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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

ELIGLUSTAT (Cerdelga)

(Sanofi Genzyme)

Indication: Gaucher Disease Type 1

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Abbreviations

CDR	CADTH Common Drug Review
CYP2D6	cytochrome P450 2D6
DS3	Gaucher disease severity scoring system
ERT	enzyme replacement therapy
GD1	type 1 Gaucher disease
ICUR	incremental cost-utility ratio
IV	intravenous
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Eliglustat (Cerdelga)
Study Question	To estimate the cost and health outcomes of treatment with eliglustat relative to two alternative ERTs in adults with GD1, from the Canadian public health care payer perspective.
Type of Economic Evaluation	Cost-utility analysis
Target Population	• Symptomatic, treatment-naive patients • Patients stable on ERT treatment that either remain on ERT or switch to eliglustat
Treatment	Eliglustat: • 84 mg once daily in CYP2D6 poor metabolizers • 84 mg twice daily in CYP2D6 intermediate metabolizers and extensive metabolizers
Outcome	QALYs
Comparators	• Imiglucerase • Velaglucerase alfa
Perspective	Canadian public health care payer
Time Horizon	Lifetime (up to 100 years)
Results for Base Case	Eliglustat dominates (is less expensive and more effective than) both comparators
Key Limitations	CDR identified the following limitations: • **A large incremental utility benefit was applied for oral vs. IV administration:** An annual utility benefit of 0.23 was added to eliglustat given its oral administration (vs. infusion). Such a large incremental benefit lacks face validity and is not supported by quality-of-life data from the comparative clinical study. • **Overestimation of the ERT dose:** The manufacturer considered a dose of 60 U/kg for ERT [redacted] may be lower in Canada). • **An uncertain assumption of comparative clinical efficacy:** No direct comparison of eliglustat and ERT was available for treatment-naive patients. For the treatment-stable group, direct comparison was only available for eliglustat and imiglucerase, and the FDA and European Medicines Agency have noted concerns regarding the noninferiority margin and the trend in slightly poorer numerical differences in the trials' primary (surrogate) outcomes. The key eliglustat clinical studies are constrained by a short time frame (9 months to 12 months); long-term outcomes are based on a retrospective observational cohort study (DS3 study).
CDR Estimates	Assuming an ERT dose of 40 U/kg, $0 nurse cost for home IV administration, and no utility benefit for oral vs. IV administration, the results are as follows: • **Treatment-naive patients**: Eliglustat is dominated by (more costly and less effective than) imiglucerase and is associated with an ICUR of ~ $1.3B/QALY vs. velaglucerase based on minuscule differences in QALYs (due to AEs). • **Treatment-stable patients**: Eliglustat is dominated by imiglucerase and velaglucerase. If it is also assumed that there are no differences in AEs, the results are as follows: • **Treatment-naive patients**: Eliglustat is more costly than imiglucerase (+ $636,798) and velaglucerase (+ $2,028,606). • **Treatment-stable patients**: Eliglustat is more costly than imiglucerase (+ $701,462) and velaglucerase (+ $2,071,406).

AE = adverse event; B = billion; CDR = CADTH Common Drug Review; CYP2D6 = cytochrome P450 2D6; ERT = enzyme replacement therapy; GD1 = type 1 Gaucher disease; ICUR = incremental cost-utility ratio; IV = intravenous; QALY = quality-adjusted life-year; vs. = versus.

Drug	Eliglustat (Cerdelga)
Indication	For the long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 poor metabolizers, intermediate metabolizers or extensive metabolizers, as determined by CYP2D6 genotype testing.
Listing Request	As per indication
Dosage Form(s)	84 mg oral capsules
NOC Date	April 21, 2017
Manufacturer	Sanofi Genzyme

CYP2D6 = cytochrome P450 2D6; GD1 = Gaucher disease type 1.

Executive Summary

Background

Eliglustat (Cerdelga) is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are poor metabolizers, intermediate metabolizers, or extensive metabolizers of the enzyme cytochrome P450 2D6 (CYP2D6).[1] The dosage is 84 mg once daily in CYP2D6 poor metabolizers, and 84 mg twice daily in CYP2D6 intermediate and extensive metabolizers. It is administered orally. The submitted price of eliglustat is $695 per capsule ($253,675 or $507,350 annually).[2]

The manufacturer submitted a cost-utility analysis comparing eliglustat with two enzyme replacement therapies (ERTs), imiglucerase and velaglucerase, in treatment-naive and treatment-stable adult patients with GD1 over a lifetime time horizon (up to 100 years). The cost-utility analysis is from the perspective of the Canadian public health care payer. The manufacturer assumed equivalence between eliglustat and the ERTs based on a review of available clinical trial data. The same transition probabilities for eliglustat and the ERTs for health states were adopted from the ENGAGE and ENCORE studies (short-term) and a retrospective cohort study (long-term).[2] Data from manufacturer-commissioned reports and the published studies of eliglustat, imiglucerase, and velaglucerase were used to determine the discontinuation and adverse event rates applied in the model. Other inputs such as costs and utility values were obtained from published literature.

In its base case, the manufacturer reported that eliglustat dominated (was more effective and less costly than) imiglucerase or velaglucerase. In a probabilistic sensitivity analysis of 50 simulations, at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY), imiglucerase or velaglucerase were preferred treatment strategies in approximately 40% of simulations.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the submitted analysis.

Firstly, there was substantial uncertainty with the assumption of comparative clinical efficacy between eliglustat and ERT, given the lack of an appropriate indirect comparison between eliglustat and velaglucerase; there was concern that the noninferiority margin used in the ENCORE trial (comparing eliglustat with imiglucerase) was not supported by published literature (see CDR Clinical Report); there was concern that the numeric estimates in the ENCORE study indicated less favourable findings on surrogate outcomes compared with imiglucerase; and the follow-up in the ENCORE and ENGAGE studies was relatively short-term (nine

months to 12 months). The assumption of continued long-term benefit with treatment is also uncertain given the substantial amount of data missing from the cohort study used.

Secondly, the manufacturer assumed an annual utility benefit of 0.23 for patients receiving an oral treatment (eliglustat) compared with patients receiving intravenous (IV) infusions (imiglucerase, velaglucerase) based on a published study of patients receiving continuous iron-chelation therapy. This utility benefit is the key driver for the benefit in QALYs for eliglustat. However, it lacks face validity given the size of the benefit (e.g., greater benefit than a patient on dialysis obtains with a kidney transplant) and is not supported by quality-of-life data from the clinical trials (no difference in Short Form [36] Health Survey scores were observed between oral and IV treatments). While a small benefit associated with an oral treatment compared with an IV infusion may have been considered, an appropriate, quantifiable benefit was not identified for consideration in the CDR base case. Furthermore, the manufacturer used an ERT dose of 60 U/kg, which overestimates the dose of ERT likely to be used in practice (thus favouring eliglustat). The median dose used in the clinical trials was [redacted] U/kg; feedback from the clinical expert consulted by CDR and CDR-participating drug plans indicated the average dose used in Canada is well below 60 U/kg (BC Ministry of Health, Medical Beneficiary and Pharmaceutical Services Division, New Westminster, BC: personal communication, 2017 May, and Christopher Chen, Alberta Health, Edmonton: personal communication, 2017 May). This supports use of a lower ERT dose. Additionally, the manufacturer overestimated the costs of adverse events and ERT administration. The overestimation of adverse event costs may favour treatment with imiglucerase and velaglucerase; however, overestimating ERT administration costs may favour eliglustat.

