CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

SEBELIPASE ALFA (KANUMA — Alexion Pharmaceuticals, Inc.)
Indication: Lysosomal acid lipase deficiency

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that sebelipase alfa be reimbursed for the treatment of patients diagnosed with lysosomal acid lipase (LAL) deficiency, if the following criterion and conditions are met:

Criterion

- Therapy may be initiated if the patient has:
  - documented biochemical evidence of deficient LAL activity; and
  - two documented pathogenic mutations in the LIPA gene; and
  - onset of clinical manifestations of LAL deficiency before six months of age.

Conditions

- Substantial reduction in price.
- The patient is under the care of a specialist with experience in the diagnosis and management of LAL deficiency.

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Indication: Lysosomal Acid Lipase Deficiency

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that Kanuma (sebelipase alfa) be reimbursed for the treatment of patients diagnosed with lysosomal acid lipase (LAL) deficiency, if the following criterion and conditions are met:

Criterion

- Therapy may be initiated if the patient has:
    - documented biochemical evidence of deficient LAL activity
    - two documented pathogenic mutations in the LIPA gene
    - onset of clinical manifestations of LAL deficiency before six months of age.

Conditions

- Substantial reduction in price.
- The patient is under the care of a specialist with experience in the diagnosis and management of LAL deficiency.

Reasons for the Recommendation

1. In one phase II/III, open-label, multi-centre, dose escalation, single-arm (historical cohort controlled) study (VITAL, N = 9) that evaluated the efficacy and safety of sebelipase alfa in patients aged two years or younger who presented with LAL deficiency as infants (documented decreased LAL activity or two documented mutations in the LIPA gene) and were considered to have rapidly progressive disease (primarily defined as growth failure with onset before six months of age), 6 of 9 patients who received any amount of sebelipase alfa and who were no older than six months when starting sebelipase alfa, survived to 12 months of age. In the historical cohort, 0 of 21 patients survived beyond eight months of age. Results from additional follow-up analyses showed five of the nine patients survived beyond 36 months of age.
2. Infantile-onset LAL deficiency is a rare, genetic, life-threatening disease of lipid metabolism with a very high risk of mortality before the age of 12 months. There is an absence of clinically effective drug and non-drug alternative treatments.
3. There is no published clinical evidence for the efficacy or safety of sebelipase alfa treatment in children with LAL deficiency with onset of symptoms between age seven months and four years of age. Efficacy results of one unpublished open-label phase II clinical trial aiming to recruit patients older than months of age (LAL-CL06) were provided by the manufacturer of sebelipase, reporting surrogate outcomes of ALT and lipid changes. However the utility of this data is severely limited by the study design, lack of statistical power and analysis, and the limited presentation of results.
4. The results of the phase III, randomized, double-blind, placebo-controlled, multi-centre ARISE trial (N = 66) suggested that sebelipase alfa, as compared with placebo, is associated with statistically significant improvements in alanine aminotransferase [ALT] levels and some lipid and liver parameters after 20 weeks of treatment. The relationships between many of the biomarker outcomes (e.g., changes in ALT levels, the primary outcome) measured in ARISE and clinical outcomes have not been well-established, limiting the usefulness of the trial outcomes in determining the efficacy of sebelipase alfa.
5. Clinical outcomes, such as liver disease progression (including the need for liver transplant), cardiovascular events, and survival, were not assessed in ARISE.
6. There were no statistically significant between-group differences in health-related quality of life (HRQoL) in the ARISE trial.

7. The diversity of presentation and variable natural history of later-onset LAL deficiency, along with the exclusion of a large portion of screened patients in the ARISE trial (approximately 30%), and the short duration of the trial, cause considerable uncertainty about who may benefit from the drug.
8. The manufacturer submitted price of sebelipase alfa is $8,546 per 10 mL vial, 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. Re-analysis of the manufacturer-provided cost-utility model by the CADTH Common Drug Review (CDR) estimated the incremental cost-utility ratio (ICUR) for sebelipase alfa compared with best supportive care (BSC) to be greater than $4.9 million per quality-adjusted life-year (QALY) in infantile-onset LAL deficiency.

