

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ELIGLUSTAT (CERDELGA — SANOFI GENZYME)

Indication: Type 1 Gaucher disease

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that eliglustat be reimbursed for the long-term treatment of adult patients with type 1 Gaucher disease who are CYP2D6 poor metabolizers, intermediate metabolizers, or extensive metabolizers, as determined by CYP2D6 genotype testing, if the following criterion and conditions are met:

Criterion:

- Eliglustat must not be administered concomitantly with enzyme replacement therapy (ERT) for type 1 Gaucher disease.

Conditions:

- Patient must be under the care of a clinician experienced in the diagnosis and management of Gaucher disease.
- Eliglustat should be reimbursed in a manner similar to that in which enzyme replacement therapies are reimbursed for type 1 Gaucher disease.
- Drug plan cost should not exceed the cost of other treatments for Gaucher disease.

Service Line: CADTH Drug Reimbursement Recommendation

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

ELIGLUSTAT (CERDELGA — SANOFI GENZYME)

Indication: Type 1 Gaucher disease

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that eliglustat be reimbursed for the long-term treatment of adult patients with type 1 Gaucher disease who are cytochrome P450 2D6 (CYP2D6) poor metabolizers, intermediate metabolizers, or extensive metabolizers, as determined by CYP2D6 genotype testing, if the following criterion and conditions are met:

Criterion:

- Eliglustat must not be administered concomitantly with enzyme replacement therapy (ERT) for type 1 Gaucher disease.

Conditions:

- Patient must be under the care of a clinician experienced in the diagnosis and management of Gaucher disease.
- Eliglustat should be reimbursed in a manner similar to that in which ERTs are reimbursed for type 1 Gaucher disease.
- Drug plan cost should not exceed the cost of other treatments for Gaucher disease.

Reasons for the Recommendation:

1. One open-label, head-to-head randomized controlled trial (RCT) (ENCORE; N = 159) demonstrated that eliglustat is noninferior to imiglucerase with respect to achieving disease stability (a composite of hematologic levels and organ volumes) over 52 weeks of treatment among ERT-experienced patients with well-controlled type 1 Gaucher disease. A supportive RCT (ENGAGE; N = 40) also demonstrated that eliglustat is superior to placebo in improving hematologic levels and organ volumes among treatment-naïve patients with type 1 Gaucher disease.
2. The manufacturer-submitted price of eliglustat is \$695 per 84 mg capsule. The recommended dosage is 84 mg once daily in CYP2D6 poor metabolizers or 84 mg twice daily in CYP2D6 intermediate and extensive metabolizers, with an annual cost of \$253,675 or \$507,350, respectively. Reanalyses of the manufacturer-provided cost-utility analysis by the CADTH Common Drug Review (CDR) indicated that eliglustat was likely dominated by (i.e., more costly and less effective than) ERTs (imiglucerase and velaglucerase). The exception was versus velaglucerase in the treatment-naïve population (the incremental cost-utility ratio was greater than \$1.3 billion per quality-adjusted life-year), due to small differences in adverse event profiles. Therefore, at the manufacturer-submitted price, eliglustat is not cost-effective for the treatment of patients with type 1 Gaucher disease.

Of Note:

CDEC heard from the patient group input to CADTH and a clinician experienced in the diagnosis and management of Gaucher disease that the availability of a treatment with an oral administration would potentially be of benefit by providing an additional therapeutic option for the management of type 1 Gaucher disease. The improvement in quality of life upon switching from bi-weekly intravenous (IV) infusions of ERT to oral eliglustat that was reported by patient groups was not evident in either of the RCTs.

Discussion Points:

- CDEC discussed the fact that, despite eliglustat achieving the pre-specified noninferiority outcomes versus imiglucerase in ENCORE, fewer patients randomized to eliglustat treatment than those who remained on imiglucerase met individual disease stability criteria (hematologic levels and spleen volume) except for reduced liver volume.
- CDEC discussed uncertainty regarding the noninferiority margins used in ENCORE, and noted similar concerns had been raised by several regulatory agencies (i.e., FDA and European Medicines Agency) and other health technology agencies (i.e., Pharmaceutical Benefits Advisory Council of Australia and the UK National Institute for Health and Care Excellence).

