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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

SEBELIPASE ALFA (KANUMA)

(Alexion Pharmaceuticals, Inc.)

Indication: Indicated for the treatment of infants, children, and adults diagnosed with lysosomal acid lipase (LAL) deficiency.

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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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Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSC	best supportive care
CDR	CADTH Common Drug Review
CE	cost-effectiveness
EQ-5D	EuroQol 5-Dimensions questionnaire
FPR	fibrosis progression rate
HDL-C	high-density lipoprotein cholesterol
HTA	health technology assessment
ICUR	incremental cost-utility ratio
LAL	lysosomal acid lipase
LAL-D	lysosomal acid lipase deficiency
LDL-C	low-density lipoprotein cholesterol
LYG	life-year gained
NASH	non-alcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
PE	pharmacoeconomic
QALY	quality-adjusted life-year
TG	triglyceride

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Sebelipase alfa (Kanuma)
Study Question	To assess the incremental benefits and costs, relative to the current standard of care, associated with sebelipase alfa treatment for lysosomal acid lipase (LAL) deficiency.
Type of Economic Evaluation	Cost-utility analysis
Target Population	1) Infants (i.e., before 6 months of age) presenting with rapidly progressive LAL deficiency. 2) Pediatric/adult patients presenting with LAL deficiency.
Treatment	• Infants: The recommended starting dose for sebelipase alfa in infants (< 6 months of age) is 1 mg/kg administered as an intravenous infusion once weekly and can be escalated up to a maximum dose of to 3 mg/kg once weekly. • Children and adults: The recommended dose for sebelipase alfa in children and adults is 1 mg/kg administered as an intravenous infusion once every other week.
Outcome	Quality-adjusted life-years (QALYs)
Comparator	Best supportive care (BSC), which includes lipid-lowering therapies, vitamin E, and liver transplantation.
Perspective	Publicly funded health care system
Time Horizon	Lifetime (up to the age of 101 years)
Results for Base Case	The incremental cost-utility ratio (ICUR) for sebelipase alfa vs. BSC (probabilistic): • Infants: $4,485,000 per QALY • Children and adults: $2,003,000 per QALY
Key Limitations	• Clinical data for the indicated populations were limited and associated with uncertainty, which impacts the confidence that can be placed on the results of the economic analyses. • The modelling approach in infantile presentation was based on survival and did not consider disease progression (e.g., development of liver disease). • In the LAL-CL02 trial (ARISE, pediatric/adult presentation) surrogate outcomes were captured instead of final clinical outcomes. In addition, no data were found showing how the surrogate outcomes directly measure or correlate with patient functioning, development, and survival. • Long-term safety and efficacy for sebelipase alfa is uncertain due to the short duration of the clinical trials and cannot be substantiated over a lifetime. • Utility values used in the analyses were not derived from patients with LAL deficiency. However, varying the utility values in pediatric/adult presentation did not significantly impact the results. • The manufacturer assumed that patients above the age of 21 years would not gain weight over the remaining duration of the model. Applying a 1% annual increase in patient weight slightly increased the ICURs due to the increased drug costs with sebelipase alfa.
CDR Estimate(s)	• There is substantial uncertainty associated with the estimated cost-effectiveness of sebelipase alfa compared with BSC in the indicated populations for which the manufacturer is seeking reimbursement, given the uncertainty with the clinical information and the concerns with the modelling approach in the infantile and pediatric/adult presentations, assumptions of long-term effect and safety, and estimation of drug cost over time based on patient weight. • CDR conducted exploratory analyses varying the patient weight over time, model time horizon, liver disease progression, and health state utility values to assess their impact on the base-case results in both infantile and pediatric/adult presentation.

	• CDR estimated the ICURs for sebelipase alfa compared with BSC to be more than $4.9 million per QALY and more than $2 million per QALY in infantile and pediatric/adult presentations, respectively. • Based on the CDR estimates, a price reduction of greater than 96% would be required to achieve ICURs less than $50,000 and $100,000 per QALY in both patient presentations.

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; LAL = lysosomal acid lipase; QALY = quality-adjusted life-year.

Drug	Sebelipase alfa (Kanuma)
Indication	Indicated for the treatment of infants, children, and adults diagnosed with lysosomal acid lipase (LAL) deficiency.
Reimbursement Request	For long-term enzyme replacement therapy in patients with LAL deficiency.
Dosage Form(s)	Solution for infusion 2 mg/mL concentrate 20 mg/10 mL (2 mg/mL) solution in single-use vials
NOC Date	December 15, 2017
Manufacturer	Alexion Pharmaceuticals, Inc.

Executive Summary

Background

Sebelipase alfa (Kanuma) is a recombinant form of the human lysosomal acid lipase (LAL) enzyme, and is indicated for the treatment of infants, pediatric, and adult patients diagnosed with LAL deficiency.[1] The recommended starting dose in infants (less than six months of age) presenting with rapidly progressive LAL deficiency is 1 mg/kg administered as an intravenous infusion once weekly, with dose escalation to 3 mg/kg once weekly, based on clinical response. In pediatric and adult patients the recommended dose is 1 mg/kg administered as an intravenous infusion once every other week. The manufacturer submitted a price of $8,546 per 10 mL vial of sebelipase alfa, containing 2 mg/mL concentrate solution for infusion. The average annual cost for sebelipase alfa in infantile-presentation patients ranges from $892,000 to $4.9 million per patient. In the pediatric/adult presentation, the average annual cost for sebelipase alfa is $892,000 per patient.

The manufacturer submitted two cost-utility analyses based on the classification of LAL deficiency by infantile presentation and a pediatric/adult presentation. For infantile-presentation patients, a survival model was used given the high mortality risk in the first year of life, as observed in the natural history study LAL-1-NH01 (Jones et al. 2016)[2], with median age at death of 3.7 months.[3] For the pediatric/adult-presentation patients, a model of liver disease progression that focused on the hepatic aspect of LAL deficiency was used.[3] The clinical efficacy of sebelipase alfa for infantile-presentation LAL deficiency patients was based on the reduction of mortality risk in infancy as reported in the VITAL clinical trial (LAL-CL03, Jones et al. 2017)[4], showing survival benefit associated with sebelipase alfa with 67% (6/9) of treated infants in VITAL surviving to 12 months of age.[4] In pediatric/adult-presentation LAL deficiency patients, efficacy for sebelipase alfa was based on liver biopsy data as derived from the ARISE clinical trial (LAL-CL02, Burton et al. 2015).[5] The comparator in both economic evaluations was the current standard of care, or best supportive care (BSC), which included lipid-lowering therapies, vitamin E, and liver transplantation. The analyses were conducted from the perspective of the publicly funded health care system in Canada, over a lifetime time horizon. In the base-case analyses costs and benefits were discounted at an annual rate of 1.5%.

The manufacturer reported that sebelipase alfa was associated with more costs ($161,654,475 in infantile and $36,337,577 in pediatric/adult presentation, respectively) and

quality-adjusted life-years (QALYs) (36.03 in infantile and 18.25 in pediatric/adult presentations, respectively) than BSC, resulting in incremental cost-utility ratios (ICURs) of $4,485,442 and $2,004,670 per QALY, for infantile and pediatric/adult presentation, respectively. When a $[redacted] cap on annual per-patient treatment cost was applied, the manufacturer reports ICURs (based on probabilistic analyses) for sebelipase alfa were $[redacted] and $[redacted] per QALY in infantile- and pediatric/adult-presentation patients, respectively.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the manufacturer's cost-effectiveness analyses, which impact the validity of the submitted analyses and CDR's ability to undertake reanalyses.

