of two to four hours, not including travel time and time off work or study. The Committee considered this causes people to require time away from work and/or education. The Committee considered access to treatment may be more difficult for people experiencing barriers to traveling to hospital, and people living rurally.

5.20. The Committee noted that in November 2018, the Rare Disorders Subcommittee considered the health needs of people caring for individuals with Gaucher disease, and the impacts this can have on their quality of life.

5.21. The Committee noted consumer feedback received as part of the submission for eliglustat from the Gaucher Association of Australia and New Zealand. The Committee noted quality-of-life improvements reported by consumers, largely relating to the oral administration of eliglustat compared to infusions of ERT.

Health benefit

5.22. The Committee noted that eliglustat is a substrate reduction therapy that specifically inhibits glucosylceramide synthetase, with the goal to reduce rate of synthesis to match impaired catabolism. The Committee noted the treatment is not intended to treat Gaucher disease types 2 or 3, and that no evidence was identified assessing the efficacy and/or safety of the treatment in these populations, although the Committee considered it biologically plausible that its substrate reduction efficacy in type 1 disease might extend to types 2 and 3 disease.

5.23. The Committee noted that eliglustat is not approved by Medsafe, however it is approved by international regulatory agencies, such as the Therapeutic Goods Administration in Australia, for the treatment of adult patients with GD1.

5.24. The Committee noted eliglustat is extensively metabolised with high clearance, mainly by CYP2D6 and to a lesser extent CYP3A4. The Committee noted that before initiation of treatment with eliglustat, the applicant recommends that patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status. The Committee noted the recommended dose of eliglustat is dependent on a patient's CYP2D6 metaboliser status; 100 mg twice daily taken orally in patients with CYP2D6 intermediate or extensive metaboliser status, and 100 mg once daily taken orally in patients with CYP2D6 poor metaboliser status. The Committee noted the treatment is not recommended for ultra-fast or indeterminate metaboliser status.

5.25. The Committee noted results from the ENCORE trial, a Phase 3, randomised, multinational, open-label, non-inferiority trial which compared eliglustat (*n* = 106) with imiglucerase (*n* = 54) in people with GD1 who were stabilised on ERT (Cox et al. Lancet. 2015;385:2355-62). The Committee noted the composite primary efficacy endpoint was the proportion of people whose patients whose haematological variables and organ volumes remained stable after 12 months, with a non-inferiority margin of 25%. The Committee noted 85% of people met the primary outcome in the eliglustat group, and 94% in the imiglucerase group, with a between group difference of -8·8% (95% CI -17·6 to +4·2), which was within the prespecified threshold of -25%, and thus the Committee considered the study showed eliglustat to be non-inferior to imiglucerase in this population.

- The Committee noted the most common adverse events (AEs) deemed related to eliglustat were diarrhoea (five people), arthralgia (four people), fatigue (four people, and headache (four people). The Committee noted ECG analysis showed no significant effect of eliglustat on heart rate or cardiac repolarisation. The Committee noted no serious AEs were considered related to eliglustat treatment. The Committee considered there were notably fewer gastrointestinal AEs & less tremor than reported with miglustat.

5.26. The Committee noted results reported in a conference abstract for a 12-month extension of the ENCORE trial where all participants received eliglustat (Rosenbloom et al. Blood. 2014;124:1406). The Committee noted that among 99 of 106 patients who continued on eliglustat, stability was seen in spleen volume (96%), haemoglobin (97%), platelet count (94%), and liver volume (96%), and in 47 of 53 patients who received imiglucerase in the primary trial and then eliglustat in the trial extension, continued stability was seen also in spleen volume (97%), haemoglobin (100%), platelet count (90%), and liver volume (95%).

5.27. The Committee noted results of an extension of the ENCORE trial, which assessed the long-term clinical stability of participants over up to 4 years of treatment (Cox et al. Blood. 2017;129:2375-83). The Committee noted 46 people completed 4-years of treatment, and of the 111 participants who did not complete 4 years, 36 switched to commercial eliglustat when it became available, 48 exited the trial for logistical

reasons, and 12 withdrew from the trial because of an adverse effect. The Committee noted mean values for haemoglobin concentration, platelet count, spleen volume, and liver volume remained stable among all eliglustat-treated patients and in the subset of patients who had 4-year data. The Committee noted statistically significant, but clinically insignificant small changes were observed in liver volumes (3%) and spleen volumes (13%).

5.28. The Committee noted results from the ENGAGE trial, a Phase 3, randomised, double-blind, placebo-controlled trial assessing the effect of eliglustat on splenomegaly in previously untreated adults with GD1 (Mistry et al. JAMA. 2015;313:695-706). The Committee noted participants received eliglustat 50 or 100 mg twice daily (n = 20) or placebo (n = 20) for 9 months with the primary end point being percentage change in spleen volume in multiples of normal from baseline to 9 months.

