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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

MIGALASTAT (GALAFOLD)

(Amicus Therapeutics)
Indication: Fabry Disease

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Table of Contents

Tables

Figure

CADTH

Abbreviations

AE	adverse event
CDR	CADTH Common Drug Review
CEFD	clinically evident Fabry disease
CFDI	Canadian Fabry Disease Initiative
DCE	discrete choice experiment
ERT	enzyme replacement therapy
ESRD	end-stage renal disease
ICUR	incremental cost-utility ratio
GFR	glomerular filtration rate
QALY	quality-adjusted life-year
PBAC	Pharmaceutical Benefits Advisory Committee

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Migalastat (Galafold)
Study Question	What are the anticipated costs and health consequences of the use of migalastat for the treatment of Fabry disease, compared with enzyme replacement therapy (ERT)?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with Fabry disease with mutations of their alpha-galactosidase A (GLA) gene determined to be amenable to treatment with migalastat
Treatment	Migalastat 123 mg (equivalent to 150 mg migalastat hydrochloride) orally once every other day at the same time of day
Outcomes	QALYs LYs
Comparators	Blended ERTs: agalsidase alfa intravenously at a dose of 0.2 mg/kg over 40 minutes and agalsidase beta intravenously at a dose of 1 mg/kg over two hours
Perspective	Canadian Ministry of Health
Time Horizon	50 years
Results for Base Case	Migalastat is dominant (i.e., less expensive and greater QALYs gained) compared with the blended ERT comparator
Key Limitations	CDR identified the following key limitations: • The clinical efficacy of migalastat is associated with some uncertainty. CDR Clinical Reviewers noted the results of the placebo-controlled trial (FACETS) indicated migalastat did not meet the primary (surrogate) end point, while the head-to-head study of migalastat and ERT (ATTRACT), which was used to support the assumption of non-inferiority of migalastat compared with ERT in the model, was associated with notable limitations, which resulted in uncertainty of the study findings. The generalizability of the findings to the Canadian setting is also uncertain. • Inappropriate comparator. Use of a blended comparator in the base case is not appropriate. An analysis should have been presented for migalastat vs. each ERT individually. • Calculation errors were identified with the disutility associated with dyspnea, the weighted cost of ERT and the annual cost of migalastat. These errors bias the comparison of cost in favour of migalastat. • The submitted model overestimates patient survival. The predicted life expectancy of Fabry disease patients in the model is 81.54 years, which is much higher than that reported in the large international Fabry registry (66.9 years). The impact of this could not be tested by CDR. • The disutility associated with ERT infusion is highly uncertain. The manufacturer assumed that ERT infusion was associated with a utility decrement of 0.048 from a UK study. The generalizability of this value to the Canadian population is uncertain. Additionally, the assumption of a significant difference in quality of life based on route of administration was not observed in the ATTRACT trial.
CDR Estimate(s)	• CDR corrected errors that reduced the costs associated with ERT and increased the costs associated with migalastat. • CDR considered migalastat compared with each ERT separately in the CDR reanalyses. • Migalastat may be associated with a small incremental QALY gain due to a different adverse event profile compared with each ERT. If a difference in utility values due to the route of administration is considered acceptable, migalastat may be associated with a larger incremental QALY gain. Migalastat may be associated with a large incremental cost, or a large incremental cost saving, depending upon the comparator or comparator price used, patient weight, and discontinuation rate. • In the CDR base case for migalastat vs. agalsidase alfa, the ICUR ranged from $200,487 per QALY to $55.9M per QALY depending on whether disutility for infusion was considered.

	• In the CDR base case for migalastat vs. agalsidase beta, migalastat was the dominant strategy regardless of whether disutility was included or not. • The results are highly sensitive to the price of ERT, disutility due to route of administration, patient weight, and discontinuation rates. Further, the results do not account for the uncertainty in comparative clinical effectiveness of migalastat.

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

Drug	Migalastat (Galafold)
Indication	Long-term treatment of adults with a confirmed diagnosis of Fabry disease [deficiency of alpha-galactosidase [alpha-Gal A]) and who have an alpha-Gal A mutation determined to be amenable by an in vitro assay.
Reimbursement Request	As per indication.
Dosage form	123 mg oral capsules.
NOC date	September 5, 2017
Manufacturer	Amicus Therapeutics, Inc.

Executive Summary

Background

Migalastat (Galafold) is indicated for the long-term treatment of adults with a confirmed diagnosis of Fabry disease (alpha-galactosidase A deficiency) who have an amenable mutation.[1] The recommended dosage is 123 mg every other day at the same time of day. At the submitted price, migalastat at $1,700 per capsule is $310,250 annually per patient, which is similar to the publicly available prices of IV enzyme replacement therapy (ERT).[2] The indication for migalastat differs with the indication for ERTs, given the requirement for an amenable mutation for migalastat.

The manufacturer submitted a cost-utility analysis comparing migalastat with a blended comparator of two ERTs (agalsidase alfa and agalsidase beta) in two patient populations: the base case, based on the mean age from the ATTRACT trial (start age in model = 49 years); and a scenario based on the product monograph (patients aged 18 years or older with Fabry disease and mutations of their alpha-galactosidase A gene determined to be amenable to treatment with migalastat; start age in model = 18 years). The model time horizon was 50 years with annual cycles, and undertaken from the perspective of the Canadian health care payer.[2] The manufacturer assumed equivalence between migalastat and the blended ERTs based on a single randomized controlled trial (ATTRACT) that was stated to demonstrate the non-inferiority of migalastat and ERT on surrogate renal outcomes, i.e., measured glomerular filtration rate (GFR) and estimated GFR. The same transition probabilities for health states for each treatment group were therefore assumed and based on a Dutch cost-effectiveness study (Rombach et al.).[3] The manufacturer assumed a treatment discontinuation rate of 1% for both migalastat and ERT. Patient weight was derived from unpublished data from the Canadian Fabry Disease Initiative. Adverse event rates were obtained from the ATTRACT trial. Health service utilization due to Fabry disease and associated complications were based on Rombach et al.[3] Unit costs and utility values were obtained from published literature.

In its base case, the manufacturer reported that migalastat was dominant (more effective and less costly) compared with ERT (cost savings of $350,953; gain of 1.01 quality-adjusted life-years [QALYs]). Migalastat was also dominant in the scenario analysis for patients entering the model at age 18 years using all-male patient weights, and was associated with

an incremental cost-utility ratio (ICUR) of $36,005 per QALY compared with ERT for patients entering the model at age 18 years using average patient weight from the ATTRACT trial.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified several limitations with the submitted analysis. First, the CDR Clinical Report indicates the clinical efficacy of migalastat is uncertain. In the placebo-controlled FACETS trial, migalastat did not meet its primary end point for the intention-to-treat population; and the comparative effectiveness of migalastat and ERT based on the ATTRACT trial was considered by the CDR clinical reviewers to be associated with uncertainty due to wide confidence intervals, concerns with imbalances in the trial populations, and use of surrogate outcomes as opposed to clinically meaningful outcomes (CDR Clinical Report). This uncertainty was not adequately captured in the model. Second, the use of a blended ERT comparator is not appropriate, particularly given the lack of information available regarding the market share of the comparator treatments. The assumption of disutility associated with ERT infusion is highly uncertain. The manufacturer assumed that ERT infusion was associated with an annual utility decrement of 0.048. This disutility value was based on a UK study that measured health utilities using a discrete choice experiment. It is unclear whether this utility estimate is generalizable to the Canadian population. Additionally, the use of a disutility for ERT infusion was not supported by the quality-of-life findings observed in the ATTRACT trial, which indicated negligible changes in health-related quality of life (as measured by the Short-Form 36-Item Health Survey [SF-36]). Furthermore, assumptions about how patients move within the model (e.g., transition probabilities between health states) do not reflect clinical evidence that suggests the risk of progression in Fabry disease increases with age; this results in an overestimation of life expectancy.[4,5] Finally, the manufacturer did not test the impact of weight (in the probabilistic analysis), which influences ERT dosing as it is based on weight.