Of Note:

- Currently available evidence does not allow prospective identification of patients with onset of symptoms after six months of age who may have a relatively severe presentation of LAL deficiency (and may benefit from treatment with sebelipase alfa), including liver fibrosis, impaired hepatic synthetic function, elevated serum lipids despite conventional lipid-lowering therapy, growth failure, and evidence of cardiovascular disease. Currently available evidence also does not support the long-term clinical efficacy and safety of sebelipase alfa in patients with LAL deficiency.
- Health Canada indicated that in order to support a favourable benefit-risk profile, further data are required related to: the long-term outcomes of infantile-onset patients who survived after taking sebelipase alfa; information specific to liver, cardiovascular, lipid, and spleen outcomes; as well as any hypersensitivity reactions and immunogenicity.
- The rate of progression of LAL deficiency and its mortality differs markedly depending on when patients present with symptoms. Infants less than six months of age who present with LAL deficiency generally have a rapidly progressive condition. The rate of progression in children and adults is slower and more variable than in infants.
- CDEC heard from clinicians with experience in the diagnosis and management of LAL deficiency, that affected patients require a multidisciplinary health care approach to managing their disease. Outcomes for these patients are more likely to be improved if they receive sebelipase alfa in combination with coordinated care from other health professionals at centres with health care teams that have experience in managing patients with LAL deficiency.

Discussion Points:

- In the context of the severe nature of infantile-onset LAL deficiency, treatment with sebelipase alfa was not associated with serious adverse events in the short term, beyond infusion-related reactions. However, the formation of anti-drug antibodies (ADA) over time has been observed in some patients. The clinical significance of this observation is not yet clear.
- CDEC noted that market authorization was granted to sebelipase alfa by Health Canada under a notice of compliance with conditions, requiring the manufacturer to provide addition evidence to confirm the clinical benefit of the drug in patients with LAL deficiency.
- CDEC discussed the US Food and Drug Administration's analysis of ARISE, which focused on changes in low-density lipoprotein cholesterol (LDL-C) as a more direct outcome measure of clinical outcomes than changes in changes in ALT, given the established association between LDL-C and cardiovascular disease.
- In the ARISE trial, despite randomized group allocation, there were baseline imbalances in lipid levels, liver transaminase levels, and liver biopsy findings between groups; i.e., closer to normal at baseline in the sebelipase alfa group for lipid levels and liver biopsy results, and closer to normal at baseline in the placebo group for liver transaminases. These imbalances might have influenced results, particularly given that these liver transaminases and lipid levels, respectively, were the primary and secondary efficacy endpoints in the ARISE trial.
- CDEC discussed that the results of the pharmacoeconomic analysis in the later-onset LAL deficiency population was considered highly uncertain because of the uncertainty associated with the clinical evidence to date in this population.

Background:

Sebelipase alfa has a Notice of Compliance with conditions from Health Canada (pending the results of trials to verify its clinical benefit) for the treatment of infants, children, and adults diagnosed with LAL deficiency. Sebelipase alfa is a recombinant human LAL that binds to cell surface receptors and is subsequently internalized into lysosomes. It catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol, and free fatty acids. The Health Canada–recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL deficiency is 1 mg/kg administered as an intravenous (IV) infusion once weekly, which may be increased to 3 mg/kg once weekly based on clinical response. The product monograph indicates that, in one infant who exhibited suboptimal growth response, doses were escalated to 5 mg/kg weekly. The Health Canada–recommended dose in children and adults who do not present with rapidly progressive LAL deficiency prior to six months of age is 1 mg/kg administered as an IV infusion once every other week.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials, pivotal studies of sebelipase alfa, and a critique of the manufacturer's pharmacoeconomic evaluation. CDEC also considered input from clinical experts with experience treating patients with LAL deficiency, and patient group–submitted information about outcomes and issues important to patients and caregivers who are affected by LAL deficiency.