Firstly, both clinical trials of sebelipase alfa (LAL-CL02 and LAL-CL03) were based on small sample sizes and lacked long-term follow-up (treatment period up to 4 years in VITAL trial). The VITAL trial was non-comparative and potentially subject to bias. In addition, in the LAL-CL02 trial (ARISE, pediatric/adult presentation) surrogate outcomes (alanine aminotransferase [ALT] normalization at the end of the double-blind period/week 20) were captured instead of final clinical outcomes. In addition, for the primary outcome of ALT normalization, no data were found showing how it directly relates to patient functioning, development, and survival. The FDA medical review indicated that "ALT neither directly measures clinical benefit of treatment nor represents a surrogate end point reasonably likely to predict clinical benefit in pediatric and adult patients with cholesteryl ester storage disease."[6] The FDA medical review also indicated that "normal ALT does not necessarily exclude the presence or progression of liver disease,"[6] and they conclude that "normalization of ALT does not reliably represent a clinical benefit."[6] This contradicts the manufacturer's economic analysis in pediatric/adult-presentation patients, which included a probability of liver disease regression of 67% in the first cycle.

The manufacturer used separate sources of data for sebelipase alfa and BSC in both analyses, possibly biasing the results in favour of sebelipase alfa:

- **Infantile presentation:** The manufacturer used data from the VITAL study to model the efficacy of sebelipase alfa in infant patients, whereas the historical control cohort from LAL-1-NH01 was used for patients on BSC. For the VITAL study, a historical control for the primary outcome (proportion of patients surviving to 12 months of age) was used. Due to the absence of a comparator arm in VITAL and the short duration of treatment, it is uncertain if sebelipase alfa delayed or stopped progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events, or death in pediatric/adult-presentation patients with LAL deficiency.
- **Pediatric/adult presentation:** The manufacturer used pre-randomization study data from ARISE to model liver disease progression in patients on BSC, while post-randomization study data from LAL-CL02 was used for sebelipase alfa, in terms of the effect on slowing or halting liver disease progression.

A more conventional approach of modelling natural history and applying treatment effects would have been more appropriate. CDR acknowledges the limitations of conducting the more suitable approach in light of the limited published information on the incidence and prevalence of LAL deficiency.

Second, the approach to modelling did not fully consider the relevant clinical aspects for either presentation. The manufacturer used a survival model to assess the cost-effectiveness of sebelipase alfa compared with BSC in infantile-presentation patients. This model did not include liver disease as part of the natural history of the condition, an expected progression in patients reaching the adolescent/adult life stages. This is based on the assumption that sebelipase alfa is effective at preventing the development of liver disease and that clinical effects are maintained throughout the lifetime of the patient. However, based on the available data, there is limited evidence to support the assumption that the effects of sebelipase alfa are maintained over the long term, and that liver disease can be prevented in patients with infantile presentation. In the submitted model for sebelipase alfa in pediatric/adult presentation, a probability of liver disease regression of 67% in the first cycle as an effect of sebelipase alfa therapy was applied. Sebelipase alfa was assumed to reverse liver without the evidence to support long term and the key clinical end point, such as the need for liver transplant.

The above limitations could not be accounted for within CDR reanalyses.

In addition, CDR identified other important limitations.

Utility scores for both patient presentations were not derived from patients with LAL deficiency. The utility values were derived from a systematic review and cost-effectiveness evaluation of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease. Specifically, the base-case analysis used utility values that were collected from patients with hepatitis C infections.[7] In an exploratory analysis, CDR considered utility values from patients with non-alcoholic steatohepatitis; the results did not change significantly.

Finally, in both presentations, the manufacturer assumed that patients above the age of 21 years would not gain weight over time for the remainder of the model time horizon. CDR conducted exploratory analyses varying patients' weight over time.

Conclusions

There is substantial uncertainty associated with the estimated cost-effectiveness of sebelipase alfa for the populations considered due to the uncertainty as to: whether the clinical efficacy of sebelipase alfa will be maintained over the lifetime of the populations; impact of treatment on liver complications; quality of the comparative clinical effectiveness of sebelipase alfa with BSC; approach in costing sebelipase alfa in adult patients throughout the time horizon in the submitted economic models.

In the infantile presentation, the submitted economic model did not include liver disease as an expected progression in LAL deficiency patients. This reflects a potentially optimistic case where patients continue to realize the beneficial effects of sebelipase alfa in terms of the prevention of liver disease and, as a result, life expectancy is similar to that of the general Canadian population. In the pediatric/adult presentation, the submitted model included a probability of liver disease regression of 67% in the first cycle as an effect of sebelipase alfa therapy. Sebelipase alfa is expected to reverse liver disease without the evidence to support long term and the key clinical end point such as the need for liver transplant.

Based on exploratory analyses considering the probability of liver disease progression in the pediatric/adult presentation; patient utility; patient weight changes over time; and time

horizons for both presentations, CDR estimated the ICURs for sebelipase alfa compared with BSC to be more than $4.9 million per QALY and more than $2 million per QALY in infantile and pediatric/adult presentations, respectively.

To reduce the manufacturer and CDR ICURs to $50,000 and $100,000 per QALY, either a price reduction of greater than 96% or a cap on annual drug costs per patient of $50,000 is required.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted two cost-utility analyses based on the classification of lysosomal acid lipase (LAL) deficiency by infantile presentation and pediatric/adult presentation.

For infantile-presentation patients, a survival model was used based on the prognosis in infantile-presentation patients as observed in the natural history study, LAL-1-NH01,[2] with median age at death of 3.7 months.[3] The model was structured as a Markov health state transition model. A lifetime horizon was used, and a monthly cycle length was chosen in order to reflect the timing of mortality (and associated neonatal intensive care) over the first 24 months of life. The manufacturer assumed that patients surviving beyond 24 months take on general-population quality-of-life norms and survival (based on Canadian life tables from Statistics Canada, 2017).[3]

For pediatric/adult-presentation patients, a model of liver disease progression was used. The manufacturer acknowledged that while LAL deficiency threatens multiple vital organ systems (including the liver, heart, spleen, and gastrointestinal tract), liver disease outcomes were the focus of the model, as they frequently occur early in the disease process, may have severe impact on quality of life and survival, and cannot be addressed with current supportive care.[3] Therefore, the economic model focused on the hepatic aspect of LAL deficiency. The model was also structured as a Markov health state transition model with a lifetime horizon and an annual cycle length.

A half-cycle correction was applied in the first and last cycles of both models.

The clinical efficacy of sebelipase alfa for infantile-presentation LAL deficiency patients was the reduction of mortality risk in infancy as reported in the VITAL clinical trial,[4] showing survival benefit associated with sebelipase alfa, with 67% (6/9) of treated infants in VITAL surviving to 12 months of age.[4] In pediatric/adult-presentation LAL deficiency patients, efficacy for sebelipase alfa was derived from liver biopsy data from the ARISE clinical trial.[5] The ARISE trial was a 20-week randomized, double-blind, placebo-controlled study that reported differences in seven disease-related efficacy measures: the primary end point of normalization of alanine aminotransferase (ALT) level, as well as six consecutive secondary end points, including (i) change from baseline in low-density lipoprotein cholesterol (LDL-C) level, (ii) change from baseline in non-high-density lipoprotein cholesterol (HDL-C) level, (iii) normalization of aspartate aminotransferase (AST) level, (iv) change from baseline in triglyceride (TG) level, (v) change from baseline in HDL-C level, and (vi) change from baseline in hepatic fat content.[5] The manufacturer assumed the clinical effects for sebelipase alfa were sustained over the patient's lifetime in both presentations (up to 101 years) without the probability of patients experiencing waning of treatment effects, treatment discontinuations, adverse events, the development of liver disease (in infantile presentation), or the progression of liver disease (in pediatric/adult presentation) over the duration of the analysis.