CDR attempted to address these issues. In a plausible CDR reference case that assumes an ERT dose of 40 U/kg, $0 nurse cost for home IV administration, and no utility benefit for oral versus IV administration, eliglustat is:

- more costly than imiglucerase (+ $636,798 to + $701,462) and velaglucerase (+ $2,028,606 to + $2,071,406) in both treatment-naive and treatment-stable populations
- associated with a QALY decrement based on adverse event profiles compared with imiglucerase in both populations and compared with velaglucerase in the treatment-stable population (i.e., dominated by ERT)
- associated with an incremental cost-utility ratio (ICUR) of ~ $1.3 billion per QALY compared with velaglucerase in treatment-naive patients.

When considering costs alone, eliglustat was more costly than both imiglucerase (+ $636,798 to + $701,462) and velaglucerase (+ $2,028,606 to + $2,071,406).

The limitations that had the greatest impact on results were the assumption of a large utility benefit associated with an oral route of administration for eliglustat, and the overestimation of ERT dose.

Additional scenario analyses were undertaken that tested alternate ERT and eliglustat doses, alternate costing assumptions, and a smaller utility increment for an oral treatment compared with an IV treatment. In each of these analyses, eliglustat is either dominated or associated with an ICUR of at least $370,000 per QALY versus imiglucerase, and at least $1,170,000 per QALY versus velaglucerase.

Conclusions

The clinical equivalence of eliglustat and imiglucerase or eliglustat and velaglucerase is associated with substantial uncertainty given the lack of evidence comparing eliglustat with velaglucerase and the concerns with the noninferiority margin (noted by the FDA and European Medicines Agency) used in the comparison of eliglustat with imiglucerase based on the ENCORE study. Further, the preference for oral administration versus IV infusion appears to be overestimated by the manufacturer and is not supported by quality-of-life data from the submitted clinical trials.

Eliglustat 84 mg twice daily is more costly than imiglucerase or velaglucerase 40 U/kg every two weeks ($507,350 versus $449,258 and $357,302, respectively).

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing eliglustat with two enzyme replacement therapies (ERTs), imiglucerase and velaglucerase, in two patient populations with Gaucher disease type 1 (GD1): treatment-naive patients initiating therapy, and patients currently treated for GD1 with ERT. The time horizon was a patient lifetime (up to 100 years) with a one-year cycle length. The analysis used the Canadian public payer perspective. Patient characteristics for the model were based on the baseline data from the ENGAGE study (a treatment-naive, 39-week study) and the ENCORE study (a treatment-stable, 52-week study). All patients in the model started in a health state described by disease severity categories (defined by the Gaucher disease severity scoring system [DS3] as mild, moderate, marked, or severe hematologic and/or visceral symptoms) and the presence or absence of specific bone disease symptoms or manifestations (according to the distribution observed in the ENGAGE and ENCORE trial participants). In the model, patients may remain in the same health state, transition to a more or less severe health state, or die. All health states had a mortality risk (GD1-specific in the reference case) that varied by patient age and sex.

The submitted analysis assumed noninferiority for efficacy based on a review of four randomized controlled trials comparing the treatments of interest,[3-6] so transition probabilities were equal for each treatment strategy. The transition probabilities for the first cycle (first year) of the model were derived from the eliglustat arm of the ENGAGE and ENCORE clinical trials and from patients' initial year of treatment from the DS3 study.[7,8] Since ENGAGE was less than a year (39 weeks), the transition matrix for the final 13 weeks of the first year was based on the second-year probabilities from observational data (see the following paragraphs). Long-term transition probabilities (after the first year) were derived from the observational DS3 study by using regression equations (time on treatment, initial DS3 categories, and splenectomy status) to estimate transition.[7-9] The model also included an annual risk of discontinuation that varied by treatment; this was derived from relevant trials and literature.[10,11] A post-discontinuation drug cost, equal for all strategies, was assumed. Mortality was estimated from the GD1-specific International Collaborative Gaucher Group (ICGG) Gaucher Registry. Three adverse events in the model (headache, diarrhea, and abdominal pain) were derived from trial data[10-14] and differed based on treatment.

Generalized regression models were used to estimate the relationships between health state and utilities using data from patients in the DS3 study (n = 50), including DS3 severity categories, bone pain, severe skeletal complications, sex, and age at treatment initiation. The Short Form (36) Health Survey scores from the DS3 study were converted to EuroQol 5-Dimensions questionnaire (EQ-5D) utilities using a method previously developed.[15] An annual utility benefit (0.23) was assigned to eliglustat-treated patients to account for the preference for an oral route of administration over infusions, obtained from a study on iron-chelation therapy.[16] Additional disutilities of –0.174 and –0.204 were assigned to the adverse events of headache and diarrhea for a duration of 2.5 days and 16 days, respectively.[17,18]

The drug cost of eliglustat was obtained from the manufacturer based on the dosage of 84 mg twice daily. This dosage was assumed, as 96% of patients in the trials were intermediate or extensive metabolizers.[2] The eliglustat metabolizer test (Luminex xTAG CYP2D6 kit v2 assay) was stated to be covered by the manufacturer and is Health Canada–approved, and results can be available on the same day.[19-21] The costs of imiglucerase and velaglucerase were calculated based on the dosage of 60 U/kg every two weeks, using a weight of 70 kg (approximating the average weight of patients in ENGAGE and ENCORE) and assuming no wastage of product. Markup and dispensing fees were not considered in the analysis. The administration and monitoring costs of ERT treatments were calculated based on a weighted average cost of four administration settings (home, home with nurse support, day unit, and outpatient). Direct medical costs by health state were derived by utilization determined with consultation from clinical experts, using unit costs from the Ontario Schedule of Benefits for Physician Services. The direct medical costs included community-based medical services (general practitioner and specialist visits), bisphosphonate, specialist centre-based care (geneticist), hospital-based acute care (hospital and emergency visits), and social services (social works, home help, and housing worker). The costs of managing adverse events were also estimated from the Ontario Schedule of Benefits for Physician Services.

Manufacturer's Base Case

Treatment-Naive Population

In the reference case, the manufacturer reported that eliglustat, compared with imiglucerase or velaglucerase, is associated with an additional 3.31 QALYs. Treatment with eliglustat resulted in lower total health care costs of −$2,497,645 versus imiglucerase and −$403,365 versus velaglucerase. Eliglustat is the dominant strategy (more effective and less costly) (Table 2). Detailed results are provided in Table 21.

Table 2: Summary of Results of the Manufacturer's Base Case – Treatment-Naive Population

	Eliglustat	Imiglucerase	Difference (Eliglustat – Imiglucerase)	Velaglucerase	Difference (Eliglustat – Velaglucerase)
QALYs	15.90	12.59	3.31	12.58	3.31
Total costs ($)	8,671,374	11,169,019	−2,497,645	9,074,739	−403,365
ICUR ($/QALY)			Eliglustat is dominant		Eliglustat is dominant

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic report.[2]

Treatment-Stable Population

In the reference case, the manufacturer reported that eliglustat, compared with imiglucerase or velaglucerase, is associated with an additional 3.60 QALYs. Treatment with eliglustat resulted in lower total health care costs of −$2,711,893 versus imiglucerase and −$650,659 versus velaglucerase. Eliglustat is the dominant strategy (more effective and less costly) (Table 3). Detailed results are provided in Table 22.