The model also included errors in the calculation of the annual migalastat cost, the weighted cost of ERT, and a disutility associated with dyspnea, which favour migalastat.

CDR attempted to address these issues, but was limited by the paucity of data, uncertainty associated with the available data, and appropriateness of the model structure. CDR conducted revised analyses that correct for errors in treatment costs and the disutility value of dyspnea, but was unable to assess the uncertainty associated with the comparative clinical effectiveness of migalastat and variation in transition probabilities.

CDR reanalyses, based on 10,000 simulations, included four different scenarios:

- migalastat compared with agalsidase alfa with a disutility applied to ERT — ICUR = $200,487 per QALY
- migalastat compared with agalsidase alfa without a disutility applied to ERT — ICUR = $55.9M per QALY
- migalastat compared with agalsidase beta with a disutility applied to ERT — migalastat is dominant
- migalastat compared with agalsidase beta without a disutility applied to ERT — migalastat is dominant.

As a stratified analysis of the ATTRACT trial based on the specific ERT was not provided, CDR was limited in the scope of the re-analysis for each comparator. Given the data

limitations, the two ERTs were assumed to be equivalent, with the difference in cost of treatment the sole differentiator.

Additional scenario analyses were conducted to explore areas of uncertainty (treatment discontinuation, disutility associated with ERT infusion, and baseline patient weight). The results were highly sensitive to each of these parameters.

At the publicly available prices, a price reduction of 3.5% is required for migalastat to be less costly than agalsidase alfa. However, the clinical expert consulted by CDR indicated that the cost of ERT for different lysosomal diseases in Canada is currently under review. Any changes or differences in the total costs paid for ERT by the provinces to the costs used by the manufacturer will affect the cost-effectiveness results and subsequent price reduction analyses.

Conclusions

Based on the both the placebo-controlled trial (FACETS) and the comparative trial of migalastat and ERT (ATTRACT), the clinically meaningful effects of migalastat are associated with uncertainty (CDR Clinical Report). While there may be a preference for an oral treatment over an infusion, the QALY benefit associated with the oral treatment is likely to be overestimated in the model.

The cost of migalastat 123 mg every other day compared with ERT (dosed per product monograph recommendations) depends on the price of the comparator treatment and patient weight. Based on the submitted and publicly available prices only, in a patient weighing 75 kg, migalastat ($310,250) has a greater annual cost than agalsidase alfa ($299,821) and a lower annual cost than agalsidase beta ($312,186).

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted a cost-utility analysis comparing migalastat with enzyme replacement therapy (ERT) in patients with Fabry disease with mutations of their alpha-galactosidase A gene determined to be amenable to treatment with migalastat.[2] The analysis was conducted from the perspective of Canada's health care system. The cost-utility analysis used a previously published Markov model[3] to project costs and health outcomes over a patient lifetime period (i.e., 50 years). The submitted model includes 10 mutually exclusive health states that represent the progression of Fabry disease over time: pain (neuropathic pain in the extremities without any other signs of clinical evident disease), clinically evident Fabry disease (CEFD), end-stage renal disease (ESRD), cardiac complications, stroke, ESRD and cardiac complications, ESRD and stroke, cardiac complications and stroke, ESRD and cardiac complications and stroke, and death. Probabilities to move from one health state to another (i.e., transition probabilities) were based on a Dutch Fabry disease cohort.[3,6] The cycle length was one year. A half-cycle correction and an annual discount rate of 1.5% were applied to both costs and outcomes.

Two patient populations with Fabry disease were separately assessed: males with classical Fabry disease, and females or males with late-onset or atypical Fabry disease. The results were presented as aggregated costs and health outcomes. The baseline patient characteristics used in the model were derived from the population randomized in the ATTRACT trial (i.e., starting age of 49 years, health state distribution at baseline)[7] and unpublished data from the Canadian Fabry Disease Initiative (CFDI; i.e., 47.8% of the starting population was female). A scenario analysis was undertaken to assess a hypothetical cohort of Fabry patients aged 18 years at baseline. The average gender-specific weight of Fabry disease patients receiving ERT was based on data from the CFDI. The average weight was assumed to be constant across age groups due to the paucity of data.

The submitted model compared migalastat with a blended comparator of the two ERTs that are currently available in Canada for patients with Fabry disease (agalsidase alfa and agalsidase beta), based on an assumption of clinical equivalence of both ERTs. ERT is administered every two weeks; agalsidase alfa is administered intravenously at a dose of 0.2 mg/kg over 40 minutes, while agalsidase beta is administered at a dose of 1 mg/kg over two hours. The costs of ERT was estimated based on an assumption about their market share (65% for agalsidase alfa and 35% for agalsidase beta).[2]

The manufacturer obtained clinical effectiveness inputs for disease progression, adverse events (AEs), and mortality from published literature. Migalastat was assumed to be clinically equivalent to ERT based on a comparable annualized change in GFR between migalastat and ERT reported in the ATTRACT trial.[7] Transition probabilities between health states were taken from a Dutch study (Rombach et al.) that estimated disease progression for untreated Fabry patients from the period before the introduction of ERT and assumed that ERT only reduced the progression to the next disease state.[3,6] Rombach et al. derived annual transition probabilities from Kaplan–Meier curves; these probabilities were assumed to remain constant over time. AE data were obtained from ATTRACT trial for events reported in > 10% of either migalastat or ERT patients;[7] the annual probability for each AE

was derived after an adjustment for duration of exposure was applied. An annual discontinuation rate of 1% for both migalastat and ERT was assumed.

The submitted model used Canadian life tables and disease-specific mortality taken from Rombach et al. to derive the probability of death for Fabry patients.[2] For each model cycle, the model chose the highest value from the age-sex–specific, all-cause mortality or disease-specific mortality for males and females to represent the transition from symptomatic states (except a pain health state) to death.

Health utility values for each symptomatic health state were obtained from Rombach et al.[3] Notably, the utility values for the pain and CEFD health states were the same (0.762), as were utility values for the ESRD, cardiac complications, and stroke health states (0.744). Disutilities associated with AEs were taken from a catalogue for chronic conditions of EuroQol 5-Dimensions questionnaire (EQ-5D) preference weights reported by Sullivan et al.[8] A utility decrement was applied to ERT associated with the route of administration (infusion; 0.048) based on a discrete choice experiment (DCE) conducted in the UK.[9]

Resource use and costs were collected from the ATTRACT trial, published literature, and expert opinion. The costs of ERT drug acquisition were based on the previous CADTH Common Drug Review (CDR) recommendations.[10,11] Migalastat was priced at approximate parity to ERT. Health-state costs per event were derived from the published literature, while the costs of AE treatments were estimated using unit costs taken from the Ontario Schedule of Benefits and Ontario Drug Benefit Formulary.