The comparator in the economic evaluations for both infantile-presentation and pediatric/adult-presentation patients was best supportive care (BSC), which included lipid-

lowering therapies, vitamin E, and liver transplantation. The manufacturer considered BSC to be supportive in nature and does not address the underlying defect in LAL deficiency (i.e., lack of LAL enzyme activity).[3] The analyses take the perspective of the publicly funded health care system in Canada in relation to costs, and consider the survival and quality of life gains accrued by patients in relation to benefits. In the base-case analyses costs and benefits were discounted at an annual rate of 1.5%.

Manufacturer's Base Case

In the infantile-presentation patient population, the manufacturer reported a probabilistic ICUR of $4,485,000 per QALY gained for sebelipase alfa compared with BSC. Sebelipase alfa was associated with more costs ($161,737,796 compared with $83,021) and QALYs (36.31 compared with 0.27) than BSC in infantile-presentation patients. In the pediatric/adult-presentation patients, the manufacturer reported a probabilistic ICUR of $2,005,000 per QALY gained for sebelipase alfa compared with BSC. Sebelipase alfa was associated with more costs ($36,391,822 compared with $54,245) and QALYs (35.26 compared with 17.01) than BSC in pediatric/adult-presentation patients (Table 2). The results of the manufacturer's deterministic analyses were similar to the probabilistic results (Table 13).

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

	Total Costs	Incremental Cost of Sebelipase Alfa	Total QALYs	Incremental QALYs of Sebelipase Alfa	Incremental Cost per QALY
Infantile-Presentation Patients					
BSC	$83,021		0.27		
Sebelipase alfa	$161,737,796	$161,654,475	36.31	36.03	$4,485,000
Pediatric/Adult-Presentation Patients					
BSC	$54,245		17.01		
Sebelipase alfa	$36,391,822	$36,337,577	35.26	18.25	$2,005,000

BSC = best supportive care; LYG = life-year gained; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic (PE) submission.[3]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted deterministic sensitivity analyses for both infantile- and pediatric/adult-presentation patients. The key deterministic analyses for infantile-presentation patients were conducted using reduced dosing at older age (1 mg/kg of body weight every week, rather than 3 mg/kg of body weight every week; starting at age 12 years in one sensitivity and at age 18 years in a second sensitivity), a reduction in health utility (of 0.15) from general-population norms at age 2+ years, reduced time horizon (from lifetime to six years), and variation in the discount rate. For pediatric/adult-presentation patients, key deterministic sensitivity analyses were conducted on the rate of progression of hepatic fibrosis in untreated patients (i.e., fibrosis progression rate [FPR] based on Bernstein et al. [2013],[8] LAL-CL02, or Burton et al. [2015]),[5] and, by association, the age at start of treatment, and variation in the discount rate (Table 3).

Table 3: Summary of Results of the Manufacturer's Base Case

Sensitivity Analysis	Original Value	Costs			QALYs			
		Sebelipase Alfa	BSC	Incremental	Sebelipase Alfa	BSC	Incremental	Incremental Cost per QALY
Infantile-Presentation Patients								
Base Case	**-**	***$125.45M***	***$0.10M***	***$125.35M***	***28.12***	***0.29***	***27.83***	***$4.504M***
Cap on annual drug costs of $[redacted]	No cap	$[redacted]	$0.10M	$[redacted]	28.12	0.29	27.83	$[redacted]
Dosing = 1 mg/kg for age 12+	3 mg/kg	$53.14M	$0.10M	$53.04M	28.12	0.29	27.83	$1.906M
Dosing = 1 mg/kg for age 18+		$60.92M	$0.10M	$60.82M	28.12	0.29	27.83	$2.185M
Horizon = 6 years	Lifetime	$3.77M	$0.10M	$3.67M	3.75	0.29	3.47	$1.058M
Pediatric/Adult-Presentation Patients								
Base Case	**-**	***$36.89M***	***$0.05M***	***$36.84M***	***35.81***	***17.03***	***18.78***	***$1.961M***
Cap on annual drug costs of $[redacted]	No cap	$[redacted]	$0.05M	$[redacted]	35.81	17.03	18.78	$[redacted]
FPR = LAL-CL02	FPR = All sources	$36.67M	$0.06M	$36.62M	35.37	15.89	19.48	$1.880M
FPR = Bernstein et al. (2013)[8]		$37.40M	$0.05M	$37.36M	37.16	22.93	14.23	$2.626M
FPR = Burton et al.		$35.88M	$0.06M	$35.82M	33.99	13.39	20.60	$1.739M
Discount rate = 0.0%	1.5%	$60.55M	$0.08M	$60.47M	56.56	21.83	34.73	$1.741M
Discount rate = 3.0%		$24.83M	$0.04M	$24.79M	24.96	13.90	11.06	$2.242M

BSC = best supportive care; FPR = fibrosis progression rate; M = millions; QALY = quality-adjusted life-year.
Source: Manufacturer's PE submission.[3]

Limitations of Manufacturer's Submission

1. Considerable uncertainty and limitations were identified with the submitted clinical trials on the evidence for sebelipase alfa efficacy in LAL deficiency (for more information, refer to the CADTH Common Drug Review [CDR] clinical review). Key limitations in both trials were the small sample size and the lack of long-term follow-up. A historical control was used for the primary outcome of sebelipase in infantile presentation, while surrogate outcomes were used instead of final clinical outcomes in the trial for sebelipase alfa in pediatric/adult presentation:
   - The clinical trial of sebelipase alfa in infantile-presentation patients (VITAL) was a non-comparative trial and may be subject to bias.[4]
   - Infantile presentation: The manufacturer used data from the VITAL study to model the efficacy of sebelipase alfa in infant patients while the historical control cohort from LAL-1-NH01 was used for patients on BSC.
     - Based on feedback from the clinical expert consulted for this review, the diagnostics and BSC options for LAL deficiency have improved since the time the historical cohort was recruited (1985 to 2012) for LAL-1-NH01.[2] Although this

means the historical control may not be reflective of current patients, improved earlier detection of LAL deficiency is not associated with improved survival at 12 months, according to the clinical expert.

- In the VITAL study the sample size was very small (only nine patients were enrolled); hence differences in one or two patients can have a substantial impact on survival rate.
- CDR noted that nearly 85% of the QALYs gained by patients receiving sebelipase alfa were accrued in the time period beyond available clinical data from the clinical trials.