Table 3: Summary of Results of the Manufacturer's Base Case – Treatment-Stable Population

	Eliglustat	Imiglucerase	Difference (Eliglustat – Imiglucerase)	Velaglucerase	Difference (Eliglustat – Velaglucerase)
QALYs	15.40	11.90	3.60	11.90	3.60
Total costs ($)	8,060,782	10,772,675	−2,711,893	8,711,441	−650,659
ICUR ($/QALY)			Eliglustat is dominant		Eliglustat is dominant

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic report.[2]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using Monte Carlo simulation and one-way deterministic sensitivity analyses that varied model parameters by using alternative values. A series of one-way sensitivity analyses were conducted by the manufacturer including time horizon (30 years to 100 years), mortality (Gaucher and general), discount rates (3% and 0%), percentage splenectomized (0% to 25%), body weight (50 kg to 90 kg), treatment discontinuation duration (0 years to 100 years), percentage of poor metabolizers (0% to 8%), costs (base-case value x 0.8 to base-case value x 1.2), health state utility (95% confidence interval), oral administration utility benefit (0.12 to 0.23), short-term transition probabilities (base-case value x 0.8 to base-case value x 1.2), regression coefficients (base-case value x 0.8 to base-case value x 1.2), and ERT doses (30 U/kg to 50 U/kg).

The reference case result for eliglustat versus imiglucerase in treatment-stable patients is eliglustat being the dominant strategy (less costly and more effective). The following parameters changed the reference case result:

- Body weight reduced to 50 kg: Incremental cost for eliglustat was $182,509, and incremental QALY was 3.31, with cost per QALY gained for eliglustat of $55,189.
- ERT doses reduced to 30 U/kg and 40 U/kg: Incremental costs for eliglustat were $2,271,189 and $681,578 respectively, and incremental QALY was 3.31, with cost per QALY gained for eliglustat of $680,406 (ERT 30 U/kg) and $202,358 (ERT 40 U/kg).

The manufacturer also provided a cost-utility analysis from the societal perspective by including productivity and travel cost. Eliglustat remained dominant.

According to the cost acceptability curve from the probabilistic sensitivity analyses of 50 simulations, at a willingness-to-pay threshold of $50,000 per QALY, eliglustat was the optimal treatment strategy in 60% of iterations.

Limitations of Manufacturer's Submission

- **Uncertain assumption of comparative clinical efficacy:** The manufacturer assumed noninferiority of eliglustat with ERT (imiglucerase or velaglucerase) in patients with GD1 based primarily on naive indirect comparisons (eliglustat versus placebo or ERT versus placebo). There is currently no direct evidence comparing eliglustat and ERT (imiglucerase or velaglucerase) in treatment-naive patients. For the treatment-stable group, direct comparison was available only for eliglustat versus imiglucerase based on one 52-week trial. The CADTH Common Drug Review (CDR) clinical reviewers noted that the noninferiority margin chosen was not supported by published literature. Thus, the noninferiority assumption may be uncertain. The CDR clinical reviewers did note that the noninferiority margin was accepted by Health Canada. Additionally, the model used data from a retrospective cohort study (DS3 study; see the CDR Clinical Report, Appendix 9, for details). These data informed long-term transition probabilities based on DS3 score categories. However, there were substantial missing data for some measures used to estimate the DS3 score in the study and there is uncertainty about the comparative long-term efficacy between eliglustat and the ERTs. The assumption of clinical noninferiority while applying utility differences based on adverse event data captured in the same trials used to assume equivalent efficacy is not appropriate, nor is an assumption of a utility increment based on different disease and different conditions.
- **Utility benefit for oral administration:** An annual utility increment of 0.23 was applied to eliglustat for oral administration compared with intravenous (IV) infusions. The utility increment was obtained from a study on iron chelation that might not be applicable to GD1 patients (very low-quality evidence). Further, the estimate obtained lacks face validity as it suggests that patients would trade 84 days of perfect health every year in order to obtain oral treatment compared with treatment via IV infusion. This magnitude is greater than the benefit a patient on dialysis obtains with a kidney transplant.[22] Additionally, the manufacturer also conducted a study (available in abstract form only; not provided with submission) that estimated utility benefits of oral administration versus IV at half this value.[23] The face validity of this study is questionable since it cannot be critiqued further, given that it is available only as an abstract. Finally, the Short Form (36) Health Survey scores from the ENGAGE and ENCORE trials were not significantly different between groups (see the CDR Clinical Report), suggesting that there may be no discernable difference in quality of life. If any utility benefit occurs, it may attenuate over time. This assumption favours eliglustat.
- **Overestimation of ERT dose:** A dose of 60 U/kg was assumed in the base case for ERT. As indicated by the clinical expert and provincial data (BC Ministry of Health, Medical Beneficiary and Pharmaceutical Services Division, New Westminster, BC: personal communication, 2017 May, and Christopher Chen, Alberta Health, Edmonton: personal communication, 2017 May), the average dose used in Canada is closer to 30 U/kg. Further, the median dose used in ENCORE was [redacted]U/kg every two weeks ([redacted]). While this likely leads to an overestimation of the cost of ERTs, the model also assumed no wastage, which might underestimate ERT costs in some scenarios.
- **Cost of ERT administration:** The resources required for administration of ERT in most settings is provided by pharmaceutical companies, with the health care payer assuming administration costs only very rarely, such as in a hospital outpatient setting (as per the clinical expert, the majority of infusions in adult patients are done at home). The manufacturer model assumes that infusion costs are covered by companies with the exception of those costs that require a nurse for home infusion, or infusion in a clinic setting. As reflected by some provincial data, manufacturers covered home infusion costs, including nursing staff, and the provincial ministry paid for some outpatient infusions where no other resources were available (BC Ministry of Health, Medical Beneficiary and Pharmaceutical Services Division, New Westminster, BC: personal communication, 2017 May, and Christopher Chen, Alberta Health, Edmonton: personal communication, 2017 May).
- **Overestimation of adverse event costs:** A specialist visit was assumed with the adverse events, which might overestimate the adverse event costs. However, this assumption may bias against eliglustat (versus velaglucerase), as adverse effects are more common with eliglustat.

CADTH Common Drug Review Reanalyses

The CDR considered the following analyses to address the limitations identified:

1. **ERT dose:** Using doses [redacted] and more likely to be used in Canada.
2. **Exploring more likely costs for ERT administration:** While these costs were likely overestimated, they are small and have minimal impact on conclusions.
3. **Exploring more likely costs to manage adverse events:**
   Adverse event costs were likely overestimated (favouring ERT), but these costs are relatively small and have minimal impact.
4. **More reasonable assumptions for the preference of oral versus IV administration**.

Table 4: CDR Reanalysis for Treatment-Naive Patients – Plausible Reference Case

	Description	Eliglustat vs. Imiglucerase			Eliglustat vs. Velaglucerase		
		Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
	Manufacturer's base case	−$2,497,645	3.31	Dominant[a]	−$403,365	3.31	Dominant[a]
1	**ERT dose**						
1a	30 U/kg	$2,192,625	3.31	$663,024/QALY	$3,230,067	3.31	$974,626/QALY
1b	40 U/kg	$629,202	3.31	$190,263/QALY	$2,018,923	3.31	$609,181/QALY
1c	50 U/kg	−$934,222	3.31	Dominant[a]	$807,779	3.31	$243,735/QALY
2	**ERT administration cost**						
2a	Home nurse cost $0	−$2,490,048	3.31	Dominant[a]	−$393,682	3.31	Dominant[a]
2b	Home nurse cost $0 and outpatient usage 50% of manufacturer's base case	−$2,478,557	3.31	Dominant[a]	−$372,553	3.31	Dominant[a]
2c	Home nurse cost $0 and no outpatient usage	−$2,462,708	3.31	Dominant[a]	−$349,963	3.31	Dominant[a]
3	**AE costs**						
3a	No specialist cost for AEs	−$2,498,149	3.31	Dominant[a]	−$402,942	3.31	Dominant[a]
4	**Utility benefit for oral vs. IV treatment**						
4a	Utility benefit is 0.12	−$2,497,645	1.72	Dominant[a]	−$403,365	1.73	Dominant[a]
4b	No utility benefit	−$2,497,645	−0.01	Less costly, less effective	−$403,365	0.001	Dominant[a]
5	**Plausible reference case (1b, 2a, 4b)**	**$636,798**	**−0.01**	**Dominated[b]**	**$2,028,606**	**0.001**	**>$1.36B/QALY**

AE = adverse event; B = billion; CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; ICUR = incremental cost-utility ratio; IV = intravenous; QALY = quality-adjusted life-year; vs. = versus.