- Most of the patients randomized to eliglustat in the studies were treated with a dosage that was different from those recommended in the product monograph. CDEC noted that the clinical implications of these dosage differences are unclear.
- There are no comparative effectiveness or safety data comparing eliglustat to other treatments in patients with Gaucher disease who are treatment-naïve and to treatments other than imiglucerase in patients who are treatment-experienced.
- A key desire reported by patients was to have a treatment that effectively manages bone manifestations associated with Gaucher disease. However, the studies provided insufficient evidence on the effects of eliglustat in this regard. Patients with symptomatic bone manifestations within the year prior to study initiation were excluded, and the studies were not designed to evaluate bone morbidity as an outcome (e.g., nine months of treatment was insufficient to detect clinically important changes in bone disease).
- CDEC noted that eliglustat is currently not approved for use in children or for use in combination with ERT; however, there may be interest in expanding its use to include these populations. There is at present no evidence available on the efficacy and safety of eliglustat in combination with ERT. In the two pivotal trials, only two patients enrolled were younger than 18 years of age.
- CDEC discussed the higher frequency of adverse events, including serious adverse events, among patients treated with eliglustat versus imiglucerase. In particular, CDEC noted eliglustat has the potential to prolong the PR, QTc, or QRS intervals. The product monograph for eliglustat includes warnings and contraindications regarding its concurrent use with drugs that could potentially interact with eliglustat, and in patients with pre-existing cardiovascular conditions. Additional electrocardiogram monitoring is recommended for specific patient populations at increased risk of having these abnormalities. Patients with many underlying cardiac conditions were excluded from ENCORE.

Background:

Eliglustat has a Health Canada indication for the long-term treatment of adult patients with type 1 Gaucher disease who are CYP2D6 poor metabolizers, intermediate metabolizers, or extensive metabolizers, as determined by CYP2D6 genotype testing. Eliglustat is a substrate reduction therapy. It is available as an 84 mg capsule. The Health Canada-approved dosage is 84 mg once daily, orally, in CYP2D6 poor metabolizers and 84 mg twice daily in intermediate and extensive metabolizers.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs of eliglustat, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- Bone complications of Gaucher disease were noted as having the greatest negative impact on quality of life. In addition, physical symptoms such as enlarged livers and spleens (which often cause body-image problems, especially for younger patients), pain, and fatigue cause significant distress to patients and impact their ability to work and participate in leisure activities. Many patients also experience social isolation, anxiety, and emotional distress as a result of their conditions.
- ERT, the primary current treatment, requires IV infusion every two weeks, which patients find very inconvenient. They would prefer an oral treatment option.
- Nearly all of the seven respondents who had taken eliglustat reported very positive results.

Clinical Trials

The systematic review included two phase III RCTs of patients with type 1 Gaucher disease.

One 39-week double blind study (ENGAGE) evaluated the efficacy and safety of eliglustat tartrate (50 mg to 100 mg twice daily) versus placebo in patients (≥ 16 years of age) with type 1 Gaucher disease who were treatment-naïve ($N = 40$).

The 52-week open-label study (ENCORE) was designed to assess if eliglustat was noninferior to imiglucerase in adults with type 1 Gaucher disease who had been treated with ERT for at least three years and had reached therapeutic goals (N = 159). Patients were randomized to eliglustat tartrate (50 mg to 150 mg twice daily orally) or imiglucerase (median dose [REDACTED] [range [REDACTED] U/kg every two weeks IV).