- Pediatric/adult presentation: The manufacturer used pre-randomization liver biopsy study data from the ARISE study to model liver disease progression in patients on BSC while liver biopsy study data from ARISE was used to support the effect of sebelipase alfa on halting liver disease progression and even improving liver function. Use of separate sources of data for sebelipase alfa and BSC may bias the results in favour of sebelipase alfa. In addition, the data from the 20-week randomized phase of ARISE is not considered long enough to determine whether liver disease had not progressed while on sebelipase alfa.
  - In the ARISE trial, surrogate outcomes (ALT normalization at the end of the double-blind period/week 20) were captured instead of final clinical outcomes. In addition, for the primary outcome (ALT normalization), no data were found showing how it directly measures or correlates with patient functioning, development, and survival. The FDA medical review indicated that "ALT neither directly measures clinical benefit of treatment nor represents a surrogate end point reasonably likely to predict clinical benefit in pediatric and adult patients with cholesteryl ester storage disease."[6] The FDA medical review also indicated that "normal ALT does not necessarily exclude the presence or progression of liver disease,"[6] and they conclude that "normalization of ALT does not reliably represent a clinical benefit."[6] This contradicts the manufacturer's economic analysis in pediatric/adult-presentation patients that included a probability of liver disease regression of 67% in the first cycle.
- The manufacturer assumed that patients without significant loss of liver function would be expected to live with normal quality of life and with survival rates similar to the general population. However, there is limited evidence available to support the manufacturer's underlying assumption that sebelipase alfa would completely halt LAL deficiency disease progression and improve liver function.
- Long-term efficacy and safety have not been established: The trials for sebelipase alfa have been short (up to four years) compared with the expected long-term use in patients with LAL deficiency. Therefore it is unclear if treatment effects would be maintained over the patient's lifetime.

  Due to model limitations, CDR was unable to vary the duration of treatment effects in the submitted models; however, conducted exploratory analyses that varied the model time horizon between 1 year and 20 years for both patient presentations. The results of these analyses are in Table 15.

  In exploratory analyses, CDR modelled efficacy scenarios for sebelipase alfa in pediatric/adult-presentation patients with LAL deficiency in which liver disease progression is halted but may then either remain stable, an optimistic scenario based on available clinical evidence, or may progress by 10% each cycle. The result in Table 16 shows that the ICUR for sebelipase alfa in pediatric/adult-presentation

patients was not significantly impacted by disease stability, remaining at more than $2 million per QALY. However, when a 10% probability of disease progression was assumed, the ICUR for sebelipase alfa in pediatric/adult-presentation increased to greater than $4.9 million per Table 17. Inappropriate modelling approach in infantile presentation: The manufacturer used a survival model to assess the cost-effectiveness of sebelipase alfa compared with BSC in infantile-presentation patients. Although this model relied on survival as a primary outcome in this patient population, it is based on the assumption that sebelipase alfa is effective at preventing the development of liver disease and that survival is maintained throughout the lifetime of the patient. However, there is limited evidence to support this assumption. Based on the survival model, the underlying assumption is that patients receiving sebelipase alfa will go on to live at mortality and quality of life similar to the general population.

2. Used utility scores in both models were not derived from patients with LAL deficiency:
   - Infantile presentation: The utility value for patients aged 0 years to 17 years was assumed to be the midpoint of perfect health (i.e., 1.000), and the age 18 years to 24 years value was derived from a publication in which values were based on value sets derived using both visual analogue scale and time trade-off responses. The utility score in the base-case analysis was therefore set at 0.970 for the age group of 0 years to 17 years. The validity of this approach for patients aged less than six months is uncertain. However, this parameter does not significantly impact the results in the infantile presentation due to the mortality rate in patients treated with BSC.
   - Pediatric/adult presentation: The utility values were derived from a systematic review and cost-effectiveness evaluation of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease. Specifically, the base-case analysis used utility values that were collected from patients with hepatitis C infections. The utility values for the mild hepatitis C patients came from patients who entered into a randomized controlled trial whereas utility values for the moderate and cirrhotic disease stages came from an observational study.[3,9] This could lead to an overestimate of the differences in utility values if the values reported for patients enrolled into the mild hepatitis C randomized trial were higher than for the more general mild hepatitis C population.

     An exploratory analysis was conducted by CDR that used utility values from a published economic evaluation in patients with non-alcoholic steatohepatitis.[10] The results of the CDR exploratory analysis did not significantly impact the results.

3. Cost of treatment: In both presentations (infantile and pediatric/adult), the manufacturer assumed that patients above the age of 21 years would not gain weight over time for the remainder of the model's time horizon. CDR conducted exploratory analyses where the patient's weight would increase by 1% annually until the age of 60, after which the weight will decrease by 1% annually.

CADTH Common Drug Review Reanalyses

CDR identified considerable uncertainty with several key parameters in the submitted models. Given the limited clinical information available for patients with LAL deficiency and the uncertainty associated with the submitted clinical evidence for sebelipase alfa in infantile presentation and pediatric/adult presentation of LAL deficiency, CDR was only able to conduct exploratory analyses for a few parameters to assess the impact of the uncertainty on model results.

A. CDR conducted an exploratory analysis that varied patient weight at 21 years of age and beyond. CDR applied an annual 1% increment to the patient's weight from the age of 21 years to 60 years, and an annual 1% decrement in weight thereafter. The full results of the exploratory analyses are presented in Table 14.

B. An exploratory analysis was conducted by CDR that applied a 10% probability of disease progression in pediatric/adult-presentation patients with LAL deficiency. However, this did not result in significant changes to the manufacturer's base-case results (full results presented in Table 17.

C. An exploratory analysis was conducted by CDR that used utility values from a published economic evaluation in patients with non-alcoholic steatohepatitis applied to pediatric/adult-presentation patients with LAL deficiency (full results presented in Table 18).[10]

D. A multi-way scenario exploratory analysis was conducted by CDR that was based on the variation in patient weight by 1% in the infantile presentation and pediatric/adult presentation, and assumption of liver disease stability (full results presented in Table 14).

Table 4: Summary of Results of the CDR Exploratory Analyses

		Incremental Cost of Sebelipase Alfa	Incremental QALYs of Sebelipase Alfa	Incremental Cost per QALY
Manufacturer's Base Case	**Infantile-presentation patients**	$161,654,475	36.03	$4,485,000
	Pediatric/adult-presentation patients	$36,337,577	18.25	$2,005,000
A - CDR analysis: 1% increment from age 21 until age 60, then 1% decrement thereafter	Infantile-presentation patients	$177,558,521	35.91	$4,944,000
	Pediatric/adult-presentation patients	$40,048,327	18.32	$2,200,000
B - CDR analysis: Stable liver disease	Pediatric/adult-presentation patients	$36,339,774	17.18	$2,131,000
B - CDR analysis: 10% probability of liver disease progression	Pediatric/adult-presentation patients	$24,393,384	5.83	$4,318,000
C - CDR analysis: Health state utility	Pediatric/adult-presentation patients	$36,347,196	17.91	$2,050,000
D - CDR multi-way analysis: 1% increase in patient weight + stable liver disease	**Infantile-presentation patients**	$177,558,521	35.91	$4,944,000
	Pediatric/adult-presentation patients	$40,104,683	17.84	$2,274,000

BSC = best supportive care; LYG = life-year gained; QALY = quality-adjusted life-year.
Source: Manufacturer's PE submission.[3]

CDR was unable to vary the duration of treatment effects in the submitted models. However, CDR did conduct exploratory analyses that varied the model time horizon between 1 year and 20 years for both patient presentations. The results of these analyses are in Table 15 below. As analysis in the infantile presentation did not include liver disease as a natural progression of LAL deficiency, patients will experience quality of life norms and survival similar to the general public; this is in contrast to the pediatric/adult-presentation patients who will have a higher risk of complications and mortality with liver disease over their lifetimes.

A series of price reduction scenario analyses were undertaken based on the manufacturer's base-case analyses in infantile and pediatric/adult presentations of LAL deficiency. The analyses varied the percentage reduction to illustrate the impact on the ICUR (Table 5) and explored an annual per-patient price cap, similar to the price cap that was considered by the manufacturer in its sensitivity analysis (Table 6). These were also applied to the CDR exploratory analysis that varied the base case in terms of patient weight and disease progression.