Note: In the plausible reference case, the very small differences in incremental QALYs are attributable to AEs. It may be suitable to consider a cost-minimization approach for this scenario, as shown in Table 7 in the price-reduction scenarios, where incremental cost was reported.

[a] "Dominant" means that eliglustat is more effective and less costly.

[b] "Dominated" means that eliglustat is as or less effective, and more costly.

Additional scenario analyses were conducted on the plausible reference case, which considered revised adverse event costs, a revised utility benefit for oral versus IV administration, a revised administration cost assumption, and revised dosages of eliglustat (48% of ENCORE patients received 150 mg twice daily [equivalent to 126 mg eliglustat]). The results are presented in Table 5.

Table 5: CDR Reanalysis for Treatment-Naive Patients – Scenario Analyses

	Description	Eliglustat vs. Imiglucerase			Eliglustat vs. Velaglucerase		
		Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
5	Plausible reference case (1b, 2a, 4b)	$636,798	−0.01	Dominated	$2,028,606	0.001	> $1.36B/QALY
6	**Scenario analyses of CDR reference case with the following:**						
6a	No AE costs	$636,295	−0.01	Dominated	$2,029,029	0.001	> $1.36B/QALY
6b	Utility benefit is 0.12	$636,798	1.72	$369,655/QALY	$2,028,606	1.73	$1,172,716/QALY
6c	ERT administration cost borne by health care system	$629,202	−0.01	Dominated	$2,018,923	0.001	> $1.36B/QALY
6d	Dosage of eliglustat is 252 mg daily (33.3% price increase as proxy)	$4,095,461	−0.01	Dominated	$5,487,269	0.001	Dominant

AE = adverse event; B = billion; CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Finally, given the uncertainty associated with the comparative effectiveness assumption, a cost comparison was undertaken as the CDR reference case, which considered the same inputs as the plausible reference case listed in Table 4 but removed the utility decrements associated with the adverse events. The results for treatment-naive patients are reported in Table 6.

Table 6: CDR Reference Case for Treatment-Naive Patients

Description	Eliglustat vs. Imiglucerase			Eliglustat vs. Velaglucerase		
	Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
CDR reference case – cost comparison	$636,798	NA	NA	$2,028,606	NA	NA

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

A series of price reduction analyses were undertaken based on the CDR reference case (Table 7).

Table 7: CDR Reanalysis Price-Reduction Scenarios (Treatment-Naive) Based on the CDR Reference Case

Incremental Cost of Eliglustat vs. Imiglucerase or Velaglucerase (Cost Minimization)				
Price	**Base-Case Analysis Submitted by Manufacturer: Eliglustat vs. Imiglucerase, $**	**Base-Case Analysis Submitted by Manufacturer: Eliglustat vs. Velaglucerase, $**	**Reanalysis by CDR: Eliglustat vs. Imiglucerase, $**	**Reanalysis by CDR: Eliglustat vs. Velaglucerase, $**
Submitted	−2,497,645	−403,365	636,798	2,028,606
10% reduction	−3,189,378	−1,095,098	−54,934	1,336,874
15% reduction	−3,535,244	−1,440,964	−400,800	991,007
20% reduction	−3,881,110	−1,786,831	−746,667	645,141
25% reduction	−4,226,977	−2,132,698	−1,092,533	299,275
30% reduction	−4,572,843	−2,478,564	−1,438,399	−46,591
40% reduction	−5,264,575	−3,170,296	−2,130,132	−738,324
50% reduction	−5,956,308	−3,862,029	−2,821,864	−1,430,056
60% reduction	−6,648,041	−4,553,762	−3,513,597	−2,121,789
70% reduction	−7,339,773	−5,245,494	−4,205,329	−2,813,521

CDR = CADTH Common Drug Review; vs. = versus.

The analyses in Table 8 pertain to the treatment-stable population.

Table 8: CDR Renalysis for Treatment-Stable Patients – Plausible Reference Case

	Description	Eliglustat vs. Imiglucerase			Eliglustat vs. Velaglucerase		
		Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
	Manufacturer's base case	−$2,711,893	3.60	Dominant[a]	−$650,659	3.60	Dominant[a]
1	**ERT dose**						
1a	30 U/kg	$2,397,337	3.60	$666,310/QALY	$3,418,561	3.60	$949,640/QALY
1b	40 U/kg	$694,260	3.60	$192,961/QALY	$2,062,155	3.60	$572,845/QALY
1c	50 U/kg	−$1,008,816	3.60	Dominant[a]	$705,748	3.60	$196,748/QALY
2	**ERT administration cost**						
2a	Home nurse cost $0	−$2,704,691	3.60	Dominant[a]	−$641,408	3.60	Dominant[a]
2b	Home nurse cost $0 and outpatient usage 50% of manufacturer's base case	−$2,692,438	3.60	Dominant[a]	−$621,471	3.60	Dominant[a]
2c	Home nurse cost $0 and no outpatient usage	−$2,679,071	3.60	Dominant[a]	−$599,707	3.60	Dominant[a]

	Description	Eliglustat vs. Imiglucerase			Eliglustat vs. Velaglucerase		
		Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
3	**AE costs**						
3a	No specialist cost for AEs	−$2,712,285	3.60	Dominant[a]	−$650,397	3.60	Dominant[a]
4	**Utility benefit for oral vs. IV treatment**						
4a	Utility benefit is 0.12	−$2,711,893	1.88	Dominant[a]	−$650,659	1.88	Dominant[a]
4b	No utility benefit	−$2,711,893	−0.002	Less costly, less effective	−$650,659	−0.0002	Less costly, less effective
5	**CDR reference case (1b, 2a, 4b)**	**$701,462**	**−0.002**	**Dominated[b]**	**$2,071,406**	**−0.0002**	**Dominated[b]**

AE = adverse event; CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; ICUR = incremental cost-utility ratio; IV = intravenous; QALY = quality-adjusted life-year; vs. = versus.

Note: In the CDR reference case, the very small differences in incremental QALYs are attributable to AEs. It may be suitable to consider a cost-minimization approach for this scenario, as shown in Table 11 in the price-reduction scenarios, where incremental cost was reported.

[a] "Dominant" means that eliglustat is more effective and less costly.

[b] "Dominated" means that eliglustat is as or less effective, and more costly.

Additional scenario analyses were conducted on the CDR reference case. These considered revised adverse event costs, a revised utility benefit for oral versus IV administration, a revised administration cost assumption, and revised dosages of eliglustat (48% of ENCORE patients received 150 mg twice daily [equivalent to 126 mg eliglustat]). Additionally, given the noninferiority assumption and uncertainty associated with the clinical benefits of eliglustat, costs were reported individually so that the contribution of each component could be examined. The results are presented in Table 9.