- The Committee noted least-square mean spleen volume decreased by 27.77% (95% CI, -32.57% to -22.97%) in the eliglustat group and increased by 2.26% (95% CI, -2.54% to +7.06%) in the placebo group, with an reported absolute treatment difference of -30.03% (95% CI, -36.82% to -23.24%; P < .001).
- The Committee also noted an overall relative treatment difference of -6.6% (95% CI: -11.37, -1.91, P<0.01) in favour of eliglustat for reduction in liver volume, and overall relative treatment different of 1.2 g/dL (95% CI: 0.57, 1.88, P<0.001) for increased haemoglobin level, and 41.1% (95% CI: 23.95%, 58.17%, P<0.001) in platelet count.
- The Committee noted AEs occurred in 18% of people in the eliglustat group, and 14% of people in the placebo group. The Committee noted all treatment emergent adverse events (TEAEs) were graded as mild or moderate, and most were considered by the investigator to be unrelated to the study drug.

5.29. The Committee noted 18 month outcomes from an extension of the ENGAGE trial, which included 38 remaining participants (people on placebo for the original trial switched to eliglustat for the extension) (Mistry et al. Am J Hematol. 2017;92:1170-6). The Committee noted placebo-treated participants switched to eliglustat experienced apparent reversal of disease with similar time course and magnitude of improvement as was seen in the original eliglustat-treated patients during their first 9 months, and the adverse event profile during the first 9 months of the extension trial was consistent with that reported during the primary analysis period.

5.30. The Committee noted 4.5 year outcomes from an extension of the ENGAGE trial, which included 34 further remaining participants (with a decrease in participants due to 4 people switching to commercially available eliglustat) (Mistry et al. Am J Hematol. 2021;96:1156-65). The Committee considered the results indicated efficacy of eliglustat was maintained over time in regard to bone parameters, and maintained reduction in pertinent metabolites. The Committee noted the authors stated that quality of life scores improved and were maintained throughout the study, but had not provided the data to support this statement.

5.31. The Committee noted results for the EDGE trial, a Phase 3, randomised, double-blind trial assessing the efficacy of once daily dosing of eliglustat in adults with type 1 Gaucher disease who had experienced clinical stability on twice daily dosing (Charrow et al. Mol Genet Metab. 2018;123:347-56). The Committee noted all participants received eliglustat twice daily for a 6 to 18 month period (*N* =156), then those receiving pre-specified treatment goals for spleen and liver size, hemoglobin and platelets were randomised to once versus twice daily dosing (*n* = 131). The Committee noted the primary efficacy endpoint was maintenance of clinical stability in five domains (liver, spleen, haemoglobin, platelets, bone symptoms).

- The Committee noted 80.4% (95% CI: 67.6, 89.8) of participants in the once daily group and 83.1% (95% CI: 71.0, 91.6) of the twice daily group met the primary endpoint, with a mean difference of -.27% (95% CI -17.7, 11.9) between the two groups. The Committee noted that because the lower bound of the CI exceeded the pre-defined non-inferiority margin of -15%, once-daily dosing could not be declared non-inferior to twice-daily dosing.
- The Committee noted AEs were reported in 78% and 77% of once-daily and twice-daily patients, respectively; severe AEs in 11% of both groups; serious AEs in 11% and 12%, respectively; and related AEs in 27% and 23%, respectively. The Committee noted gastrointestinal AEs were again less common then reported in studies for miglustat.

5.32. The Committee noted results of a Phase 2, single arm study exploring the efficacy of eliglustat for adults with type 1 Gaucher disease (*N* = 26) for a period of up to 8 years (Lukina et al. Blood cells. Mol Dis. 2014;53:274-6; Lukina et al. Am J Hematol. 2019;94:29-38). The Committee considered the results indicated mean quality-of-life and disease severity improved in the first 3-4 years and were then maintained, but noted the data to support these claims was not shown in full. The Committee noted that across 169 patient years, 98% of AEs were mild-moderate, and 94% were considered unrelated to eliglustat. The Committee noted 8 serious AEs occurred over 8 years in five people, with one deemed possibly related to eliglustat (supraventricular tachycardia).

5.33. The Committee noted results published in a systematic review of the effective and safety of eliglustat for type 1 Gaucher disease, which included 16 publications published prior to ENCORE ENGAGE, and EDGE outcomes (Smid et al. Expert Opin Orphan Drugs. 2014;2:523-9). The Committee considered the review indicated that oral treatment was a promising alternative to ERT infusions for Gaucher disease and did not cause the same gastrointestinal AEs, but that frequently prescribed concomitant CYP2D6-inducing medications may restrict its use.

5.34. The Committee noted results from a pooled analysis of adverse events in 393 adults with Gaucher disease type 1 from the ENCORE, ENGAGE, EDGE, Phase 2 trials (Peterschmitt et al. Blood Cells Mol Dis. 2018;68:185-91; Peterschmitt et al. Orphanet J Rare Dis. 2019;14:128). The Committee noted rates of diarrhoea (10%), weight decrease (2%), tremor (1%), or peripheral neuropathy (2%) associated with eliglustat were markedly lower than noted in the product label for miglustat. The Committee noted a proportion (approximately 20%) of people required doses of 150 mg twice daily and considered this an important consideration when modelling the potential cost of eliglustat.