Manufacturer's Base case

In the base-case analysis, the manufacturer reported the results of both a deterministic analysis and probabilistic analysis.

The deterministic analysis reported that migalastat is associated with lower total costs ($6,168,792 versus $6,519,745) and greater health benefits (18.26 qualify-adjusted life-years [QALYs] versus 17.25 QALYs) compared with ERT (i.e., migalastat is dominant). With 1,000 iterations, the probabilistic analysis consistently showed that migalastat is cost-saving ($6,070,182 versus $6,448,076) and associated with improved QALYs gained (18.62 versus 17.59) compared with ERT. The cost-effectiveness acceptability curve shows that at a willingness-to-pay-value of $50,000 per QALY gained, migalastat was the optimal treatment in 96% of iterations. Detailed results are shown in Table 2.

Table 2: Summary of the Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Migalastat ($)	Total QALYs	Incremental QALYs of Migalastat	Incremental Cost per QALY
Deterministic analysis					
Migalastat	6,168,792	-350,953	18.26	1.01	Migalastat is dominant
ERT (blended)	6,519,745		17.25		
Probabilistic analysis					
Migalastat	$6,070,182	-377,894	18.26	1.01	Migalastat is dominant
ERT(blended)	$6,448,076		17.25		

ERT = enzyme replacement therapy; QALY = quality-adjusted life-year.

Source: Manufacturer's Pharmacoeconomic Submission.[2]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer did not undertake one-way sensitivity analyses. However, several scenario analyses were undertaken to explore patient weight, age at model entry, gender, ERT price, and infusion costs. Deterministic results are reported (Table 14). Scenario 1 assessed the impact of average weight on the results. If patient weight is based on the ATTRACT trial as opposed to the CFDI, migalastat is no longer dominant but associated with greater costs ($6,065,481 versus $6,019,047) and greater QALYs (18.26 versus 17.25) than ERT, with an incremental cost-effectiveness ratio (ICER) of $45,894 per QALY gained. Similar impact of weight is observed in Scenario 2, although the starting age is reduced to 18 years. Scenario 3 reveals that migalastat is associated with larger cost-savings (i.e., $470,561) and greater QALYs (1.32) if a target population consists of males aged 18 years and weight is based on male CFDI patients. Scenario 4 shows that if the ERT list price is reduced by 10%, the ICER of migalastat will increase to $290,681 per QALY gained. For Scenario 5, if manufacturers do not pay for ERT infusion costs, migalastat will be more favourable compared with ERT, with a saving of $415,611 and 1.01 QALYs gained. Findings obtained from manufacturer sensitivity analyses suggest that the cost-effectiveness of migalastat is highly dependent on patient weight and ERT costs.

Limitations of Manufacturer's Submission

- **The clinical efficacy of migalastat is associated with some uncertainty.** The results of the placebo-controlled FACETS trial indicate that migalastat did not meet its primary end point (surrogate outcome: changes in inclusions of globotriaosylceramide in interstitial capillary cells) for the intention-to-treat population (see CDR Clinical Report). Furthermore, the assumption of non-inferiority of migalastat when compared with ERT in patients with Fabry disease was based on the ATTRACT trial,[7] suggesting that migalastat and ERT had comparable effects on two primary (surrogate) outcomes (measured GFR and estimated GFR). The sample size of the ATTRACT trial was calculated based on the annual decline of a surrogate outcome (i.e., iohexal GFR) in the ERT group. It is unclear whether the sample size is adequate to infer non-inferiority of migalastat compared with ERT in the long-term outcomes considered in the model: ESRD, cardiac complications, stroke, death, and health utility values. CDR clinical reviewers noted that the impact of migalastat on clinically meaningful outcomes was uncertain, mainly because any observed effects on clinically meaningful outcomes (e.g., health-related quality of life [HRQoL], hard outcomes, and patient-reported symptoms) were marginal and limited by methodological considerations. Therefore, the assumption of comparable disease progression for migalastat and ERT may not be appropriate, given the limitations with the available evidence (see CDR Clinical Report for a full appraisal of the comparative clinical evidence). The model did not adequately account for this uncertainty, and CDR was unable to test this limitation in reanalyses.
- **Inappropriate comparator.** The use of a blended comparator is not appropriate. The manufacturer should have considered both comparator ERTs separately, particularly as there is a lack of information available regarding the current market share of the two ERT comparators. CDR undertook reanalyses that focused on the cost of ERT. As treatment efficacy and AE data were based on the ATTRACT trial, and stratified information based on the type of ERT was not provided, it was assumed these treatments were equivalent.
- **Disutility associated with ERT infusion is highly uncertain and lacks face validity.** ERT infusion was associated with a utility decrement (disutility) of 0.048. This disutility value was based on a UK study that measured health utilities using a DCE. It is unclear whether this utility estimate is generalizable to the Canadian population. Although the manufacturer attempted to adjust for the difference between the UK and the Canadian utility values using the methods shown in a previous study,[12] such a method was not

applicable to the submitted model due to different study populations (pancreatic cancer versus Fabry disease) and measurement tools (three-level EQ-5D versus DCE). Moreover, the use of a disutility of ERT infusion was inconsistent with the findings observed in the ATTRACT trial, suggesting negligible changes in HRQoL measured by SF-36 from baseline to 18 months in migalastat and ERT. Given that there are no disutility values associated with infusion for Canadian patients with Fabry disease and the lack of a notable quality-of-life difference between migalastat and ERT in the ATTRACT trial, CDR performed a scenario by varying the disutility associated with ERT infusion.

- **Transition probabilities between health states are assumed to be constant and do not vary by age.** This assumption is likely to be implausible as the clinical expert consulted by CDR and existing evidence have suggested that risk of progression in Fabry disease increases with age.[4,5] Due to the paucity of evidence, CDR was unable to test this limitation.
- **The submitted model overestimates patient survival.** A large international Fabry registry estimated a male life expectancy of 58.2 years and a female life expectancy of 74.7 years.[13] Applying the female percentage of 47.8% used in the model, the aggregated life expectancy at birth is 66.9 years. In the submitted base case, the predicted life expectancy for patients with Fabry disease was 81.54 years, longer than that reported in the international Fabry registry by 14.7 years. The overestimation of predicted life expectancy might be due to the use of low probabilities that patients are transitioning to death. A more reasonable approach may have been to use excess mortality associated with each complication that varies by age. Due to the model structure, CDR was unable to test this limitation in the model. This limitation likely biases the submitted results in favour of migalastat.
- **The submitted model did not test all relevant parameters in the probabilistic analysis.** The model results are highly dependent upon patient weight as the ERT product monographs recommend weight-based dosing. In patients of a lower body weight, migalastat is notably more costly than ERT. CDR tested the impact of weight in a scenario analysis.