Table 9: CDR Reanalysis for Treatment-Stable Patients – Scenario Analyses

	Description	Eliglustat vs. Imiglucerase			Eliglustat vs. Velaglucerase		
		Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
5	CDR reference case (1b, 2a, 4b)	$701,462	−0.002	Dominated[a]	$2,071,406	−0.0002	Dominated[a]
6	**Sensitivity analyses of CDR reference case with the following:**						
6a	No AE costs	$701,071	−0.002	Dominated[a]	$2,071,667	−0.0002	Dominated[a]
6b	Utility benefit is 0.12	$701,462	1.88	$373,882/QALY	$2,071,406	1.88	$1,102,936/QALY
6c	ERT administration cost borne by health care system	$694,260	−0.002	Dominated[a]	$2,062,155	−0.0002	Dominated[a]
6d	Dosage of eliglustat is 252 mg daily (33.3% price increase as proxy)	$4,470,960	−0.002	Dominated[a]	$5,840,903	−0.0002	Dominant[b]

AE = adverse event; CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

[a] "Dominated" means that eliglustat is as or less effective, and more costly.

[b] "Dominant" means that eliglustat is more effective and less costly.

Finally, given the uncertainty associated with the comparative effectiveness assumption, a cost comparison was undertaken as the CDR reference case, which considered the same inputs as the plausible reference case listed in Table 8 but removed the utility decrements associated with the adverse events. The results for the treatment-stable patients are reported in Table 10.

Table 10: CDR Reference Case for Treatment-Stable Patients

	Description	Eliglustat vs. Imiglucerase			Eliglustat vs. Velaglucerase		
		Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
7	CDR reference case – Cost comparison	$701,462	NA	NA	$2,071,406	NA	NA

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

A series of price-reduction analyses were undertaken based on the CDR reference case (Table 11).

Table 11: CDR Reanalysis Price-Reduction Scenarios (Treatment-Stable) Based on the CDR Reference Case

Incremental Cost of Eliglustat vs. Imiglucerase or Velaglucerase (Cost Minimization)				
Price	**Base-Case Analysis Submitted by Manufacturer Eliglustat vs. Imiglucerase, $**	**Base-Case Analysis Submitted by Manufacturer Eliglustat vs. Velaglucerase, $**	**Reanalysis by CDR Eliglustat vs. Imiglucerase, $**	**Reanalysis by CDR Eliglustat vs. Velaglucerase, $**
Submitted	−2,711,893	−650,659	701,462	2,071,406
10% reduction	−3,465,792	−1,404,559	−52,437	1,317,506
15% reduction	−3,842,741	−1,781,508	−429,387	940,556
20% reduction	−4,219,691	−2,158,458	−806,336	563,606
25% reduction	−4,596,641	−2,535,408	−1,183,286	186,657
30% reduction	−4,973,591	−2,912,358	−1,560,236	−190,293
40% reduction	−5,727,491	−3,666,257	−2,314,136	−944,192
50% reduction	−6,481,390	−4,420,157	−3,086,035	−1,698,092
60% reduction	−7,235,289	−5,174,056	−3,821,935	−2,451,992
70% reduction	−7,989,189	−5,927,955	−4,757,834	−3,205,891

CDR = CADTH Common Drug Review; vs. = versus.

Additional CDR analyses (same discontinuation rate and average weight of 65 kg) were undertaken and are presented in Appendix 5.

Issues for Consideration

- According to the clinical expert, there is a possibility that eliglustat might be used off-label, especially in children when IV administration is not preferred.
- More convenient administration may lead to indication creep where patients who were previously not treated (due to adverse events on ERT) now receive treatment. However, the clinical expert suggests this is unlikely.
- The approved dosage is 84 mg twice daily for the majority of patients (intermediate metabolizers, extensive metabolizers). However, 48% of patients in the ENCORE trial received a higher dosage (252 mg eliglustat daily [three capsules]). If this approach to dosage is used in practice, the drug acquisition cost of eliglustat increases and it becomes less attractive.

- The manufacturer has provided documentation to indicate that it will cover the cost of the genotype test ($[redacted]).If this is not able to be operationalized in practice, the incremental costs associated with eliglustat increase and it becomes less attractive. This is particularly important for the small proportion of patients who are ultra-rapid metabolizers and not suitable for treatment with eliglustat.
- No subgroup information was provided based on the genotype test and different metabolizer status of patients. Thus, it is unknown if there are different clinical impacts for poor metabolizers compared with intermediate metabolizers or excessive metabolizers.
- The product monograph states that electrocardiogram monitoring should be considered for some patients on eliglustat, which might increase the cost of eliglustat.
- This analysis does not assess the cost-effectiveness of treating Gaucher disease versus no ERT or substrate reduction therapy (placebo), and assumes that patients who meet indication for ERT or substrate reduction therapy currently have access to the comparators used in this analysis.
- While use of eliglustat in other patient populations or off-label is not a significant concern, the clinical expert relayed an anecdotal report of use in combination with ERT.

Patient Input

Patients and caregivers reported that an ongoing concern, even throughout treatment, is that GD1 patients frequently suffer from residual bone disease, which can limit normal activities, make slight movements painful, make sleeping difficult, and may require hospitalization. Costs associated with hospitalization were included in the economic analysis. Patients and caregivers reported two unmet needs based on currently available treatments: patients are seeking a more effective treatment for their disease that reduces residual bone disease or skeletal complications, and the current standard of therapy — biweekly IV infusions — is inconvenient, disruptive, and a sometimes costly burden. Patients and caregivers expect eliglustat to result in an improvement in quality of life based on mode of administration (which was modelled as a lifetime utility benefit in the model). Bone pain was considered as an adverse event in the model; however, as noted in the CDR Clinical Report, neither ENGAGE nor ENCORE was designed or powered to detect differences in bone disease.

Conclusions

The clinical equivalence of eliglustat and imiglucerase or eliglustat and velaglucerase is associated with substantial uncertainty given the lack of evidence comparing eliglustat with velaglucerase and the concerns with the noninferiority margin (noted by the FDA and European Medicines Agency) used in the comparison of eliglustat with imiglucerase based on the ENCORE study. Further, the preference for oral administration versus IV infusion appears to be overestimated by the manufacturer and is not supported by quality-of-life data from the submitted clinical trials.

Eliglustat 84 mg twice daily is more costly than imiglucerase or velaglucerase 40 U/kg every two weeks ($507,350 versus $449,258 and $357,302, respectively).

Appendix 1: Cost Comparison

The comparators presented in Table 12 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice rather than actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product reimbursement agreements are not reflected in the table; as a result, prices may not represent the actual costs to public drug plans.

Table 12: CDR Cost Comparison Table for Drug Therapies for GD1

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Cost ($)	Average Annual Drug Cost ($)
Eliglustat (Cerdelga)	**84 mg**	**capsule**	**695.0000[a]**	**84 mg once daily for PM patients** **84 mg twice daily for IM or EM patients**	**PM: 695.00** **IM/EM: 1,390.00**	**PM: 253,675** **IM/EM: 507,350**
ERTs[b]						
Imiglucerase (Cerezyme)	400 U/vial	IV	2,460.0000[c]	60 U/kg q.2.w. (initial dosage range: 2.5 U/kg 3 times a week to 60 U/kg q.2.w.)	1,054.29 to 1,932.86	384,814 to 705,493
Taliglucerase alfa (Elelyso)	200 U/vial	IV	648.3600[d]	60 U/kg q.2.w. (initial dosage range: 30 U/kg q.2.w. to 60 U/kg q.2.w.)	509.43 to 972.54	185,940 to 354,977
Velaglucerase alfa (VPRIV)	400 U/vial	IV	1,955.0000[e]	60 U/kg q.2.w. (range: 15 U/kg q.2.w. to 60 U/kg q.2.w.)	418.93 to 1,536.07	152,909 to 560,666

AQPP = Association québécoise des pharmaciens propriètaires; CDR = CADTH Common Drug Review; EM = CYP2D6 extensive metabolizer; ERT = enzyme replacement therapy; GD1 = Gaucher disease type 1; IM = CYP2D6 intermediate metabolizer; IV = intravenous; PM = CYP2D6 poor metabolizer; q.2.w. = every other week.