Patient Input Information

Two patient groups responded to the call for patient input for this CDR review: the Canadian Liver Foundation and the Isaac Foundation. The following is a summary of key input from the perspective of the patient groups:

- LAL deficiency is an ultra-rare, genetic, chronic, and progressive disease whereby the enzyme responsible for cholesterol ester and triglyceride metabolism is deficient or absent, leading to harmful lipid buildup in the lysosomes. LAL deficiency is predominantly a pediatric condition, with a large number of patients being diagnosed as infants, but is also diagnosed in older children and adults.
- The early-onset LAL deficiency in infants is characterized by a failure to grow, difficulties in absorbing nutrients from food (malabsorption), persistent vomiting and diarrhea, swollen belly, and jaundice. 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.
- Late-onset LAL deficiency in children and adults is characterized by a buildup of fat in the liver, spleen, and other organs. As the liver damage progresses, patients may experience ascites (fluid buildup in the abdomen), easy bleeding or bruising, and jaundice. Patients can also experience esophageal varices, microvesicular or mixed hepatic steatosis, fibrosis, and cirrhosis. In addition, patients also experience gastrointestinal symptoms and cardiovascular complications.
- Patients with LAL deficiency experience life-altering impacts of the disease on their day-to-day lives and on their quality of life, including on their physical health, school and everyday life (especially missed days of school), and on their mental well-being. Specific symptoms include constant pains (including abdominal pain), enlarging liver and spleen, headaches, bouts of extreme fatigue, getting sick easily and having it last a long time, itching, and skin lesions with scarring.
- The patient input described the experience of several individuals who had received treatment with sebelipase alfa for LAL deficiency and all reported marked improvement of their symptoms and quality of life, with few adverse effects. Families believe that sebelipase alfa will have a dramatically positive effect on both the patient and the caregivers, with an increased chance at a longer life being the main consideration.

Clinical Trials

The CDR systematic review included two trials (ARISE and VITAL). The VITAL trial (N = 9) was a phase II/III, multi-centre, open-label, single-arm study of sebelipase alfa in patients with LAL deficiency with growth failure or other evidence of rapidly progressive disease prior to six months of age. The age range at study entry was 1 month to 6 months. Patients received sebelipase

alfa at 0.35 mg/kg once weekly for the first two weeks and then 1 mg/kg once weekly. Based on clinical response, dose escalation to 3 mg/kg once weekly could be considered after receiving at least four infusions at a dose of 1 mg/kg once weekly. A further dose escalation to 5 mg/kg once weekly was allowed. The VITAL trial consisted of a screening period of up to three weeks, a treatment period of up to four years, and a follow-up visit at least 30 days after the last dose of sebelipase alfa.

The ARISE trial (N = 66) was a phase III, randomized, multi-centre, double-blind, placebo-controlled study of children and adults with LAL deficiency. Patients were randomized to receive sebelipase alfa at a dose of 1 mg/kg (n = 36) or placebo (n = 30) once every other week for 20 weeks in the double-blind period. After completing the double-blind period, each patient was to begin open-label treatment with sebelipase alfa for up to 130 weeks.

Key limitations in both trials were the small sample size and the lack of long-term follow-up. In addition, in the ARISE trial, surrogate outcomes were used instead of hard clinical outcomes, and, in the VITAL trial, a historical control for the primary outcome was used.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Survival.
- Normalization of ALT levels based on age- and gender-specific upper limit of normal (ULN) provided by the central laboratory performing the assay.
- Normalization of aspartate aminotransferase (AST) levels based on age- and gender-specific normal ranges provided by the central laboratory performing the assay.
- Reduction in low-density lipoprotein cholesterol (LDL-C).
- Increase in high-density lipoprotein cholesterol (HDL-C).
- Reduction in non-HDL-C.
- Reduction in triglycerides (TG).
- Reduction in liver fat content.
- Changes from baseline in weight-for-age (WFA).
- Changes from baseline in length-for-age (LFA) and/or height-for-age.
- Chronic Liver Disease Questionnaire (CLDQ): An instrument that measures HRQoL for patients with chronic liver disease. It includes 29 items in the following six domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry. A 7-point Likert scale is used to grade the response to each item, in which a score of 1 point indicates the worst and a score of 7 the best possible function. Each domain score is calculated by dividing the total of the scores for each item in the domain by the number of items in the domain. Higher CLDQ scores indicate less HRQoL impairment. The minimal clinically important difference (MCID) has not been defined for patients with LAL deficiency.
- Pediatric Quality of Life Inventory (PedsQL): An HRQoL measure that uses a modular approach and incorporates both generic and disease/symptom-specific items that are appropriate for the assessment of pediatric chronic conditions. A 5-point Likert response scale is used across the child reports (from ages eight years to 18 years) and the corresponding parent report, where 0 represents “never a problem” and 4 represents “almost always a problem.” In addition, a 3-point scale is used for simplification and ease of use for children who are aged five years to seven years, with scores of 0 (“not at all a problem”), 2 (“sometimes a problem”), and 4 (“a lot of a problem”), with each of the response choices anchored to a happy-to-sad faces scale. The scores are transformed linearly to a 0 to 100 scale, whereby 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0, with higher scores indicative of a higher HRQoL. The MCID has not been defined for patients with LAL deficiency.