The following errors were identified in the model:

- *Migalastat costs were underestimated*. The manufacturer calculated the annual cost of migalastat by rounding down the number of prescriptions required per year to 13 (one every four weeks, assuming a 52-week year). As the time horizon is 50 years, the correct calculation would have been to use 365.25 days and divide by the pack duration (14 capsules, one every two days, 28 days). CDR used this calculation in all CDR reanalyses. Though not an error, CDR noted that resource costs were assumed to be the same for both migalastat and ERT. The clinical expert consulted by CDR indicated additional monitoring costs may be experienced in patients switching from ERT after being on ERT for an extended period of time, due to the additional visits and tests required to assess treatment response. CDR was unable to test this parameter in the reanalysis.
- *ERT costs were overestimated*. The manufacturer multiplied the unit costs of agalsidase beta with the market share of agalsidase alfa as opposed to the market share of agalsidase beta. CDR undertook reanalyses for each comparator individually.
- *Disutility associated with dyspnea is incorrect*. The PE report and the submitted model used a disutility of 0.084 for dyspnea. However, its 95% confidence interval (–0.109 to –0.060) does not contain this mean value. Given the reported confidence intervals, CDR interpreted the appropriate value to be –0.084 and used this in all CDR reanalyses.

CADTH Common Drug Review Reanalyses

The manufacturer's submission contained errors in the calculation of the migalastat cost, the weighted costs of ERT, and a disutility value of dyspnea. The revised calculations used by CDR are outlined below:

- Annual number of migalastat prescriptions: 365.25 (days/year) / 14 (number of capsules per pack) * 2 (days between doses)
- The disutility value of dyspnea is changed from 0.084 to –0.084.

Additionally, CDR noted that the probabilistic analysis was not stable at the 1,000 iterations used by the manufacturer. Thus CDR undertook all subsequent reanalyses using 10,000 iterations. These revisions were then applied to the following four populations to form the CDR base case:

1. Comparator is agalsidase alfa
   a. disutility associated with ERT applied
   b. no disutility associated with ERT
2. Comparator is agalsidase beta
   a. disutility associated with ERT applied
   b. no disutility associated with ERT

The results of the CDR revised base-case analyses are shown in Table 3. CDR noted that the results of the probabilistic analysis differed from the results of the deterministic analysis (Table 15).

Table 3: CDR Reanalysis: CDR Revised Base Case

	Description		Total Cost, Migalastat ($)	Total Cost, ERT ($)	Incremental Cost ($)	Total QALYs, Migalastat ($)	Total QALYs, ERT ($)	Incremental QALYs ($)	ICUR ($/QALY Gained)
	Manufacturer's probabilistic base case (1,000 iterations)		6,070,182	6,448,076	–377,894	18.26	17.25	1.01	Migalastat is dominant
	Revised analyses run with error corrections and 10,000 iterations:								
1a	Comparator: agalsidase alfa	ERT disutility applied	6,089,023	5,886,056	202,967	18.27	17.26	1.01	$200,487
1b		No ERT disutility	6,103,839	5,903,285	200,554	18.28	18.27	0.0036	55,935,921
2a	Comparator: agalsidase beta	ERT disutility applied	6,095,424	6,747,673	–652,249	18.30	17.29	1.01	Migalastat is dominant
2b		No ERT disutility	6,088,057	6,746,480	–658,422	18.25	18.25	0.0032	Migalastat is dominant

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

Note: CDR identified variability in the results of the CDR reanalyses when run multiple times using 10,000 iterations.

CDR undertook several supplemental analyses testing the impact of several parameters of interest, including discontinuation rate, disutility associated with infusion administration, and patient weight. The results of these reanalyses can be viewed in the Reviewer Worksheets (Table 16 to Table 19).

The comparative discontinuation rate is uncertain, though the discontinuation rates from the ATTRACT trial indicate that there may be a greater proportion of patients discontinuing ERT compared with migalastat (see CDR Clinical Report). Based on the submitted model, a higher discontinuation rate for ERT compared with migalastat increases the total cost of migalastat relative to ERT, as well as the total number of QALYs (Table 17).

As is noted in the CDR base case, the application of a disutility rate impacts the cost-effectiveness of migalastat. If an incremental quality-of-life benefit is considered appropriate, the magnitude of that benefit also has a notable impact on the cost-effectiveness consideration (Table 18).

As ERT dosing is based on patient weight, the consideration of patient weight is integral to determining the comparative cost of migalastat and ERT. At the submitted price of migalastat and publicly available prices of ERT, migalastat may be more costly than ERT in patients with a lower body weight, and in patients with a higher body weight migalastat may be less costly than ERT (depending on the price of the ERT) (Table 19).

CDR undertook a price reduction analysis based on the comparison of migalastat versus agalsidase alfa. At the publicly available prices, a price reduction of 3.5% is required for migalastat to be less costly than agalsidase alfa. The clinical expert consulted by CDR indicated that the cost of ERT for different lysosomal diseases in Canada is currently under review. Any changes or differences in the total costs paid for ERT by the provinces to the costs used by the manufacturer will affect the cost-effectiveness results and subsequent price reduction analyses.

Issues for Consideration

- The clinical expert consulted by CDR indicated that the study population enrolled in the pivotal trials for migalastat (including ATTRACT) had extremely early and mild Fabry disease, which makes it difficult to generalize the results to patients with advanced disease who are switching therapies.
- The submitted model assumes the same baseline disease distribution for males and females. The clinical expert suggested that clinical manifestation and disease progression are likely to vary by sex.
- Although the indication for migalastat may not be as broad as for ERT, the availability of a more convenient form of administration (oral versus infusion) may lead to an increase in the number of treated patients, as patients who were previously not treated (due to AEs on ERT) may receive treatment.
- The product monograph indicates that patients are required to have a mutation determined to be amenable by an in vitro assay. Feedback from the CDR clinical expert indicated that no additional mutation testing will be required, as this is part of the genetic testing required for all Fabry disease patients. If additional mutation testing is required, it may lead to additional health system costs.
- The manufacturer's base case assumed that manufacturers pay all ERT infusion costs. If these costs are incurred by the publicly funded health care system, ERT would be associated with a greater total cost while the cost of migalastat would remain the same,

altering the difference in comparative costs, and affecting the cost-effectiveness of migalastat.

- Although the costs of ERT vary by weight, the submitted model assumes no vial sharing, which is appropriate based on the product monographs and feedback from the clinical expert. The clinical expert indicated that in practice the dose is rounded up or down to the nearest vial to ensure there is no wastage.
- The clinical expert consulted by CDR noted that the cost of ERT for different lysosomal diseases in Canada is currently under review. Any changes or differences in the total costs paid for ERT by the provinces to the costs used by the manufacturer will affect the cost-effectiveness results presented by CDR and the manufacturer.

Patient Input

Input was received from the Canadian Fabry Association and the Canadian Organization for Rare Disorders. The most impactful symptoms were noted to be pain and swelling; although fatigue, lack of energy, gastrointestinal problems, cognitive impairment, cardiovascular problems, stroke, and nervous system issues were also noted to have a severe impact on patients' daily lives. Considerable experience with the current standard of care (ERT) was noted. While positive feedback about the improvements associated with ERT was provided, some patients continued to experience moderate to severe symptoms, and the mode of administration was noted to be cumbersome and problematic. Patients also noted that ERT may not work for them because of the specific mutation they have, and would welcome having a new treatment alternative, one that is potentially more effective in allowing the enzyme to remain in the body longer at a stable level. Patients are hopeful that migalastat, an oral treatment, will circumvent the need for lengthy infusions, have no special requirements for storage and handling, allow for better compliance, and have reduced costs. The submitted economic evaluation assumes no difference in clinical outcomes, but does assume a utility benefit associated with the mode of administration.