The results indicate that a price reduction of greater than 96% (Table 5) may be required for sebelipase alfa to result in ICURs of $50,000 and $100,000 per QALY in both patient presentations of LAL deficiency.

Table 5: CDR Reanalysis Probabilistic Price Reduction Scenarios

ICURs of Sebelipase Alfa Compared With BSC ($/QALY)				
	Manufacturer Base-Case Analysis		CDR Multi-Way Analysis	
	Infantile-Presentation	Pediatric/ Adult-Presentation	Infantile-Presentation	Pediatric/ Adult-Presentation
Submitted ($8,546/20ml)	$4,485,000	$2,005,000	$4,944,000	$2,274,000
50%	$2,244,000	$1,005,000	$2,473,000	$1,134,000
75%	$1,122,000	$502,000	$1,237,000	$568,000
90%	$450,000	$200,000	$495,000	$228,000
95%	$225,000	$100,000	$248,000	$115,000
96%	$180,000	$80,000	$199,000	$92,000
97%	$136,000	$60,000	$149,000	$69,000
98%	$91,000	$41,000	$100,000	$46,000
99%	$46,000	$21,000	$50,000	$23,000

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

Similar to the manufacturer's sensitivity analysis considering the impact of a $[redacted] cap on annual per-patient costs, CDR conducted exploratory analyses that tested the impact of a series of caps on annual per-patient costs using both the manufacturer's base case and CDR's multi-way analyses. The results indicate that a cap between $50,000 and $100,000 may be required for sebelipase alfa to result in ICURs of $50,000 and $100,000 per QALY at the manufacturer's submitted price.

Table 6: CDR Reanalysis Probabilistic Scenarios With Cap on Annual Drug Costs

ICURs of Sebelipase Alfa Compared With BSC ($/QALY)				
	Manufacturer Base-Case Analysis		CDR Multi-Way Analysis	
	Infantile Presentation	Pediatric/ Adult Presentation	Infantile Presentation	Pediatric/ Adult Presentation
Submitted (no annual cap)	$ 4,485,000	$2,005,000	$4,944,000	$2,274,000
$1,000,000	$1,106,000	$2,006,000	$1,107,000	$2,154,000
$750,000	$839,000	$1,705,000	$840,000	$1,741,000
$500,000	$560,000	$1,158,000	$560,000	$1,190,000
$250,000	$281,000	$581,000	$281,000	$593,000
$100,000	$113,000	$231,000	$113,000	$237,000
$50,000	$57,000	$116,000	$57,000	$119,000
$25,000	$29,000	$58,000	$29,000	$60,000

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

Patient Input

Two patient groups submitted input for sebelipase alfa: The Canadian Liver Foundation and the Isaac Foundation. The number of patients providing input has not been disclosed by the two patient groups but is expected to be low, due to LAL deficiency being an ultra-rare disease. According to the patient input received by CDR for this submission, LAL deficiency is predominantly a pediatric condition, with a large number of patients being diagnosed as infants, but is also diagnosed in older pediatric and adult patients. The median age of death for patients with early onset LAL deficiency is under four months of age, while survival beyond one year is typically rare. The manufacturer's submission included two models: infantile and pediatric/adult presentations. For infantile presentation a survival model was used, while a liver disease model was used for pediatric/adult presentation.

Conclusions

There is substantial uncertainty associated with the estimated cost-effectiveness of sebelipase alfa for the populations considered due to: uncertainty as to whether the clinical efficacy of sebelipase alfa will be maintained over the lifetime of the populations for which the manufacturer is seeking reimbursement; the quality of the comparative clinical effectiveness of sebelipase alfa with BSC; and the approach in costing sebelipase alfa in adult patients throughout the time horizon in the submitted economic models. In the infantile presentation, the submitted economic model did not include liver disease as an expected progression in
LAL deficiency patients. This suggests that sebelipase alfa's long-term efficacy in preventing or slowing the progression of liver disease is maintained throughout the infant's lifetime despite the lack of long-term evidence to support this assumption. In the pediatric/adult presentation, the submitted model included a probability of liver disease regression of 67% in the first cycle as an effect of sebelipase alfa therapy. Sebelipase alfa is expected to reverse liver disease without the evidence to support long-term and the key clinical end point such as the need for liver transplant.

CDR conducted exploratory analyses with model time horizon, probability of liver disease progression, patient utility, and patient weight changes over time. CDR's analyses resulted in ICURs of more than $2 million per QALY compared with BSC in both patient presentations.

In summary, the results of the manufacturer's analyses and the exploratory analyses by CDR appear to reflect a best-case scenario for patients with LAL deficiency in which patients are completely responsive to treatment, maintain that treatment effect throughout their lifetimes, and experience no harms or adverse events with sebelipase alfa.

To reduce the manufacturer and CDR ICURs of $50,000 and $100,000 per QALY, either a price reduction of greater than 96% or a cap on annual drug costs per patient of $50,000 is required.

Appendix 1: Cost Comparison

The comparators presented in Table 7 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 the Table 7 and as such may not represent the actual costs to public drug plans.

Table 7: CDR Cost Comparison Table for Sebelipase Alfa in LAL Deficiency

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Sebelipase alfa (Kanuma)	20 mg in 10 mL (2 mg/mL)	Solution for injection	$8,546.0000 [a]	*Infants (< 6 months of age)* Starting dose: 1 mg/kg once weekly Dose escalation to 3 mg/kg once weekly	$2,447 to $13,625	$891,936 to $4,905,100
				Children and adults 1 mg/kg once every other week	$1,833 to $2,443	$668,877 to $891,836

CDR = CADTH Common Drug Review; LAL-D = lysosomal acid lipase deficiency.
[a] Manufacturer-submitted price.[3]

Appendix 2: Summary of Key Outcomes

Table 8: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Sebelipase Alfa Relative to BSC in LAL Deficiency Patients?

Sebelipase Alfa vs. BSC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	Manufacturer's base case: • For infantile presentation: $4,504,000 per QALY • For pediatric/adult presentation: 1,961,000 per QALY					

BSC = best supportive care; CE = cost-effectiveness; LAL-D = lysosomal acid lipase deficiency; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

Table 10: 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 HTA Reviews of Drug

The cost-effectiveness of sebelipase alfa has been assessed by the National Institute for Health and Care Excellence (NICE)[11] in the UK, although a final guidance has not been published yet by NICE at the time of this CDR review. From the available guidance documents, NICE did not recommend sebelipase alfa for long-term enzyme replacement therapy for LAL deficiency in babies with rapidly progressive disease, nor did it recommend it for treating LAL deficiency in pediatric and adult patients.