- The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F): A questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, and energy, as well as fatigue's impact on daily activities and function. The fatigue subscale has a 7-day recall period and includes 13 items scored using a 4-point Likert scale (subscale score range 0 to 52). Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale (40 items in total), make up the total score, ranging from 0 (worst) to 160 (best). The MCID has not been defined for patients with LAL deficiency; however, it may range from 3 to 4 points in other populations.
- Serious adverse events (SAE), total adverse events, withdrawal due to adverse events, and notable harms.

In the VITAL trial, the primary efficacy end point was the proportion of patients surviving to 12 months of age. In the ARISE trial, the primary efficacy outcome measure was the proportion of patients who achieved ALT normalization (i.e., ALT below the age- and gender-specific ULN provided by the central laboratory performing the assay) at the end of the double-blind period (week 20).

Efficacy

- In the VITAL trial, the percentage of patients in the primary efficacy analysis set surviving to 12 months of age was 67% (6 of 9 patients), with an exact 95% confidence interval (CI) for survival of 29.9% to 92.5%. As of May 2017, five patients have survived beyond 4 years of age and continue to receive sebelipase alfa. The median age (range) at last exposure in the study was 4 years and 7 months (4 years and 2 months to 6 years and 5 months). The median follow-up time in the study was 4 years and 1 month. All five patients are living at home and are reported by the manufacturer as making normal social and developmental progress. The patients have transitioned from an in-patient critical care unit to outpatient care, and do not require constant medical attention, with reduced need for assisted feeding.
- There were no deaths in ARISE during the double-blind period; however, the double-blind period was short (20 weeks), and there is no evidence to address long-term and key clinical end points such as the need for liver transplant, cardiovascular events, and death.
- No statistically significant differences between sebelipase alfa and placebo groups were observed from baseline to last double-blind measurement with respect to HRQoL and fatigue in ARISE.
- In the VITAL trial, growth deceleration from birth was observed for all eight patients with available weight data. Improvements in growth were observed for all six surviving patients. WFA percentile improved significantly for all patients from baseline through the last assessment prior to data cut-off provided by the manufacturer (June 10, 2014). Data for other growth parameters (LFA) supported the trends observed for WFA. In the ARISE trial, there were small increases in the change from baseline to week 20 in weight in both the sebelipase alfa and placebo groups (1.5 kg and 1.9 kg, respectively). Similarly, small mean increases from baseline to week 20 in height were seen in both the sebelipase alfa and placebo groups (2.6 cm and 2.5 cm, respectively) suggesting that sebelipase alfa as compared with placebo had no impact on growth in children and adults who did not present with rapidly progressive LAL deficiency prior to six months of age. However, these results should be interpreted with caution, as subgroup results by age were not available and no between-group statistical comparison was reported.
- In both trials, sebelipase alfa reduced lipid levels, liver enzymes, and liver fat content (assessed in the ARISE trial only), however, it is unclear how these surrogate outcomes related to key clinical outcomes on long-term survival. In particular, it is uncertain to what degree sebelipase alfa may delay (or stop) progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events, or death. While the VITAL trial had treatment for up to four years, this is only a fraction of the expected lifelong treatment people in clinical practice would receive. Hence, the long-term safety and efficacy profile of sebelipase alfa beyond four years is uncertain.