Conclusions

Based on the both the placebo-controlled trial (FACETS) and the comparative trial of migalastat to ERT (ATTRACT), the clinically meaningful effects of migalastat are associated with uncertainty (CDR Clinical Report). While there may be a preference for an oral treatment over an infusion, the QALY benefit associated with the oral treatment is likely to be overestimated in the model.

The cost of migalastat 123 mg every other day compared with ERT (dosed per product monograph recommendations) depends on the price of the comparator treatment and patient weight. Based on the submitted and publicly available prices only, in a patient weighing 75 kg, migalastat ($310,250) has a greater annual cost than agalsidase alfa ($299,821) and a lower annual cost than agalsidase beta ($312,186).

Appendix 1: Cost Comparison

The comparators presented in Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in Table 4 and as such may not represent the actual costs to public drug plans.

Table 4: CDR Cost Comparison Table for Fabry Disease

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Migalastat (Galafold)	123 mg	Capsule	1,700.0000[ab]	123 mg orally once every other day	850.00	310,250
Enzyme replacement therapies						
Agalsidase alfa (Replagal)	3.5 mg	Vial for IV infusion	2,300.0000[cd]	0.2 mg/kg IV infusion every other week	821.43	299,821
Agalsidase beta (Fabrazyme)	5 mg 35 mg	Vial for IV infusion	798.2900[cd] 5,588.0000[cd]	1.0 mg/kg IV infusion every two weeks	855.31	312,186

CDR = CADTH Common Drug Review; IV = intravenous.

[a] Note: 123 mg of migalastat (equivalent to 150 mg migalastat hydrochloride).

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

[c] Assumes 75 kg average patient weight.

[d] Association québécoise des pharmaciens proprietaries price, reported by IMS Health Delta PA, July 2017.[14]

Appendix 2: Summary of Key Outcomes

Table 5: When Considering Only Costs, Outcomes & Quality of Life, How Attractive Is Migalastat Relative to Agalsidase alfa?

Migalastat vs. Agalsidase alfa	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
ICER or net benefit calculation	CDR revised base case: the ICUR for migalastat vs. agalsidase alfa ranges from $200,487 per QALY to $55,935,921 per QALY. CDR noted that there is a substantial uncertainty around the efficacy equivalence and the disutility value assumptions.					

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

Table 6: When Considering Only Costs, Outcomes & Quality of Life, How Attractive Is Migalastat Relative to Agalsidase beta?

Migalastat vs. Agalsidase beta	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes			X			
Quality of life			X			
ICER or net benefit calculation	CDR revised base case: migalastat is dominant compared with agalsidase beta. CDR noted that there is a substantial uncertainty around the efficacy equivalence and the disutility value assumptions.					

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; vs. = versus.

Appendix 3: Additional Information

Table 7: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	The PE report provides limited details regarding the description of methods used to derive transition probabilities, utility values, and costs. Scenario analyses were based on a deterministic analysis as opposed to a probabilistic analysis.		
Was the material included (content) sufficient?		X	
Comments	The PE report contains limited detailed descriptions of data sources used for the model.		
Was the submission well organized and was information easy to locate?		X	
Comments	The PE report does not include a section describing migalastat. The report does not provide the descriptions of adjustment for inflation and exchange rate.		

PE = pharmacoeconomic.

Table 8: Author 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		

CDR = CADTH Common Drug Review.

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

Scotland's Scottish Medicines Consortium (SMC), UK's National Institutes for Health and Clinical Excellence (NICE), and Australia's Pharmaceutical Benefits Advisory Committee (PBAC) have assessed migalastat for the treatment of Fabry disease. Both SMC (October 2016)[15] and NICE recommended migalastat for listing (with a price reduction);[16] the details of these decisions are summarized in Table 9 and Table 10. In March 2017, PBAC deferred the decision to a later date to await regulatory approval of the drug, although it noted issues with assumption of comparative clinical efficacy.[17] In July, PBAC decided not to recommend migalastat; as PBAC did not accept the clinical claim that migalastat would provide a benefit of similar extent as ERT in either treatment-naive patients or in treatment-experienced patients switching from one treatment to another.[18]

Table 9: Other HTA Findings (NICE, England)

	NICE (February 2017)[16]
Treatment	Migalastat (Galafold) capsules
Price	Not reported
Similarities with CDR submission	The model type (Markov state transition model) and structure (10 health states that represented the progression of Fabry disease over time) appear to be the same between NICE and CDR submissions. Assumptions that appear to be similar between submissions, per NICE documentation include: • ERTs are equivalent and grouped as a "blended comparator" • Migalastat is clinically equivalent to ERT • Treatment adherence is 100% • Distribution of people's base health states based on baseline data from ATTRACT trial • Resource use is based on Dutch practice patterns • Utility scores for health states based on a Dutch study • Utility decrements for treatment based on a UK study • Transition probabilities do not vary over time • A lifetime time horizon is used (although the lifetime duration differs slightly between models) • Similar cost information sources were used between submissions • Disutilities associated with infusion were responsible for virtually all of the QALY differences between migalastat and ERT.
Differences with CDR submission	The manufacturer's economic submission was a cost-consequence analysis. Average body weight was based on the UK general population, compared with trial data in the CDR submission. Different transition probabilities were used for males and females in the CDR submission (NICE unknown). Lower prevalence of disease was reported in the NICE submission. NICE submission assumed about 50% of people self-administer ERT; for the remainder treatment is given by a nurse at home. CDR assumed manufacturer funds all infusion costs.
Manufacturer's results	Migalastat QALYs = 14.33, ERT QALYs = 13.36 Incremental QALYs = 0.98 Total and incremental costs were not reported publicly.
Issues noted by the review group	ERG noted concerns with the design of the pivotal RCTs, including: small sample size, short duration, differences in baseline characteristics within trials, duration of treatment, patient population included (no severe Fabry patients).

	NICE (February 2017)[16]
	ERG noted the model structure was too simplistic. ERG noted the transition probabilities are unlikely to remain constant, which underestimates the disease state transition probability. ERG noted the mortality rate was overestimated life expectancy in the model. ERG noted the disutility for infusion was high and greater than for developing a new complication.
Results of reanalyses by the review group (if any)	ERG revised: ERT price, proportion starting in each health state, increasing age at model entry, revised mortality estimates, reduced body weight (from RCT), reduced life expectancy (66.5 years), reducing health state utilities, reducing disutility for infusion. ERG revisions resulted in incremental QALYs = 0.34.
Recommendation	Recommended as an option for treating Fabry disease in people over 16 years of age with an amenable mutation, if the discount agreed in the patient access scheme is provided, and only if ERT would otherwise be offered. Criteria for starting and stopping ERT for Fabry disease are described in the UK adult Fabry disease standard operating procedures (Hughes et al. 2013).

CDR = CADTH Common Drug Review; ERG = evidence review group; ERT = enzyme replacement therapy; HTA = health technology assessment; NICE = National Institutes for Health and Clinical Excellence; QALY = quality-adjusted life-year; RCT = randomized controlled trial.