Limitations of the trials include the small sample size of ENGAGE (N = 40), relatively short duration (nine months to 12 months), and the lack of support from the literature for the noninferiority margin in ENCORE. Neither trial was designed to assess outcomes identified as important by patient groups, such as bone disease, symptoms of Gaucher disease, or quality of life. A higher dosage range was used in ENCORE (up to 150 mg eliglustat tartrate twice daily) compared with the Health Canada–approved dose (84 mg eliglustat equivalent to 100 mg eliglustat tartrate twice daily). No studies were found that compared eliglustat to imiglucerase in treatment-naïve patients or that compared eliglustat to drugs other than imiglucerase in treatment-experienced patients with Gaucher disease.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following: disease stability, liver and spleen volume changes, hemoglobin and platelet level changes, bone disease, quality of life, and adverse events and serious adverse events. The primary outcome in the ENGAGE study was the percentage change from baseline to week 39 in spleen volume (measured in multiples of normal). In the ENCORE study, the primary outcome was the proportion of patients who remained stable at 52 weeks, defined as the change from baseline in the following measures: hemoglobin level did not decrease > 15 g/L, platelet count did not decrease > 25%, spleen volume (in multiples of normal) did not increase > 25%, and liver volume (in multiples of normal) did not increase > 20%.

The Short Form (36) Health Survey, a generic health status instrument, was used to measure health-related quality of life. Bone disease was assessed based on the change from baseline in bone mineral density of the femur and spine (T-scores and Z-scores), the bone marrow burden score (a measure of infiltration of Gaucher cells into the bone), and bone crises events.

Efficacy

- In treatment-naïve patients, eliglustat showed statistically significant reductions in spleen volume after 39 weeks of treatment compared with placebo (treatment difference in percentage change from baseline: -30%; 95% CI, -37% to -23%; $P < 0.0001$). Statistically significant differences between eliglustat and placebo were also detected in the percentage change from baseline in liver volume (-6.6%; 95% CI, -11.4% to -1.9%; $P = 0.007$) and platelet counts (41%; 95% CI, 24% to 58%; $P < 0.0001$), and in the absolute change from baseline in hemoglobin levels (12 g/L; 95% CI, 6 to 19 g/L, $P = 0.0006$).
- Among treatment-experienced patients with well-controlled Gaucher disease, 85% of those who received eliglustat remained stable for 52 weeks compared with 94% of patients treated with imiglucerase (absolute difference -8.8%; 95% CI, -17.6% to 4.2%). Eliglustat met the noninferiority criteria set by the manufacturer, as the lower limit of the 95% CI was within the pre-defined 25% noninferiority margin.
- Eliglustat met the noninferiority criteria versus imiglucerase, based on the percentage change in spleen volume (-2.8%; 95% CI, -8.1 to 2.5%), as the upper limit of the 95% CI was less than the 15% noninferiority margin in ENCORE.
- In the ENGAGE study, no statistically significant differences were detected between eliglustat and placebo in the individual domains or component scores of the Short Form (36) Health Survey, except for the physical functioning domain. Although the ENCORE study also reported data on the Short Form (36) Health Survey, there were no between-group comparisons. Thus, no conclusions can be made on the relative treatment effects.
- The studies were of too short a duration to provide meaningful data regarding reduction of bone complications, which, according to the information submitted by patient groups, have a large negative impact on patients' quality of life.

Harms (Safety and Tolerability)

- Serious adverse events were reported in 11 patients (10%) in the eliglustat group and no patients in the imiglucerase group in the ENCORE study. Except for syncope, which occurred in two patients, all other specific events were reported in one patient with no clustering in a particular system organ class. Two per cent of patients per treatment group stopped treatment due to adverse events.

- No serious adverse events were reported and no patients stopped treatment due to adverse events in the ENGAGE study.
- There were no deaths in either study.
- [REDACTED] neoplasms were reported in the eliglustat group ([REDACTED]) in the ENCORE study. No neoplasms were reported in the imiglucerase group in the ENCORE study, or in either group in the ENGAGE study.
- Cardiac arrhythmias or syncope were observed in [REDACTED] eliglustat patients ([REDACTED]) and no imiglucerase patients in the ENCORE study, and one patient (5%) in the placebo group and no patients in the eliglustat group in the ENGAGE study.
- Overall, 90% and 92% of patients who received eliglustat reported one or more adverse events in the ENGAGE and ENCORE trials, compared with 70% of patients who received placebo and 79% who received imiglucerase. The most frequently reported adverse events in the eliglustat groups were arthralgia, headache, nasopharyngitis, diarrhea, fatigue, nausea, and back pain.