Harms (Safety and Tolerability)

- In the VITAL trial, treatment-emergent adverse events (TEAEs) have been reported for all nine (100%) patients. The most frequently reported TEAEs were vomiting, diarrhea, pyrexia, rhinitis, anemia, cough, catheter-site infection, device-related infection, dermatitis diaper, nasopharyngitis, urticaria, tachycardia, rash, chills, and decreased appetite.

- In the ARISE trial, the percentage of patients treated with sebelipase alfa who experienced TEAEs was 86% versus 93% of those who received placebo. Overall, the most common (i.e., incidence > 10%) TEAEs reported among the 36 patients in the sebelipase alfa group were headache (28%), pyrexia (19%), diarrhea, oropharyngeal pain, and upper respiratory tract infection (each 17%), and epistaxis and nasopharyngitis (each 11%).
- In the VITAL trial, no patient discontinued treatment due to infusion-associated reactions (IARs) or other study drug-related TEAEs, and no patient had a permanent dose reduction due to poor tolerability. One patient was discontinued from treatment following a non–study drug-related TEAE of bradycardia, and died of hepatic failure prior to the next scheduled infusion. In the ARISE trial, one patient in the sebelipase alfa group discontinued from the double-blind period because of an IAR. No other patient discontinued from the double-blind period because of an IAR or other TEAE.
- In the VITAL trial, a total of 31 SAEs were reported for eight (89%) patients. One patient experienced four study drug-related SAEs, which were characterized as IARs. In the ARISE trial the incidence of SAEs in the double-blind period of the study was low (2 patients in the sebelipase alfa group and one patient in the placebo group).
- In the VITAL trial, IARs have been reported for four patients, most commonly pyrexia, vomiting, tachycardia, and chills, and have been predominantly mild and non-serious. Four patients have had a dose modification (interruption or decrease) during one or more study infusions due to a TEAE. There is evidence of ADA formation in four of the seven patients who have been tested. ADA positivity was confirmed as early as weeks 5 and 8 (three patients), and the fourth patient became positive at week 59. Three patients have persistent ADA positivity.
- In the ARISE trial, during the double-blind period, two (6%) of 36 patients in the sebelipase alfa group experienced a total of 10 IARs, and four (13%) of 30 patients in the placebo group experienced a total of five IARs. A total of 14.3% of patients in the sebelipase alfa group had at least one positive ADA test during the double-blind period.
- In the VITAL trial, three patients died due to complications related to disease progression (hepatic failure or cardiac arrest) or a non-study-related procedure (peritoneal hemorrhage following abdominal paracentesis). These patients died after receiving between one and four infusions of sebelipase alfa. In the ARISE trial, there were no deaths.

Cost and Cost-Effectiveness

The manufacturer submitted a price of $8,546 per 10 mL vial of sebelipase alfa, containing 20 mg 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 later-onset (pediatric/adult presentation) LAL deficiency, 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 based on study LAL-1-NH01. For the pediatric/adult-presentation patients, a model of liver disease progression that focused on the hepatic aspect of LAL deficiency was used. 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. In pediatric/adult-presentation LAL deficiency patients, efficacy for sebelipase alfa was based on liver biopsy data as derived from the ARISE clinical trial. The comparator in both economic evaluations was the current standard of care, or 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 ICURs of $4.485 million and $2 million per QALY for infantile-presentation and pediatric/adult-presentation patients, respectively. [redacted]

CDR identified the following key limitations with the manufacturer's economic submissions:

- Clinical data for the indicated populations were limited and associated with uncertainty, which impacts the confidence that can be placed in 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 ARISE (pediatric/adult presentation) biomarker 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.

Most identified limitations could not be addressed by CDR, either because of the model structure or lack of clinical information. CDR conducted exploratory analyses varying the patient weight over time, model time horizon, liver disease progression, and health state utility values.

The results of the CDR reanalyses 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 CDR reanalyses, a price reduction of greater than 96% (or a cap on annual drug costs per patient of $50,000) is required to achieve an ICUR of $100,000 per QALY, or a price reduction of greater than 98% (or a cap on annual drug costs per patient of $25,000) is required to achieve an ICUR of $50,000 per QALY, regardless of presentation.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 11, 2018 Meeting

Regrets:

None

Conflicts of Interest:

None

September, 2018 Meeting (Reconsideration)

Regrets:

Two CDEC members

Conflicts of Interest:

None