Table 10: Other HTA Findings (SMC, Scotland)

	SMC (October 2016)[15]
Treatment	Migalastat (Galafold) capsules, 123 mg orally once every other day
Price	£210,000 per patient per year
Similarities with CDR submission	A cost-utility analysis was submitted (as a secondary analysis; details not reported).
Differences with CDR submission	Primary economic submission was a cost-minimization analysis. Weighted average of ERTs differed slightly between SMC and CDR submissions. Time horizon was 26 years in the SMC submission, approximately half what it was in the CDR submission. Average body weight was based on Scottish population, compared with trial data in the CDR submission. A PAS (likely price reduction) was submitted with the SMC submission.
Manufacturer's results	Without the PAS, migalastat was associated with an incremental cost of £1,157,518 compared with ERT. With the PAS, migalastat was associated with a lower overall cost than ERT.
Issues noted by the review group	The patient weight used was higher than the average weight in the RCTs. Some uncertainty with the conclusion of comparative efficacy was noted due to small patient numbers, lack of non-inferiority study design, and lack of longer-term data. The review group noted that despite these limitations, the economic case was demonstrated, as with the PAS migalastat provides health benefits at a lower overall cost than ERT.
Recommendation	Migalastat was accepted for restricted use within NHS Scotland, contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

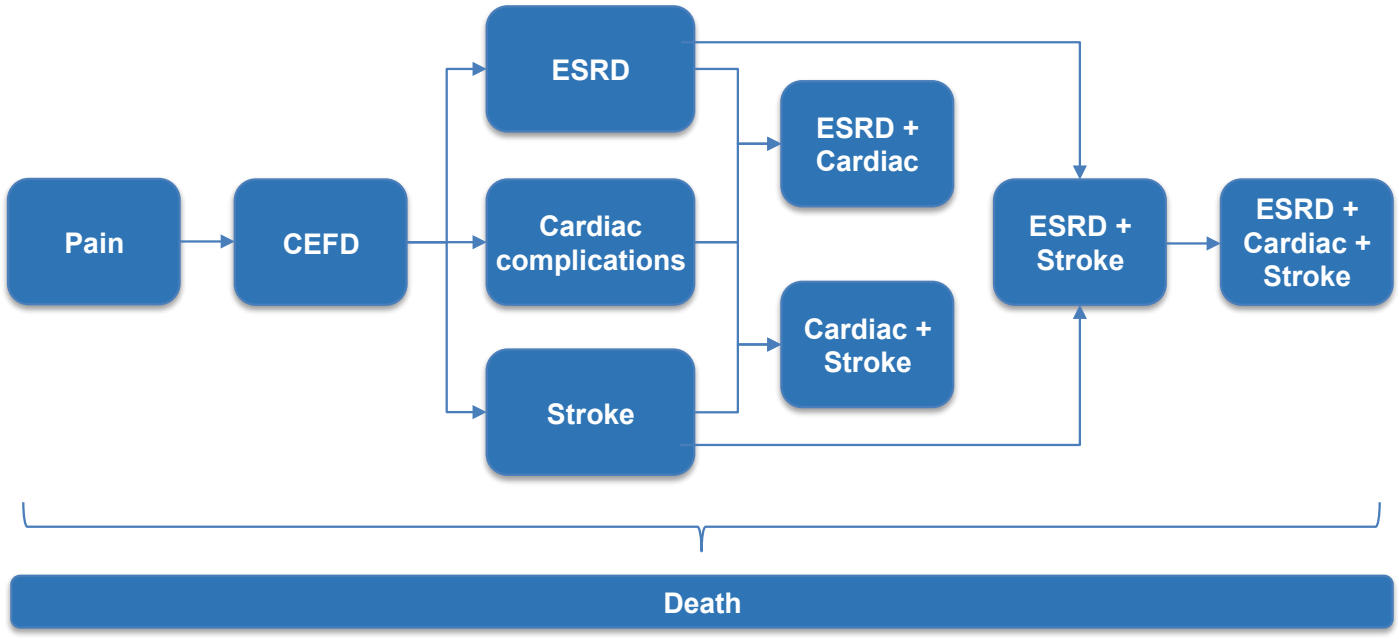
CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; NHS = National Health Service; PAS = patient access scheme; RCT = randomized controlled trial; SMC = Scottish Medicines Consortium.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer adapted a Markov model developed by Rombach et al.[3] The model consists of 10 health states reflecting the progression of Fabry disease (Figure 1). All health states were divided into incident and prevalent events. The incident event captures new cases, and the prevalent event includes both new and existing cases. The model starts to follow a patient from the pain health state. This patient may progress to the CEFD health state or die. From the CEFD health state, the patient may progress to any single complication state including end-stage renal disease (ESRD), stroke, or cardiac complication. A patient with any of the single complications may progress to a health state with a second complication or die. After experiencing the second complication, the patient may progress to a third complication or die. The submitted model used a cycle length of one year and a lifetime horizon.[2]

Figure 1: Manufacturer's Model Structure



Source: Manufacturer's Pharmacoeconomic Submission.[2]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Assumed clinical equivalence between migalastat and ERT based on ATTRACT trial.[7] Patients in ATTRACT received both agalsidase alfa and agalsidase beta. Weighted use and cost of ERTs in the model based on assumed market share.	The effect of the clinical equivalence assumption is uncertain. It is unclear whether the sample size is adequate to infer non-inferiority of migalastat compared with ERT to long-term outcomes considered in the model: ESRD, cardiac complications, stroke, death, and health utility values.
Natural history	Transition probabilities between health states were based on a Dutch cohort of Fabry disease patients.[6] Transition probabilities varied by gender but did not vary by age.	Time-invariant transition probabilities may underestimate the progression of Fabry disease while overestimating patient survival.
Utilities	Utilities specific to each health state were obtained from Rombach et al.[3] Disutilities associated with adverse events were taken from a health utility catalogue estimated using community-based UK preferences applied to EQ-5D descriptive questionnaire responses in the US-based Medical Expenditure Panel Survey.[8] A utility decrement associated with ERT infusion was obtained from a UK study that measured health utilities of patients with Fabry disease using a DCE.[9]	Utility values were estimated from the UK population. It is unclear whether these utility values are generalizable to the Canadian population. Although a published method was used to adjust the UK to the Canadian values,[12] such method was not applicable to the submitted model due to different study populations (pancreatic cancer vs. Fabry disease) and measurement tools (three-level EQ-5D vs. DCE). Utilities unique to each disease condition, such as stroke, cardiac complications, or ESRD, should be used. However, these utility values are unlikely to affect the cost-effectiveness findings due to an equivalent clinical assumption.
Adverse events	AE rates were obtained from ATTRACT trial.[7] AEs that were > 10% in either migalastat or ERT group were considered. These events included headache, influenza, dyspnea, upper respiratory tract infection, urinary tract infection, and gastritis.	The clinical expert suggests that the included AEs are appropriate.
Mortality	Age and gender-specific mortality rates were taken from Statistics Canada Life Tables, 2009–2011. Disease gender-specific mortality probabilities were obtained from Rombach et al.[3]	Data sources are appropriate, but disease-specific mortality should be varied by age. The submitted model predicted a life expectancy of 81.54 years. This estimate was higher than the average life expectancy of Fabry disease patients obtained from the international Fabry disease patient cohort (66.9 years).[13]
Resource Use and Costs		
Drug	Costs of ERT were estimated based on the previous CDR recommendations.[10,11] The manufacturer assumed a clinical equivalence of ERT drug; the submitted model, therefore, considered ERT as a blended comparator. The costs of ERT were weighted by the assumed market share of algasidase alfa (65%) and algasidase beta (35%). Agalsidase alfa is administered intravenously at a dose of 0.2 mg/kg over 40 minutes, while agalsidase beta is administered at a dose of 1 mg/kg over two hours. The average weight by gender was based on data obtained from the CFDI. The model assumes no vial sharing.	CDR detected calculation errors for migalastat and ERT costs. Use of a blended comparator is not appropriate.