Note: Costs are based on a patient weight of 70 kg and include wastage of excess medication. Costs do not include administration or dispensing fees. A year is assumed to be 365 days, or 26.07 14-day periods.

[a] Manufacturer's submitted price.[2]

[b] Although the recommended doses may differ in range, feedback from the clinical expert consulted for this review indicated that if a patient is switched between ERTs, they will remain at the same dose between treatments before being titrated to the lowest effective dose, if possible.

[c] The AQPP price as reported by Quintiles IMS DeltaPA (March 2017).[24] This is also the price used in CDR's VPRIV recommendation report[25] and confirmed by Sanofi, the manufacturer of both Cerezyme and Cerdelga.[2]

[d] The wholesale list price, as reported by Quintiles IMS Delta PA (March 2017).[24]

[e] Ontario Drug Benefit Program's Exceptional Access Program list price (March 2017).

Appendix 2: Summary of Key Outcomes

The following summaries have been provided based on the CADTH Common Drug Review reference case.

Table 13: When considering only costs, outcomes, and quality of life, how attractive is eliglustat relative to the imiglucerase?

Eliglustat vs. Imiglucerase	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	CDR reference case: Eliglustat more costly (+ $636,798 for treatment-naive patients and + $701,462 for treatment-stable patients).					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; vs. = versus.

Note: Based on the assumption of equivalent efficacy.

Table 14: When considering only costs, outcomes, and quality of life, how attractive is eliglustat relative to velaglucerase?

Eliglustat vs. Velaglucerase	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	CDR reference case: eliglustat more costly (+ $2,028,606 for treatment-naive patients and + $2,071,406 for treatment-stable patients).					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; vs. = versus.

Note: Based on the assumption of equivalent efficacy.

Appendix 3: Additional Information

Table 15: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 16: Authors’ Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of global model/Canadian model done by the manufacturer
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Table 17: Other HTA Findings

	PBAC, July 2015[26]
Treatment	Eliglustat 100 mg once or twice daily vs. imiglucerase and velaglucerase alfa
Price	Confidential
Similarities With CDR Submission	Noninferiority was assumed between eliglustat and ERTs based on the ENCORE trials.
Differences With CDR Submission	A cost-minimization analysis was performed, based on calculated equi-effective doses of eliglustat and ERT.
Manufacturer's Results	Confidential
Issues Noted by the Review Group	PBAC considered that the data did not adequately support the claim of noninferior comparative effectiveness; thus, a cost-minimization approach was not supported.
Results of Reanalyses by the Review Group	A mean daily dose of eliglustat of 228.3 mg instead of 196.81 mg was used to calculate drug cost, compared with imiglucerase 42.4 U/kg twice weekly.
Recommendation	PBAC rejected the request to list eliglustat on the PBS for the treatment of GD1 on the bases that the results of the direct randomized trial (ENCORE) suggested inferiority and that clinically important inferiority could not be excluded with confidence.

ERT = enzyme replacement therapy; GD1 = Gaucher disease type 1; HTA = Health Technology Assessment; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PBS = Pharmaceutical Benefits Scheme; vs. = versus.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer's Markov model used annual cycles in which patients with GD1 enter the model at different health states based on Gaucher disease severity scoring system (DS3) categories, with the distribution of patients in each health state based on patients in the ENGAGE and ENCORE trials. Between each Markov cycle, patients can either remain in the same health state, transition to a more or less severe health state, or die (Table 18).

Table 18: Health States in Manufacturer's Model

Health state	DS3 category (score)	Bone disease status
1	Mild (0 — 3.5)	No clinical symptoms (no bone or joint pain in the past 30 days, no bone crisis in the past 12 months.
2	Mild + Bone pain (0 — 3.5)	Bone or joint pain present in the past 30 days or at least 1 bone crisis in the past 12 months. No new lytic lesions, AVN, or pathological fracture in the past 12 months.
3	Mild + SSC (0 — 3.5)	New lytic lesions, AVN, or pathological fracture in the past 12 months.
4	Moderate (>3.5 — 6.5)	No new lytic lesions, AVN, or pathological fracture in the past 12 months.
5	Moderate + SSC (>3.5 — 6.5)	New lytic lesions, AVN, or pathological fracture in the past 12 months.
6	Marked (>6.5 — 9.5)	No new lytic lesions, AVN, or pathological fracture in the past 12 months.
7	Marked + SSC (>6.5 — 9.5)	New lytic lesions, AVN, or pathological fracture in the past 12 months.
8	Severe (>9.5)	No new lytic lesions, AVN, or pathological fracture in the past 12 months.
9	Severe + SSC (>9.5)	New lytic lesions, AVN, or pathological fracture in the past 12 months.

AVN = avascular necrosis; DS3 = Disease Severity Scoring System; SSC = severe skeletal complication.

Source: Manufacturer's pharmacoeconomic report.[2]

Short-term transition probabilities were estimated from the eliglustat arm of the ENGAGE trial (treatment-naive) and pooled analysis of the eliglustat and imiglucerase arms of the ENCORE trial (treatment-stable) applied to eliglustat and ERTs. Long-term transition probabilities were derived from regression equations fitted using data on patients in the DS3 study.

Table 19 and Table 20 report the relevant data sources and assumptions incorporated by the manufacturer.

Table 19: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Assumed noninferiority based on four RCTs: 1. ENCORE: eliglustat vs. imiglucerase in treatment-stable patients, open-label noninferiority trial 2. ENGAGE: eliglustat vs. placebo in treatment-naive patients, randomized and double blinded 3. velaglucerase 60 U/kg vs.	Uncertain. There is concern regarding the noninferiority threshold set in the trial (see CDR Clinical Report). Also, there is no direct evidence on eliglustat vs. velaglucerase and no direct evidence available in treatment-naive patients. No indirect treatment comparison was performed (paucity of data to conduct). The duration of studies is short (39 weeks to 52 weeks) and long-term relative efficacy is unknown.

Data Input	Description of Data Source	Comment
	velaglucerase 45 U/kg in treatment-naive patients, randomized and double blinded 4. velaglucerase switched from imiglucerase in treatment-stable patients, open label	
Natural History	Transition probabilities between health state for the first cycle were derived from ENGAGE (treatment-naive) and ENCORE (treatment-stable). Long-term health state transitions were informed by regression using data from the DS3 study.[7,8]	Appropriate for short-term transitions. The DS3 study was observational and might be susceptible to certain limitations (see CDR Clinical Report appendix). However, since long-term transition probabilities were assumed to be independent of treatment, this would not change the ICURs.
Utilities	Utility by health state was obtained from the DS3 study, where SF-36 scores were converted to EQ-5D utilities and regression models were then used to estimate the utility value for each health state. Utility benefit for oral administration (vs. IV) was obtained from a study that reported on utility for alternate administration of iron-chelation therapy and applied to each cycle indefinitely.	Appropriate for utility by health state. Disutility of IV vs. PO administration was likely overestimated, lacks face validity (in favour of eliglustat), and is not supported by quality-of-life data captured in the clinical studies.
Resource Use	See costs section.	
AEs	AEs reported as occurring in >2% of the population more frequent than placebo from the trial data.	Appropriate
Mortality	Base case used GD1-specific mortality derived from the ICGG Gaucher Registry; SAs used Canadian life table data.	Appropriate
Costs		
Drug	Costs for ERT (imiglucerase and velaglucerase) were obtained from the ODB EAP price list. The manufacturer provided the costs for eliglustat. The annual cost was calculated based on the dosage of 60 U/kg for ERT and 84 mg b.i.d. for eliglustat (4% once daily). The model assumes no dose wastage for ERTs.	The CADTH clinical expert suggested average dose for ERT in Canada is much less than the 60 U/kg recommended by product monographs for ERTs; thus, the dose of ERT is likely overestimated. This is supported by data provided by the provinces, which indicate that the average dose of ERT is approximately 30 U/kg. The overestimation of ERT dose favours eliglustat. In contrast, assuming no wastage of ERTs biases against eliglustat.
Administration	The cost of ERT administration and monitoring costs were verified by the manufacturer's clinical panel.	The clinical expert stated that the cost of ERT administration might be covered by the manufacturers for almost all patients and settings (with the possible exception of administration in the outpatient setting, which is uncommon). Provincial data indicated that manufacturers covered home infusion costs,