The NICE committee recognized that sebelipase alfa is a potentially life-saving treatment in babies with rapidly progressing LAL deficiency but was concerned that the proposed cost of sebelipase alfa by the manufacturer is exceptionally high and was too high to be considered value for money in light of the uncertainties about the potential long-term benefits associated with sebelipase alfa treatment.[11]

Appendix 5: Reviewer Worksheets

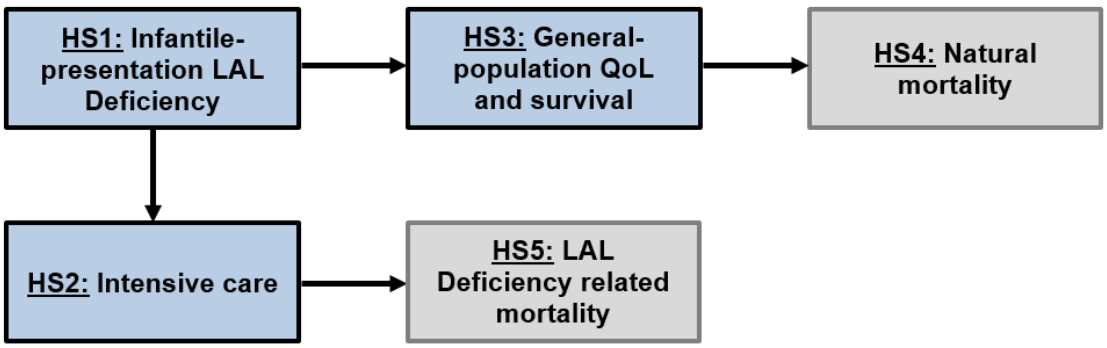
Manufacturer's Model Structure

For infantile-presentation patients, a survival model was used based on the prognosis in infantile-presentation patients as observed in the natural history study, LAL-1-NH01 (Jones et al. 2016),[2] with median age at death of 3.7 months (including those patients who received hematopoietic stem cell transplant [Figure 1]).

The model was structured as a Markov health state transition model. A lifetime horizon was used, and a monthly cycle length was chosen in order to reflect the timing of mortality (and associated neonatal intensive care) over the first 24 months of life. A half-cycle correction was applied in the first and last cycles of the model, to reflect transitions occurring throughout the cycle (i.e., as opposed to at the end of the cycle).

Additional health states were included in the model to account for intensive care medical resource utilization for patients who proceed to LAL deficiency-related death, and quality of life and background mortality in patients who do not proceed to LAL deficiency-related death. For neonatal intensive care, patients were assumed to spend a month in this state prior to LAL deficiency-related death; in sensitivity analysis, the length of time in neonatal intensive care was extended. The manufacturer assumed that patients surviving beyond 24 months take on general-population quality-of-life norms (based on UK values from Szende et al. [2014],[7] as none are available for Canada) and survival (based on Canadian life tables from Statistics Canada [2017]).[12]

Figure 1: Manufacturer Model Structure for Infantile-Presentation Patients



HS = health state; LAL = lysosomal acid lipase; QoL = quality of life.
Source: Adapted from manufacturer's PE submission.[3]

Transition probabilities in the model for infantile-presentation patients include (i) the monthly mortality risk from LAL deficiency-related causes and (ii) the monthly mortality risk from background (i.e., non–LAL deficiency-related) causes. Monthly background mortality rates are modelled based on Canadian life tables available from Statistics Canada (2017).[12] The monthly mortality risk from LAL deficiency-related causes is based on survival observed in the natural history study LAL-1-NH01 and the VITAL study, as reported in Jones et al. (2017).[4] Based on the observed mortality rates for infantile-presentation LAL deficiency patients aged 0 to 24 months, parametric survival modelling was also conducted to predict mortality risk for treated and untreated patients. Predicted survival was estimated under

various assumptions regarding the survival distribution, including exponential (i.e., constant hazard function), Weibull and Gompertz (i.e., accelerated failure time with monotonic hazard functions), and log-normal (i.e., accelerated failure time with non-monotonic hazard function).[3]

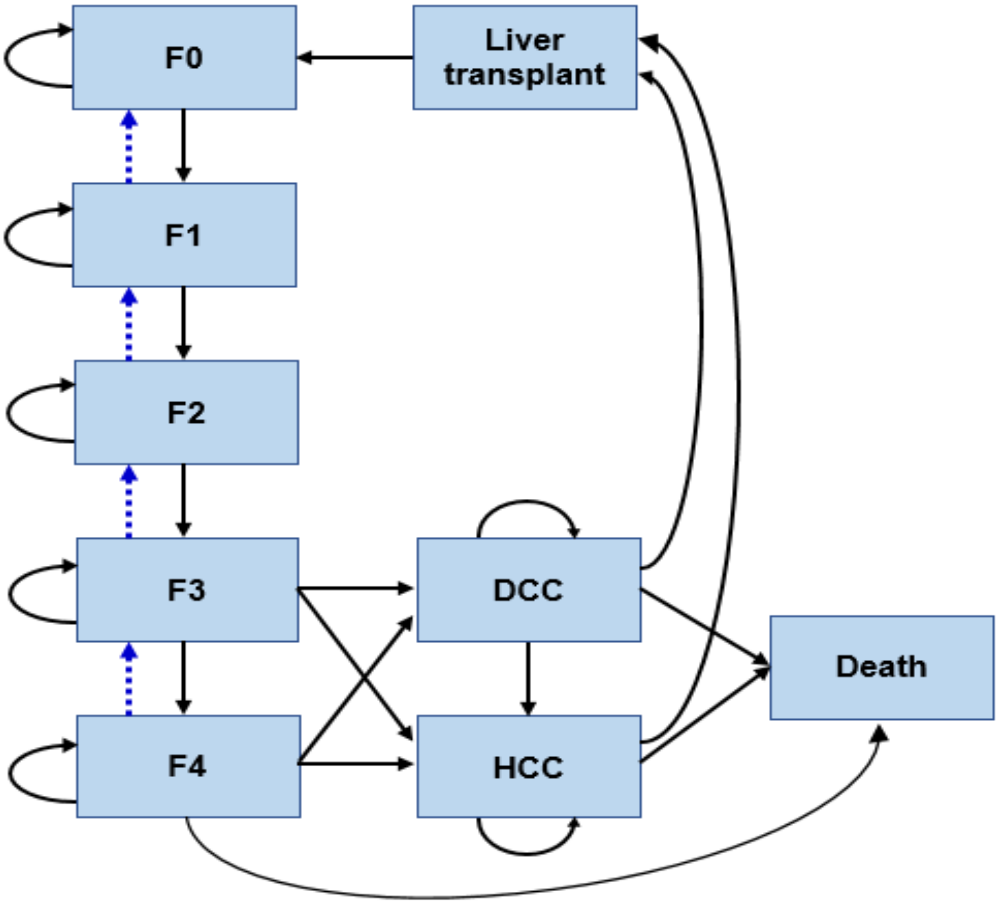
For pediatric/adult-presentation patients, a model of liver disease progression was used. The manufacturer acknowledged that, while LAL deficiency threatens multiple vital organ systems including the liver, heart, spleen, and gastrointestinal tract, liver disease outcomes were focused on in the model, as they frequently occur early in the disease process, may have severe impact on quality of life and survival, and cannot be addressed with current supportive care.[3] Therefore, the economic model focused on the hepatic aspect of LAL deficiency: the progression from hepatic fibrosis to compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma, with the potential for liver transplantation (Figure 2).

The manufacturer considered that non-alcoholic fatty liver disease, which involves deposition of fat (steatosis) in the liver due to causes other than excessive alcohol use, or its progressive form, non-alcoholic steatohepatitis (NASH), might be the best disease analogue for LAL deficiency.[3] The manufacturer obtained confirmation from clinical experts who indicated that NASH is the most appropriate disease analogue, and that disease progression up to the point of cirrhosis would likely differ in LAL deficiency versus NASH, but from the point of cirrhosis onwards, it would likely be similar.

As such, in the cost-effectiveness analysis of sebelipase alfa for LAL deficiency, the model structure for advanced liver disease health states was derived from the consensus in NASH cost-utility studies.[3] In addition, the fibrosis state included in such studies is expanded to reflect the METAVIR fibrosis stages (i.e., F0 to F4) to capture the impact of treatment on timing of progression to advanced liver disease states.