Data Input	Description of Data Source	Comment
	Migalastat is an oral treatment taken once every two days and will be available in a pack of 14 capsules. It was priced at approximate parity to ERT.[2]	
Administration	The model includes bi-weekly administration costs of receiving infusion and the costs of pre-infusion medication (Ontario Schedule of Benefits). Resource use for treatment administration was based on clinical opinion. Infusion costs, including nurse time, transportation, scheduling and consumable supplies were assumed to be paid by the manufacturer.	Appropriate
AEs	The manufacturer made the assumptions regarding resources required to manage AEs. Unit costs for each health service use were based on the Ontario Schedule of Benefits and the Ontario Drug Benefit	The assumptions were made without supporting evidence or verification by clinical experts.
Health state	Health state costs were divided into acute event and follow-up costs. Acute event costs were obtained from the published studies conducted in Canada and the UK.[2] The follow-up costs consisted of ambulatory care, diagnostics, imaging, and laboratory testing. The frequency of visits was taken from Rombach et al., assuming comparable clinical practices between Canada and the Netherlands. Unit costs for each ambulatory care visit were gathered from the Ontario Schedule of Benefits.	From the PE report, it is unclear whether the manufacturer adjusted for inflation. This limitation is unlikely to change the cost-effectiveness findings due to a clinical equivalence assumption. The clinical expert agreed that the clinical practices between Canada and the Netherlands are comparable.

AE = adverse event; CDR = CADTH Common Drug Review; CFDI = Canadian Fabry Disease Initiative; DCE = discrete choice experiment; EQ-5D = EuroQol 5-Dimensions; ERT = enzyme replacement therapy; ESRD = end-stage renal disease; PE = pharmacoeconomic vs. = versuS.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Migalastat and ERT are clinically equivalent.	This assumption is uncertain. It is unclear whether the sample size is adequate to infer non-inferiority of migalastat compared with ERT to long-term outcomes considered in the model: ESRD, cardiac complications, stroke, death, and health utility values. See CDR Clinical Report for further information on the clinical efficacy concerns.
Agalsidase alfa and agalsidase beta are clinically equivalent.	This assumption was based on the evidence from the CFDI[19] suggesting that two formulations of ERT were not statistically different (hazard ratio: 1.29, *P* value = 0.67). It should be noted that the power to detect a significant difference was limited as the number of patients randomized to agalsidase alfa (N = 62) and beta (N = 30) was small. The use of a blended comparator is not appropriate. The manufacturer should have considered both comparator ERTs separately, particularly as there is a lack of information available regarding the current market share of the two ERT comparators.
Transition probabilities do not vary by age.	This assumption is likely to be implausible as existing evidence has shown that risk of progression in Fabry disease increases with age, and may underestimate the progression of Fabry disease and overestimate the life expectancy of patients with Fabry disease. However, its impact on the cost-effectiveness findings is unknown.
1% annual discontinuation rate applies to both migalastat and ERT.	The assumption was used without supporting evidence and justification. The model is sensitive to a discontinuation rate. If ERT has a higher discontinuation rate than migalastat, migalastat is no longer associated with a lower cost.

Assumption	Comment
Resource use associated with follow-up/ambulatory care was based on Dutch practice patterns.	Clinical practices in the Netherland may not entirely match Canadian practices. The CDR clinical expert agrees that the clinical practices in Canada and the Netherlands are comparable. At the time of the PE submission, no resource use data are available in Canadian Fabry disease patients.
If patients discontinued treatment (either migalastat or ERT), they were assumed to be untreated. No switching between treatments was allowed in the submitted model.	The effect of switching between treatments on the cost-effectiveness findings is unknown.

CDR = CADTH Common Drug Review; ERT= enzyme replacement therapy; ESRD = end-stage renal disease; CFDI = Canadian Fabry Disease Initiative; PE = pharmacoeconomic.

Manufacturer's Results

In the base case, the manufacturer reported that migalastat is a dominant strategy (less costly and improved quality-adjusted life-years [QALYs]) compared with enzyme replacement therapy (ERT). The cost-saving findings were driven by a substantially lower costs of migalastat compared with ERT (Table 13).

Table 13: Results of the Manufacturer's Base Case (Deterministic Analysis)

	Migalastat	ERT	Incremental
QALYs	18.26	17.25	1.01
Cost ($)			
Treatment costs	6,065,481	6,416,341	–350,860
Admin costs	0	0	0
Diagnostics, laboratory and imaging	38,180	38,180	0
Hospitalization costs	7,062	7,062	0
Health state follow-up costs	43,566	43,566	0
HCP contacts	14,232	14,232	0
AE costs	271	364	–93
Total costs ($)	6,168,792	6,519,745	–350,953
ICUR ($/QALY)			Migalastat is dominant

AE = adverse event; ERT = enzyme replacement therapy; HCP = health care practitioner; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Manufacturer's PE Report.[2]

In a probabilistic sensitivity analysis of 1,000 simulations, at a willingness to pay threshold of $50,000 per QALY, migalastat is considered a preferred treatment strategy in approximately 96% of simulations.

The manufacturer undertook a series of scenario analyses, as described in the "Information on the Pharmacoeconomic Submission" Section. The results are reported in Table 14 below:

Table 14: Summary of Deterministic Results of the Manufacturer's Sensitivity Analyses

Description	Total Cost, Migalastat ($)	Total Cost, ERT ($)	Incremental Cost ($)	Total QALYs, Migalastat ($)	Total QALYs, ERT ($)	Incremental QALYs ($)	ICUR ($/QALY Gained)
Manufacturer's base case	6,168,792	6,519,745	–350,953	18.26	17.25	1.01	Migalastat is dominant
Scenario 1: Weight based on ATTRACT trial subjects	6,168,792	6,122,450	46,341	18.26	17.25	1.01	45,894
Scenario 2: Weight based on ATTRACT trial subjects and starting age 18	6,368,071	6,320,415	47,656	25.06	23.74	1.32	36,005
Scenario 3: Starting age 18, all-male population and weight based on male CFDI patients	6,028,500	6,499,061	–470,561	24.88	23.57	1.32	Migalastat is dominant
Scenario 4: 10% discount from list ERT prices	6,168,792	5,878,111	290,681	18.26	17.25	1.01	287,873
Scenario 5: Infusion costs are not paid by manufacturers	6,168,792	6,584,402	–415,611	18.26	17.25	1.01	Migalastat is dominant

CFDI = Canadian Fabry Disease Initiative; ERT = enzyme replacement therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic Submission.[2]

CADTH Common Drug Review Reanalyses

The main CDR reanalyses are provided in the "Information on the Pharmacoeconomic Submission" Section. Table 15 reports the deterministic results of the CADTH Common Drug Review (CDR) reanalyses.