Data Input	Description of Data Source	Comment
		including nursing staff, and the ministry paid for some outpatient infusions where no other resources were available. The overestimation of ERT administration costs favours eliglustat.
AEs	A specialist repeat consult ($105.25) was assumed with each AE.	The clinical expert stated that this might be an overestimation. This would bias against velaglucerase, as its AE rate was larger.
Health State	Health state costs included community-based medical services (GP and specialists), bisphosphonate use, specialist centre-based care (geneticist specialist), hospital-based acute care, and social services. The manufacturer's clinical panel was consulted on these costs.	Social services are not direct medical costs. However, since noninferiority was assumed, inclusion or exclusion would not change the ICURs.

AE = adverse event; b.i.d. = twice daily; CDR = CADTH Common Drug Review; DS3 = Gaucher disease severity scoring system; EQ-5D = EuroQol 5-Dimensions questionnaire; ERT = enzyme replacement therapy; GD1 = Gaucher disease type 1; GP = general practitioner; ICGG = International Collaborative Gaucher Group; ICUR = incremental cost-utility ratio; IV = intravenous; ODB EAP= Ontario Drug Benefit Program's Exceptional Access Program; PO = oral administration; RCT = randomized controlled trial; SA = scenario analysis; SF-36 = Short Form (36) Health Survey; vs. = versus.

Table 20: Manufacturer's Key Assumptions

Assumption	Comment
Natural History and Efficacy	
Assumed noninferiority for efficacy within the clinical trial period. Long-term transition probabilities were independent of treatment.	No direct evidence for the treatment-naive patient group. Short-term studies relied on surrogate outcomes. No data on relative efficacy over a longer time frame (beyond 52 weeks).
Treatment-naive and treatment-stable patients who were not splenectomized were assumed to not receive a splenectomy during their time within the model.	Unknown; however, given assumption of noninferiority, does not impact results.
Assumed switching treatments following discontinuation did not affect efficacy of ERT/SRT treatment.	Unknown
Adherence was set to 100% and only influenced treatment costs.	Patients on oral drugs might have lower adherence rate, and this might cause their health to deteriorate faster. This not only influenced treatment costs but also affected long-term transition probabilities and increased health state costs. This might favour eliglustat.
Eliglustat has higher discontinuation rates compared with the ERTs.	This assumption is tested in the CDR reference case (see Table 23) and does not alter the conclusion.
Mortality	
Assumed to be equivalent across all patients regardless of their current health state or the proportion with splenectomy.	Uncertain but did not affect ICURs, as noninferiority was assumed.

CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; ICUR = incremental cost-utility ratio; SRT = substrate replacement therapy.

Detailed Manufacturer's Results

Manufacturer's Base Case

Treatment-Naive Population

In the reference case, the manufacturer reported that eliglustat compared with imiglucerase (velaglucerase in bracket) is associated with an additional 3.31 (3.31) quality-adjusted life-years (QALYs). Treatment with eliglustat resulted in lower total health care costs of −$2,497,645 (−$403,365). Eliglustat is the dominant strategy (more effective and less costly) (Table 21).

Table 21: Results of the Manufacturer's Base Case – Treatment-Naive Population

	Eliglustat	Imiglucerase	Difference	Velaglucerase	Difference
QALYs	15.90	12.59	3.31	12.58	3.31
Cost ($)					
Treatment costs	8,663,840	11,127,054	−2,463,214	9,013,379	−349,539
Admin costs	0	34,937	−34,937	53,403	−53,403
AE costs	701	195	506	1,125	−424
Management	6,775	6,775	0	6,775	0
Social Services	58	58	0	58	0
Total costs ($)	8,671,374	11,169,019	−2,497,645	9,074,739	−403,365
ICUR ($/QALY)			Eliglustat is dominant		Eliglustat is dominant

AE = adverse event; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic report.[2]

Treatment-Stable Population

In the reference case, the manufacturer reported that eliglustat compared with imiglucerase (velaglucerase in bracket) is associated with an additional 3.60 (3.60) QALYs. Treatment with eliglustat resulted in lower total health care costs of −$2,711,893 (−$650,659). Eliglustat is the dominant strategy (more effective and less costly) (Table 22).

Table 22: Results of the Manufacturer's Base Case – Treatment-Stable Population

	Eliglustat	Imiglucerase	Difference	Velaglucerase	Difference
QALYs	15.40	11.90	3.60	11.90	3.60
Cost ($)					
Treatment costs	8,054,762	10,734,225	−2,463,214	8,654,207	−599,445
Admin costs	0	32,822	−32,822	50,952	−50,952
AE costs	570	177	393	832	−262
Management	5,327	5,327	0	5,327	0
Social Services	124	124	0	124	0
Total costs ($)	8,060,782	10,772,675	−2,711,893	8,711,441	−650,659
ICUR ($/QALY)			Eliglustat is dominant		Eliglustat is dominant

AE = adverse event; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic report.2

Additional CADTH Common Drug Review Reanalyses

The primary CADTH Common Drug Review reanalyses are presented in the main body of the report. Additional reanalyses consider alternative assumptions around discontinuation rates (Table 23) and a price-reduction analysis on the scenario analysis assuming a 0.12 utility increment for oral versus intravenous administration (Table 24 and Table 25).

Table 23: CDR Additional Reanalyses

Description	Eliglustat vs. Imiglucerase			Eliglustat vs. Velaglucerase		
	Incremental Cost	Incremental QALYs	ICUR	Incremental Cost	Incremental QALYs	ICUR
Treatment-Naive Population						
CDR reference case	$636,798	−0.01	Dominated	$2,028,606	0.001	>$1.36B/QALY
CDR reference case with same (eliglustat) discontinuation rates	$644,406	−0.01	Dominated	$1,910,599	0.001	>$1.28B/QALY
Treatment-Stable Population						
CDR reference case	$701,462	−0.002	Dominated	$2,071,406	−0.0002	Dominated
CDR reference case with same (eliglustat) discontinuation rates	$706,374	−0.002	Dominated	$2,086,974	−0.0002	Dominated

B = billion; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Table 24: CDR Reanalysis Price-Reduction Scenarios (Treatment-Naive), Assuming Annual Utility Benefit of 0.12 for Oral vs. Intravenous Administration

ICURs of Eliglustat vs. Imiglucerase or Velaglucerase			
Price	**Base-Case Analysis Submitted by Manufacturer Eliglustat vs. ERTs**	**Reanalysis by CDR Eliglustat vs. Imiglucerase**	**Reanalysis by CDR Eliglustat vs. Velaglucerase**
Submitted	Eliglustat dominates (less expensive and more effective)	$369,655/QALY	$1,172,716/QALY
10% reduction	Eliglustat dominates	Eliglustat dominates	$772,832/QALY
15% reduction	Eliglustat dominates	Eliglustat dominates	$572,891/QALY
20% reduction	Eliglustat dominates	Eliglustat dominates	$372,949/QALY
25% reduction	Eliglustat dominates	Eliglustat dominates	$173,008/QALY
30% reduction	Eliglustat dominates	Eliglustat dominates	Eliglustat dominates

CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Table 25: CDR Reanalysis Price-Reduction Scenarios (Treatment-Stable), Assuming Annual Utility Benefit of 0.12 for Oral vs. Intravenous Administration

ICURs of Eliglustat vs. Imiglucerase or Velaglucerase			
Price	**Base-Case Analysis Submitted by Manufacturer Eliglustat vs. ERTs**	**Reanalysis by CDR Eliglustat vs. Imiglucerase**	**Reanalysis by CDR Eliglustat vs. Velaglucerase**
Submitted	Eliglustat dominates (less expensive and more effective)	$373,882/QALY	$1,102,936/QALY
10% reduction	Eliglustat dominates	Eliglustat dominates	$701,516/QALY
15% reduction	Eliglustat dominates	Eliglustat dominates	$500,807/QALY
20% reduction	Eliglustat dominates	Eliglustat dominates	$300,097/QALY
25% reduction	Eliglustat dominates	Eliglustat dominates	$99,387/QALY
30% reduction	Eliglustat dominates	Eliglustat dominates	Eliglustat dominates

CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

References

1. Cerdelga (eliglustat): 84 mg eliglustat capsules (as eliglustat tartrate) [product monograph]. Mississauga (ON): Genzyme Canada, a division of sanofi-aventis Canada Inc.; 2017 Apr 21.
2. Pharmacoeconomic evaluation. In: CDR submission: Cerdelga (eliglustat), 84 mg capsule. Company: Sanofi Genzyme.[CONFIDENTIAL manufacturer's submission]. Mississauga (ON): Sanofi Genzyme; 2017 Jan 15.
3. Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, et al. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. Lancet. 2015 Jun 13;385(9985):2355-62.
4. Mistry PK, Lukina E, Ben TH, Amato D, Baris H, Dasouki M, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. JAMA. 2015 Feb 17 [cited 2017 May 2];313(7):695-706. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4962880
5. Gonzalez DE, Turkia HB, Lukina EA, Kisinovsky I, Dridi MF, Elstein D, et al. Enzyme replacement therapy with velaglucerase alfa in Gaucher disease: Results from a randomized, double-blind, multinational, Phase 3 study. Am J Hematol. 2013 Mar;88(3):166-71.
6. Zimran A, Pastores GM, Tylki-Szymanska A, Hughes DA, Elstein D, Mardach R, et al. Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase. Am J Hematol [Internet]. 2013 Mar [cited 2017 Apr 26];88(3):172-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3586535
7. Weinreb NJ, Finegold DN, Feingold E, Zeng Z, Rosenbloom BE, Shankar SP, et al. Evaluation of disease burden and response to treatment in adults with type 1 Gaucher disease using a validated disease severity scoring system (DS3). Orphanet J Rare Dis [Internet]. 2015 May 22 [cited 2017 Mar 9];10:64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471923
8. Weinreb NJ, Cappellini MD, Cox TM, Giannini EH, Grabowski GA, Hwu WL, et al. A validated disease severity scoring system for adults with type 1 Gaucher disease. Genet Med. 2010 Jan;12(1):44-51.
9. Rosenbloom BE, Weinreb NJ. Gaucher disease: a comprehensive review. Crit Rev Oncog. 2013;18(3):163-75.
10. Xu Y, Zhang J, Byrnes M, Fahrbach K. Feasibility assessment and Bucher indirect treatment comparison of eliglustat to miglustat in ERT-treated patients [CONFIDENTIAL internal manufacturer's report]. London (GB): Evidera; 2014.
11. Xu Y, Zhang J, Sugarman R, Rotella P, Byrnes M. Systematic literature review of the clinical efficacy and safety of enzyme replacement therapy and substrate reduction therapy for Gaucher disease type 1 [CONFIDENTIAL internal manufacturer's report]. London (GB): Evidera; 2014.
12. Burrow TA, Balwani M, Cox TM. ENCORE: A randomized, controlled, open-label noninferiority study comparing eliglustat to imiglucerase in Gaucher disease type 1 patients on enzyme replacement therapy who have reached therapeutic goals [abstract]. Blood [Internet]. 2013 [cited 2017 Apr 26];122. Available from: http://www.bloodjournal.org/content/122/21/3468?sso-checked=true
13. Clinical Study Report: GZGD00304. A phase 2, open-label, multi-center study evaluating the efficacy, safety, and pharmacokinetics of Genz-112638 in Gaucher Type 1 patients [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Genzyme Corporation, a Sanofi Company; 2012 Sep 28.
14. Mistry PK, Lukina EA. A phase 3, randomized, double-blind, placebo-controlled, multi-center study to investigate the efficacy and safety of eliglustat in patients with Gaucher disease type 1 (ENGAGE): results after 9 months of treatment [abstract]. Mol Genet Metab. 2013;108:S66-S67.
15. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care. 2004 Sep;42(9):851-9.
16. Osborne RH, De Abreu LR, Dalton A, Houltram J, Dowton D, Joshua DE, et al. Quality of life related to oral versus subcutaneous iron chelation: a time trade-off study. Value Health. 2007 Nov;10(6):451-6.
17. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011 Nov;31(6):800-4.
18. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin. 2010 May;26(5):1091-6.
19. xTAG CYP2D6 kit v3: product details [Internet]. Austin (TX): Luminex Corporation; 2017. [cited 2017 Apr 19]. Available from: https://www.luminexcorp.com/clinical/genetic-testing/pharmacogenetics/cyp2d6/product-details/
20. Table summarizing clarifaxes for Cerdelga™ (eliglustat) - updated March 15, 2017 [CONFIDENTIAL]. In: Pre-NOC new drug CDR submission. Ottawa: CADTH; 2017.
21. Sanofi Genzyme response to April 20, 2017 request for additional information regarding SR0511-Cerdelga™ (eliglustat) CDR new drug submission [additional manufacturer's information]. Mississauga (ON): Sanofi Genzyme; 2017 Apr 24.
22. Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, et al. A study of the quality of life and cost-utility of renal transplantation. Kidney Int. 1996 Jul;50(1):235-42.
23. Hadi M, Nalysnyk L, Hamed A, Swinburn P. Estimating utilities associated with the mode of treatment administration in Gaucher disease. Poster presented at: ISPOR 19th Annual European Congress; 2016 Oct 29 - Nov 2; Vienna.
24. DeltaPA [database on Internet]. Ottawa: QuintilesIMS; 2017 [cited 2017 May 25]. Available from: http://www.imsbrogancapabilities.com/en/market-insights/delta-pa.html
25. Common Drug Review. CEDAC final recommendation: Velaglucerase alfa (VPRIV - Shire Human Genetic Therapies Inc.). Indication: Gaucher disease [Internet]. Ottawa: CADTH; 2011 Apr 25. [cited 2017 Mar 10]. Available from: https://cadth.ca/sites/default/files/cdr/complete/cdr_complete_Vpriv_April-29-11.pdf
26. Pharmaceutical Benefit Advisory Committee. Public summary document: Eliglustat, oral capsule, 100 mg, Cerdelga®, Genzyme [Internet]. Canberra (AU): Pharmaceutical Benefits Scheme; 2015 Jul. [cited 2017 Apr 26]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-07/files/eliglustat-psd-july-2015.pdf