Cost and Cost-Effectiveness

Eliglustat is available as a 84 mg capsule. The recommended dosage of eliglustat is 84 mg once daily in CYP2D6 poor metabolizers or 84 mg twice daily in CYP2D6 intermediate and extensive metabolizers. At a price of \$695 per capsule, the annual cost is \$253,675 for poor metabolizers or \$507,350 for intermediate and extensive metabolizers.

The manufacturer submitted a cost-utility analysis comparing eliglustat with two ERTs, imiglucerase and velaglucerase, in adult patients with type 1 Gaucher disease (treatment-naïve or treatment-stable) over a lifetime time horizon (up to 100 years) from the perspective of the Canadian health care payer. The manufacturer's model included health states based on disease severity. The manufacturer assumed equivalence of eliglustat with imiglucerase and velaglucerase based on a review of available clinical trial data. Thus, the same transition probabilities for health states were adopted from the eliglustat studies (short-term) and a retrospective cohort study (long-term). Data from manufacturer-commissioned systematic reviews and the published studies of eliglustat, imiglucerase, and velaglucerase were used to determine discontinuation and adverse event rates. Costs and utility values were obtained from published literature. In the base case, 96% of patients were assumed to receive two capsules of eliglustat per day. Based on a patient weight of 70 kg, the manufacturer reported in its base case that eliglustat dominated (i.e., is more effective and less costly than) both imiglucerase and velaglucerase.

CDR identified several key limitations with the submitted analysis:

- The assumption of comparative clinical efficacy between eliglustat and ERT is uncertain. Concerns were noted with the methodology (noninferiority margins) and results in the ENCORE trial. The eliglustat studies were conducted with short follow-up periods; thus, no information is available on continued long-term benefit. Furthermore, no appropriate comparison of eliglustat with velaglucerase was presented.
- The utility benefit for oral treatment compared with IV infusions (required for ERT) was overestimated. The manufacturer assumed a 0.23 utility benefit associated with oral therapy, which lacks face validity (i.e., the size of the benefit is greater than that of a patient on dialysis who obtains a kidney transplant) and is not supported by quality-of-life data from the clinical trials. This utility benefit is the key driver for the benefit in quality-adjusted life-years for eliglustat.
- The manufacturer overestimated the treatment dose of ERT. The manufacturer used a treatment dose of 60 U/kg of ERT, though the median dose used in the clinical trials was approximately [REDACTED] U/kg. Feedback from the clinical expert consulted by CDR and participating drug plans indicated that the average dose of ERT used in Canada is well below 60 U/kg.

Based on a CDR reference case, with the following assumptions – a patient of 70 kg, ERT dose of 40 U/kg, no nurse cost for home IV administration, and no utility benefit for oral versus IV administration – eliglustat is dominated (less effective and more costly) by both ERTs in the treatment-stable population and by imiglucerase in the treatment-naïve population based on minor differences in adverse event profiles. The incremental cost-utility ratio for eliglustat versus velaglucerase in the treatment-naïve population is more than \$1.3 billion per quality-adjusted life-year. When only costs were assessed, eliglustat is \$636,798 to \$701,462 more costly than imiglucerase and \$2,028,606 to \$2,071,406 more costly than velaglucerase (treatment-naïve and treatment-stable populations, respectively). The limitations that had the greatest impact on results were the assumption of large utility benefit associated with an oral route of administration for eliglustat and the overestimation of the ERT dose.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini,
Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson,
Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers,
Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

June 21, 2017 Meeting**Regrets:**

Two CDEC members did not attend the meeting.

Conflicts of Interest:

None