Table 15: CDR Reanalysis: CDR Revised Base Case (Deterministic Results)

	Description	Total Cost, Migalastat ($)	Total Cost, ERT ($)	Incremental Cost ($)	Total QALYs, Migalastat ($)	Total QALYs, ERT ($)	Incremental QALYs ($)	ICUR ($/QALY Gained)
	Manufacturer's deterministic base case	6,168,792	6,519,745	–350,953	18.26	17.25	1.01	Migalastat is dominant
	Revised analyses run with error corrections:							
1	ERT = agalsidase alfa, ERT disutility applied	6,189,621	5,965,003	224,618	18.26	17.25	1.01	222,685
2	ERT = agalsidase alfa, no ERT disutility applied	6,189,621	5,965,003	224,618	18.26	18.26	0.0033	68,406,137
3	ERT = agalsidase beta, ERT disutility applied	6,189,621	6,818,452	–628,831	18.26	17.25	1.01	Migalastat is dominant
4	ERT = agalsidase beta, ERT disutility not applied	6,189,621	6,818,452	–628,831	18.26	18.26	0.0033	Migalastat is dominant

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

Discontinuation rate. The higher the treatment discontinuation rate, the less costs and QALYs are generated for each treatment, due to a reduced duration of treatment. As these changes apply to both costs and QALYs, the incremental cost-utility ratios (ICURs) remained relatively stable (Table 16). CDR noted that if the discontinuation rate with ERT was higher than the discontinuation rate with migalastat, migalastat would be associated with an increased cost, and thus, a higher ICUR (Table 17). As per the manufacturer's model, if patients discontinue the treatment they are on, they do not receive an alternative treatment.

Table 16: CDR Reanalysis: Scenario Analyses (Alternative Discontinuation Rates for Both Migalastat and ERTs)

Comparator	Agalsidase alfa		Agalsidase beta	
Discontinuation Rate (Both Treatments)	Disutility Applied ICUR ($/QALY Gained)	Disutility Not Applied ICUR ($/QALY Gained)	Disutility Applied ICUR ($/QALY Gained)	Disutility Not Applied ICUR ($/QALY Gained)
CDR base case	200,487	55,935,921	Migalastat is dominant	Migalastat is dominant
2%	181,989	40,728,351	Migalastat is dominant	Migalastat is dominant
3%	192,590	93,046,880	Migalastat is dominant	Migalastat is dominant
4%	181,408	93,946,981	Migalastat is dominant	Migalastat is dominant

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

Note: As previously noted, even with 10,000 iterations, variance in the results was noted between model runs. Therefore, the non-linear ICURs for which there are smaller differences between parameters may be attributable to the volatility of the model.

Table 17: CDR Reanalysis: Scenario analyses (Alternative Discontinuation Rates that Differ Between Migalastat and ERT)

Comparator	Agalsidase alfa		Agalsidase beta	
Discontinuation Rate Migalastat/ERT	Disutility Applied ICUR ($/QALY Gained)	Disutility Not Applied ICUR ($/QALY Gained)	Disutility Applied ICUR ($/QALY Gained)	Disutility Not Applied ICUR ($/QALY Gained)
CDR base case	200,487	55,935,921	Migalastat is dominant	Migalastat is dominant
1% / 2%	1,092,215	26,271,471	269,276	6,479,257
1% / 5%	3,403,966	19,788,118	2,885,226	17,198,458
5% / 10%	2,949,073	13,288,860	2,320,303	10,547,153
10% / 5%	Migalastat is dominant	10,688,574 (agalsidase alfa vs. migalastat)[a]	Migalastat is dominant	16,659,703 (agalsidase beta vs. migalastat)[a]

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

Note: As previously noted, even with 10,000 iterations, variance in the results was evident between model runs. Therefore, the non-linear ICURs for which there are smaller differences between parameters may be attributable to the volatility of the model.

[a] Comparator is more costly and more effective than migalastat due to discontinuation rate and assumption that patients who discontinue are not treated.

Disutility associated with ERT infusion. The assumption of a disutility due to ERT infusion may be acceptable based on feedback provided by patient groups, although this is not borne out by the quality of life measures used in the ATTRACT study. However, there is notable uncertainty regarding the magnitude of the benefit associated with the use of an oral agent compared with an infusion. CDR undertook a scenario analysis by varying the disutility of ERT infusion from –0.048 (manufacturer's base case) to 0.01 (assumed no utility decrement associated with ERT infusion) for comparison against both agalsidase alfa and agalsidase

beta. The results show a notable reduction in QALYs gained if the disutility associated with ERT infusion was assumed to be lower (Table 18).

Table 18: CDR Reanalysis: Scenario Analysis (Alternative Disutility Values of ERT Infusion)

	Description	Migalastat vs. Agalsidase alfa ICUR ($/QALY Gained)	Migalastat vs. Agalsidase beta ICUR ($/QALY Gained)
	CDR base case (with disutility applied)	200,487	Migalastat is dominant
1	Assumed disutility value of 0.04	250,348	Migalastat is dominant
2	Assumed disutility value of 0.03	295,984	Migalastat is dominant
3	Assumed disutility value of 0.02	463,838	Migalastat is dominant
4	Assumed disutility value of 0.01	864,542	Migalastat is dominant
5	Assumed no disutility value	55,935,921	Migalastat is dominant

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

Note: A 10% difference from the mean disutility value was used for the lower and upper bounds for the probabilistic analysis.

Patient weight. As ERT product monographs recommend weight-based dosing, small changes in the patient weight assumptions in the submitted analysis affect the comparative costs of migalastat and ERT. CDR performed a scenario analysis varying the baseline patient weight for all patients. The results show that the cost-effectiveness of migalastat is sensitive to patient weight (Table 19). In a patient weighing less than 88 kg, at the submitted and publicly available prices, migalastat is more costly than agalsidase alfa. In a patient weighing less than 70 kg, at the submitted and publicly available prices, migalastat is more costly than agalsidase beta.

Table 19: CDR Reanalysis: Scenario Analysis (Alternate Average Patient Weight Estimates)

Comparator	Agalsidase alfa		Agalsidase beta	
Patient Weight	Disutility Applied ICUR ($/QALY Gained)	Disutility Not Applied ICUR ($/QALY Gained)	Disutility Applied ICUR ($/QALY Gained)	Disutility Not Applied ICUR ($/QALY Gained)
CDR base case	200,487	55,935,921	Migalastat is dominant	Migalastat is dominant
All patients = 50 kg	2,470,773	724,389,629	1,948,258	550,165,554
All patients = 75 kg	185,879	46,550,905	Migalastat is dominant	Migalastat is dominant
All patients = 80 kg	195,090	48,129,398	Migalastat is dominant	Migalastat is dominant
All patients = 90 kg	Migalastat is dominant	Migalastat is dominant	Migalastat is dominant	Migalastat is dominant

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

Note: As previously noted, even with 10,000 iterations, variance in the results was evident between model runs. Therefore, the non-linear ICURs for which there are smaller differences between parameters may be attributable to the volatility of the model.

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