The model was structured as a Markov health state transition model. A lifetime horizon was used, and an annual cycle length was chosen, consistent with other models of NASH. A half-cycle correction was applied in the first and last cycles of the model, to reflect transitions occurring throughout the cycle (i.e., as opposed to at the end of the cycle). Background mortality rates were modelled based on Canadian life tables available from Statistics Canada (2017).[12] Age at baseline was assumed to be 11 years of age and was based on (i) the mean age of onset reported in Bernstein et al. (2013)[8] of 5 years, plus (ii) the time between mean age of onset and age of diagnosis reported in Burton et al. (2015) of 6 years.[5]

Figure 2: Manufacturer's Model Structure for Pediatric/Adult Presentation



F0 to F4 = METAVIR fibrosis stages; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma.
Note: Transitions possible due to the sebelipase alfa treatment effect (i.e., regression between fibrosis stages) are reflected by blue, dashed arrows.
Source: Adapted from manufacturer's PE submission.[3]

The manufacturer calculated the fibrosis progression rate (FPR) as reflecting the average number of fibrosis stages progressed per year, and used the FPR to model patient transitions between stages on the F0 to F4 range. The FPR for pediatric/adult presentation LAL deficiency was calculated based on biopsy data from the ARISE trial, Bernstein et al. (2013),[8] and Burton et al. (2015).[5] In order to parametrize transitions to advanced liver disease, estimates of transition probabilities from Crossan et al. (2015)[9] and a systematic literature review performed by the UK's National Health Service National Institute for Health Research, were considered.[3]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Efficacy **Natural History**	*For infantile-presentation patients:* • Sebelipase alfa: based on survival data from the LAL-CL03 study (VITAL, Jones et al. [2017]).[4] • BSC: based on the natural history study LAL-1-NH01.[2] *For pediatric/adult-presentation patients:* • Sebelipase alfa: based on liver biopsy data from LAL-CL02, a 20-week randomized, double-blind, placebo-controlled study (ARISE, Burton et al. [2015]).[5] • BSC: based on pre-randomization liver biopsy data from the ARISE study.[5]	• The clinical trial of sebelipase alfa in infantile presentation of LAL-D (VITAL) was a non-comparative trial and may be subject to bias. • Use of separate sources of data for sebelipase alfa and BSC is biasing the results in favour of sebelipase alfa. • Data from the 20-week randomized phase of ARISE is not considered long enough to determine whether liver disease had not progressed while on sebelipase alfa.
Utilities	Derived from a published systematic review and cost-effectiveness evaluation of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease by Crossan et al.(2015).[9] The utility value for patients 0 to 17 years was assumed to be the midpoint of perfect health (i.e., 1.000) and the age 18 to 24 years value from the publication by Szende et al. (2013).[7]	• The utility values for the mild hepatitis C patients came from patients who entered into a randomized controlled trial whereas utility values for the moderate and cirrhotic disease stages came from an observational study. • The validity of this approach for patients aged less than 6 months is uncertain.
Adverse Events	Adverse events were not included in the economic evaluation.	Manufacturer reported that sebelipase alfa is generally well tolerated.[3]
Mortality	For infantile-presentation patients: The monthly mortality risk from LAL-D-related causes is based on survival observed in the natural history study LAL-1-NH01 and the LAL-CL03 study, as reported in Jones et al. (2016, 2017).[2,4]	Appropriate based on feedback from clinical expert.
Costs and Resource Use		
Drug	Manufacturer-submitted price.	Appropriate.
Administration	Unit costs for treatments including procedures and monitoring visits were based on Ontario physician services schedule of benefits.	Appropriate.
Disease Management	Cost of a month of neonatal intensive care was calculated based on estimates from the Canadian Institute for Health Information (2016).[3] For pediatric/adult presentation, estimates of annual costs of relevant NASH health states from Zhang et al. (2015),[10] a Canadian cost-effectiveness analysis of NASH screening that calculated annual health care costs by liver disease health states in 2013 C$.[10]	Appropriate.

BSC = best supportive care; LAL-D = lysosomal acid lipase deficiency; NASH = non-alcoholic steatohepatitis.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Quality of life is binary in the first 24 months of life (i.e., 1 = survival, 0 = death).	Appropriate. No measures of health-related quality of life are available for patients in this age range. The impact of a health utility decrement of 0.50 for this age range was tested in sensitivity analysis.[3]
Survival rates in the LAL-1-NH01 and VITAL studies, for untreated and treated infantile-presentation patients, respectively, are representative of survival rates for Canadian patients.[2-4]	Appropriate due to the lack of Canadian data.
Surviving beyond the first 24 months of life experience general-population quality of life and survival.[3]	Uncertain. The duration of the available clinical trials for sebelipase alfa are very short to determine if treatment effect can be maintained over time.
General-population quality of life matches that for the UK, reported in Szende et al. (2014).[3,7]	Appropriate No population norms for the EQ-5D are available for Canada.
Patients proceeding to LAL-D-related mortality experience one month of intensive care prior to death.[3]	Appropriate as per clinical expert feedback.
NASH is the most appropriate analogue disease to pediatric-/adult-presentation LAL-D, and accordingly, that NASH model structure is appropriate for modelling LAL-D. It is assumed that there is a constant rate and probability of progression from one fibrosis stage to the next.[3]	Uncertain. There is limited information on the rate of liver disease progression in LAL-D compared with NASH.

EQ-5D = EuroQol 5 Dimensions questionnaire; LAL-D = lysosomal acid lipase deficiency; NASH = non-alcoholic steatohepatitis.

Manufacturer's Results

The manufacturer's deterministic base-case results are presented in Table 13.

Table 13: Summary of Results of the Manufacturer's Base Case

	Total Costs	Incremental Cost of Sebelipase Alfa	Total LYGs	Incremental LYGs	Incremental Cost per LYG	Total QALYs	Incremental QALYs of Sebelipase Alfa	Incremental Cost per QALY
Infantile-Presentation Patients								
BSC	$99,191		0.29			0.29		
Sebelipase alfa	$125,448,770	$125,349,580	31.21	30.91	$4,055,000	28.12	27.83	$4,504,000
Pediatric/Adult-Presentation Patients								
BSC	$54,505		18.35			17.03		
Sebelipase alfa	$36,892,222	$36,837,717	40.59	22.24	$1,656,000	35.81	18.78	$1,961,000

BSC = best supportive care; LYG = life-year gained; QALY = quality-adjusted life-year.
Source: Manufacturer's PE submission.[3]

CADTH Common Drug Review Reanalyses

Given the limited clinical information available on patients with LAL deficiency and the uncertainty associated with the clinical evidence on the efficacy of sebelipase alfa for infantile and pediatric/adult presentations of LAL deficiency, CDR undertook exploratory analyses that tested alternate assumptions on the efficacy of sebelipase alfa on halting or improving liver disease in pediatric/adult-presentation patients with LAL deficiency as well as alternate assumptions on patient weight changes over time, model time horizon, and health state utility based on a search of the available literature and based on feedback from the clinical expert.

CDR conducted an exploratory analysis that varied the patient weight at 21 years of age and beyond applied an annual 1% increment to the patient's weight from the age of 21 to 60, and an annual 1% decrement in weight thereafter. The results of the exploratory analyses are presented in Table 14 and show that the total costs with sebelipase alfa had increased based on the increasing total drug costs as the patient gains additional weight up to the age of 60 years.