5.35. The Committee noted Cox et al. Genet Med. 2023;25:100329, which utilised the ENCORE, ENGAGE, EDGE, Phase 2 trials to assess the long-term effects of eliglustat on skeletal manifestations in clinical trials of patients with GD1. The Committee considered the results showed the potential for osteopenia to resolve with eliglustat treatment.

5.36. The Committee also reviewed the following publications provided by the applicant regarding evidence for the efficacy of eliglustat for Gaucher disease:

- Belmatoug et al. Eur J Intern Med. 2017;37:25-32
- Peat et al. Mol Genet Metab Rep. 2016;9:25-8
- Peterschmitt et al. Mol Genet Metab. 2023;138:107527
- Ibrahim et al. Mol genet Metab rep. 2016;8:17-9
- Mistry et al. Am J Hematol. 2020;95:1038-46

- Basiri et al. Elife. 2023;12:e8537
- Dumunico et al. Clin Ther. 2023;45:1105-10.

5.37. The Committee noted that all available evidence for eliglustat was limited to type 1 Gaucher disease in adults and no evidence was identified for the other disease subtypes, or for the use of eliglustat in children. Some Committee members considered that type 3 patients would be likely to benefit from eliglustat, however it was noted that there is no evidence in this group and unlikely that any will be generated. The Committee considered that type 2 was significantly different to types 1 and 3, and it was therefore appropriate to exclude this subgroup from this proposal.

5.38. The Committee considered there is uncertainty regarding the safety and efficacy of eliglustat in type 3 Gaucher disease, however it is unlikely that evidence of this will be become available given the rarity of the condition, and the Committee considered it would be reasonable to regard Gaucher disease as spectrum of disease and include this very small group (GD3) in the recommended population.

5.39. The Committee considered that in children under the age of 18 years there is uncertainty about safety of eliglustat, and considered that the decision to initiate treatment should be that of the treating clinician.

5.40. The Committee noted there was no data available directly comparing eliglustat with taliglucerase.

5.41. The Committee considered that good quality data indicates that disease stability can be achieved with eliglustat for GD1, and outcomes (including spleen and liver volumes, and haematological and bone parameters) were enduring for up to approximately 8 years. The Committee considered the available safety data indicates eliglustat appears to be well tolerated.

Suitability

5.42. The Committee considered that as an oral treatment, eliglustat has the potential to relieve pressure on infusion service, if it is used for people who would otherwise receive ERT treatments (ie imiglucerase and taliglucerase alfa) administered via intravenous infusion. The Committee noted that as a tablet-only formulation, eliglustat may not be suitable for very young children or people with swallowing difficulties.

5.43. The Committee considered the CYP2D6 metabolism of eliglustat limits is use in people requiring use of concomitant CYP2D6 inhibiting and inducing medications, including selective serotonin reuptake inhibitors, amiodarone, and treatments that prolong the QT interval.

5.44. The Committee noted the need for genotyping prior to commencing eliglustat. The Committee considered using a private company for this genotyping may be associated with risks of this system not being able to be maintained long-term, thus requiring testing capabilities and resource from New Zealand laboratories.

Cost and savings

5.45. The Committee noted that eliglustat is more expensive than the currently funded treatment for Gaucher disease (taliglucerase). However, the Committee considered there may be cost savings to the person, and to the health system associated with eliglustat due to the oral administration of the treatment (ie not needing IV infusion time and/or resource). The Committee also noted that many adults are unable to adhere to strictly fortnightly infusions, so the current predicted incremental cost may be lower than expected for these patients.

5.46. The Committee considered that genotype testing costs for CYP2D6 metaboliser status may need to be factored into economic analysis if cost-utility models are sensitive to this.

5.47. The Committee considered funded eliglustat would replace some use of taliglucerase, but not all, as some people would be indeterminate (2-4% in ENCORE) or ultra rapid (2-4% in ENCORE) metabolisers, and some will be on concomitant CYP2D6 metabolised drugs. The Committee noted eliglustat would not be used in combination with ERT.

5.48. The Committee considered it is unlikely that uptake to treatment would be significantly greater if an oral tablet were available instead of infusions.

Summary for assessment

5.49. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for [the pharmaceutical] if it were to be funded in New Zealand for [the indication]. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Adults with type 1 Gaucher disease, with slow, moderate, or extensive metaboliser status.
Intervention	The recommended dose of eliglustat is dependent on a patient's CYP2D6 metaboliser status: •100 mg twice daily taken orally in patients whose livers are CYP2D6 intermediate (IM) or extensive (EM) metabolisers; • 150mg twice daily in 20% of total patients •100 mg once daily taken orally in patients whose livers are CYP2D6 poor metabolisers (PM).
Comparator(s) (NZ context)	Taliglucerase, doses range from 30 units/kg to 60 units/kg, once every 2 weeks.
Outcome(s)	• Eliglustat met the criteria for non-inferiority to imiglucerase (an ERT) in maintaining stability of haematological and organ variables. • In line with previous clinical advice, taliglucerase is assumed to have similar efficacy to imiglucerase (Advice available in Appendix 4) • Suitability benefit as oral tablets compared to IV in the comparator.

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.