Table 14: Results of the CDR Exploratory Probabilistic Analysis on Patient Weight

		Total Costs	Incremental Cost of Sebelipase Alfa	Total QALYs	Incremental QALYs of Sebelipase Alfa	Incremental Cost per QALY
Manufacturer's Base Case: Constant Weight of 70.3 kg at 21 years and Beyond	**Infantile-Presentation Patients**					
	BSC	$83,021		0.27		
	Sebelipase alfa	$161,737,796	$161,654,475	36.31	36.03	$4,485,000
	Pediatric/Adult-Presentation Patients					
	BSC	$54,245		17.01		
	Sebelipase alfa	$36,391,822	$36,337,577	35.26	18.25	$2,005,000
CDR Analysis: 1% increment from age 21 until age 60, then 1% decrement thereafter	**Infantile-Presentation Patients**					
	BSC	$81,183		027		
	Sebelipase alfa	$177,639,704	$177,558,521	36.18	35.91	$4,944,000
	Pediatric/Adult-Presentation Patients					
	BSC	$54,019		16.68		
	Sebelipase alfa	$40,102,346	$40,048,327	35.01	18.32	$2,200,000

BSC = best supportive care; QALY = quality-adjusted life-year.
Source: manufacturer's PE submission[3]

Due to model limitations, CDR was unable to vary the duration of treatment effects in the submitted models; however, conducted exploratory analyses that varied the model time horizon between 1 and 20 years for both patient presentations. The results of these analyses are in Table 15 below.

Table 15: Results of the CDR Exploratory Probabilistic Analysis on Model Time Horizon

Sensitivity Analysis	Original Value	Costs			QALYs			
		Sebelipase Alfa	BSC	Incremental	Sebelipase Alfa	BSC	Incremental	Incremental Cost per QALY
Infantile-Presentation Patients								
Base case	Lifetime	***$125,450,000***	$100,000	***$125,350,000***	***28.12***	***0.29***	***27.83***	***$4,504,000***
1 year		$680,000	$100,000	$580,000	0.70	0.29	0.41	$1,402,000
5 years		$2,950,000	$100,000	$2,850,000	3.16	0.29	2.88	$0.991,000
10 years		$8,220,000	$100,000	$8,120,000	6.04	0.29	5.75	$1,412,000
15 years		$17,290,000	$100,000	$17,190,000	8.71	0.29	8.42	$2,041,000
20 years		$28,890,000	$100,000	$28,790,000	11.15	0.29	10.87	$2,649,000
Pediatric/Adult-Presentation Patients								
Base case	Lifetime	***$36,890,000***	***$54,505***	***$36,840,000***	***35.81***	***17.03***	***18.78***	***$1,961,000***
1 year		$1,307,000	$1,149	$1,306,000	1.78	1.74	0.04	$34,656,000
5 years		$3,998,000	$4,935	$3,993,000	5.22	4.89	0.33	$12,281,000
10 years		$7,862,000	$12,285	$7,850,000	9.13	8.10	1.02	$7,664,000
15 years		$11,437,000	$21,091	$11,416,000	12.71	10.59	2.12	$5,389,000
20 years		$14,746,000	$29,564	$14,717,000	15.99	12.44	3.55	$4,148,000

BSC = best supportive care; FPR = fibrosis progression rate; QALY = quality-adjusted life-year.
Source: Manufacturer's PE submission.[3]

Based on the uncertainty with the key efficacy outcomes in the ARISE trial being surrogate outcomes instead of hard clinical outcomes, and based on the FDA medical review's indication that "normal ALT does not necessarily exclude the presence or progression of liver disease,"[6] and that "normalization of ALT does not reliably represent a clinical benefit,"[6] exploratory analyses were conducted by CDR. In these exploratory analyses, CDR modelled efficacy scenarios for sebelipase alfa in pediatric/adult-presentation patients with LAL deficiency in which liver disease progression is halted but may then either remain stable, an optimistic scenario based on available clinical evidence, or may progress by 10% each cycle. The results in Table 16 and Table 17 show that ICUR values for sebelipase alfa in pediatric/adult-presentation patients are not significantly impact by the assumption of disease stability or progression.

Table 16: Results of the CDR Exploratory Probabilistic Analysis on Probability of Disease Stability in Pediatric/Adult Presentation

	Total Costs	Incremental Cost of Sebelipase Alfa	Total QALYs	Incremental QALYs of Sebelipase Alfa	Incremental Cost per QALY
Manufacturer's Base Case					
BSC	$54,245		17.01		
Sebelipase alfa	$36,391,822	$36,337,577	35.26	18.25	$2,005,000
CDR Reanalysis					
BSC	$53,474		17.09		
Sebelipase alfa	$36,393,247	$36,339,774	34.27	17.18	$2,131,000

BSC = best supportive care; QALY = quality-adjusted life-year.
Source: Manufacturer's PE submission.[3]

Table 17: Results of the CDR Exploratory Probabilistic Analysis on Probability of Disease Progression in Pediatric/Adult Presentation

	Total Costs	Incremental Cost of Sebelipase Alfa	Total QALYs	Incremental QALYs of Sebelipase Alfa	Incremental Cost per QALY
Manufacturer's Base Case					
BSC	$54,245		17.01		
Sebelipase alfa	$36,391,822	$36,337,577	35.26	18.25	$2,005,000
CDR Reanalysis					
BSC	$54,926		16.91		
Sebelipase alfa	$24,448,310	$24,393,384	22.74	5.83	$4,318,000

BSC = best supportive care; QALY = quality-adjusted life-year.
Source: Manufacturer's PE submission.[3]

An exploratory analysis was conducted by CDR that used utility values from a published economic evaluation in patients with non-alcoholic steatohepatitis.[10] The results of the CDR exploratory analysis did not significantly impact the results (Table 18).

Table 18: Results of the CDR Exploratory Probabilistic Analysis on Health State Utility in Pediatric/Adult Presentation

	Total Costs	Incremental Cost of Sebelipase Alfa	Total QALYs	Incremental QALYs of Sebelipase Alfa	Incremental Cost per QALY
Manufacturer's Base Case					
BSC	$54,245		17.01		
Sebelipase alfa	$36,391,822	$36,337,577	35.26	18.25	$2,005,000
CDR Reanalysis					
BSC	$53,978		17.91		
Sebelipase alfa	$36,401,174	$36,347,196	36.92	17.91	$2,050,000

BSC = best supportive care; QALY = quality-adjusted life-year.
Source: Manufacturer's PE submission.[3]

The CDR exploratory multi-way analysis consisted of varying the patient weight by 1% in the infantile and pediatric/adult-presentation LDL and using the optimistic scenario of sebelipase alfa effectively stabilizing liver disease progression in pediatric/adult-presentation patients (Table 19).

Table 19: Results of the CDR Exploratory Probabilistic Multi-Way Analysis

	Total Costs	Incremental Cost of Sebelipase Alfa	Total QALYs	Incremental QALYs of Sebelipase Alfa	Incremental Cost Per QALY
Infantile-Presentation Patients					
BSC	$81,183		027		
Sebelipase alfa	$177,639,704	$177,558,521	36.18	35.91	$4,944,000
Pediatric/Adult-Presentation Patients					
BSC	$53,607		18.99		
Sebelipase alfa	$40,158,290	$40,104,683	36.83	17.84	$2,274,000

BSC = best supportive care; QALY = quality-adjusted life-year.
Source: Manufacturer's PE submission.[3]

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