CADTH

CADTH Drug Implementation Advice

SEBELIPASE ALFA (KANUMA)

(Alexion Pharmaceuticals, Inc.)

Indication: For the treatment of infants, children, and adults diagnosed with lysosomal acid lipase deficiency.

Service Line:	CADTH Drug Implementation Advice
Version:	Final
Publication Date:	January 2020
Report Length:	7 Pages

CADTH

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

CADTH

Drug	Sebelipase alfa (Kanuma)
Indication	Treatment of infants, children, and adults diagnosed with lysosomal acid lipase deficiency
Dosage Form	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.
Date CDEC Recommendation Issued	September 26, 2018

Background

Based on the 2018 review of sebelipase alfa (Kanuma) for the treatment of lysosomal acid lipase (LAL) deficiency through the CADTH Common Drug Review (CDR), the CADTH Canadian Drug Expert Committee (CDEC) issued the following reimbursement recommendation:

CDEC Recommendation for Sebelipase Alfa (Kanuma)

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.

CDEC also noted:

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.

Implementation Issue

Since the CDEC recommendation for sebelipase alfa was issued, CADTH has received a request from the CDR-participating drug plans to help understand the use of sebelipase alfa in patients who may have severe disease and who experienced the onset of clinical manifestations after six months of age given the seriousness of LAL deficiency and a persistent unmet medical need for these patients.

Consultation Process

CADTH convened a panel of clinical experts with experience in the diagnosis and management of patients with LAL deficiency. One panel meeting was held on September 12, 2019, to discuss appropriate initiation, renewal, and discontinuation criteria for sebelipase alfa in patients who experienced the onset of clinical manifestations after six months of age and who may have severe disease.

Following the panel meeting, CADTH staff, with help from panellists, prepared a summary of the input provided by the panel. CDR-participating drug plans and the manufacturer of sebelipase alfa were given the opportunity to comment on the draft document.

Objectives of the Clinical Panel

The objective of the panel was to discuss the clinical use of sebelipase alfa in patients with LAL deficiency who may have severe disease, and who experienced the onset of clinical manifestations after six months of age, and, if appropriate, to recommend initiation, renewal, discontinuation, and administration criteria for those patients.

Implementation Advice

The initiation, discontinuation, and administration criteria for sebelipase alfa for the treatment of LAL deficiency are shown in Table 1. A summary of the relevant clinical panel input is also provided.

The panellists expanded on the original CDEC recommendation, which recommended the reimbursement of sebelipase alfa for patients with a confirmed diagnosis of LAL deficiency and with onset of clinical manifestations of LAL deficiency before six months of age. The additional criteria would expand reimbursement to also include patients with onset of LAL deficiency at six months of age and older. A subgroup of patients with more severe LAL deficiency and who would likely benefit from treatment with sebelipase alfa could not be identified in part because of the variable nature of the disease in patients with onset at six months of age and older. Furthermore, as noted in Table 1 and the following summary, the panellists indicated that patients with more advanced disease (e.g., signs of severe liver disease and/or those who have progressed to end-stage liver disease) are not expected to benefit from treatment with sebelipase alfa.

Table 1: Summary of Recommended Initiation, Discontinuation, and Administration Criteria

Initiation Criteria
The initiation criteria defined in the original CDEC recommendation plus the following. Patients six months of age and older may have treatment with sebelipase alfa reimbursed with a confirmed diagnosis of LAL deficiency and if at least one of the following clinical manifestations is present: • Persistently elevated transaminases (ALT > 1.5 × ULN[a] or AST > 1.5 × ULN[a]) as measured by two assessments three to six months apart • Persistent dyslipidemia (LDL-c and/or TG values in the top fifth percentile based on sex and age) as measured by two assessments three to six months apart • Any documented hepatomegaly or hepatosplenomegaly • Liver fibrosis confirmed by biopsy • Failure to thrive

Initiation Criteria (Cont'd)

- Growth impairment[b]
- Evidence of intestinal affection and/or malabsorption

Patients with onset of clinical manifestations at six months of age and older must not have evidence of:

- Increased portal vein pressures, or de novo evidence of portal hypertension on ultrasound and Doppler, or new clinical presentation of portal hypertension (e.g., esophageal varices)
- Severe hepatic dysfunction (Child-Pugh class C)
- End-stage liver disease

The physician must provide baseline values for the chosen clinical manifestation at the time of initial request for reimbursement.

The maximum duration of initial authorization is 12 months.

Continuation Criteria

The maximum duration of subsequent authorizations following the initial authorization is six months.

Reimbursement of treatment with sebelipase alfa for patients with onset of clinical manifestations of LAL deficiency before six months of age should continue if the patient continues to survive and has not experienced an adverse event related to sebelipase alfa as described in the reimbursement discontinuation criteria.

Reimbursement of treatment with sebelipase alfa for patients with onset of clinical manifestations of LAL deficiency at six months of age and older should continue if none of the reimbursement discontinuation criteria are met.

Discontinuation Criteria

Reimbursement of treatment should be discontinued, regardless of age of onset, for adverse events from sebelipase alfa (particularly hypersensitivity reactions including anaphylaxis, hypotension, or fever), which cannot be managed with standard treatment, and/or have a significant impact on the patient's quality of life, or are life-threatening.

For patients with onset of clinical manifestations of LAL deficiency at six months of age and older, sebelipase alfa treatment is determined not to benefit the patient as defined by progression to end-stage liver failure or multi-organ failure, and/or at least three out of the following response components compared with baseline values after 12 months of therapy:

- Less than 10% improvement in ALT or AST
- Worsening of liver fibrosis confirmed by biopsy
- Persisting growth impairment[b] despite sebelipase alfa therapy and nutritional interventions
- At least a 15% increase in spleen volume and/or a greater than 15% increase in liver volume on ultrasound
- Increased portal vein pressures, or de novo evidence of portal hypertension on ultrasound and Doppler, or new clinical presentation of portal hypertension (e.g., esophageal varices)

Administration Criteria

The patient should be under the care of a specialist with experience in the diagnosis and management of LAL deficiency.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LAL = lysosomal acid lipase; LDL-c = low-density lipoprotein – cholesterol; ULN = upper limit of normal; TG = triglycerides; WHO = World Health Organization.

[a] Based on age- and sex-specific normal values for ALT and AST.

[b] Growth impairment is defined as decreased body weight across at least two of the major centiles on a WHO weight-for-age chart, or body weight below 10th centile and no weight gain within two weeks and/or decreased height across at least two of the major centiles on a WHO height-for-age chart.

Recommended Initiation Criteria

The panellists agreed with the original CDEC recommendation that required patients with onset of LAL deficiency before six months of age to have a confirmed diagnosis based on documented biochemical evidence of deficient LAL activity and two documented pathogenic mutations in the LIPA gene. It was noted that these are consistent with clinical practice and reimbursement criteria from private payers for sebelipase alfa. Moreover, these criteria for diagnosis would apply to identifying older patients (i.e., those with onset of clinical manifestations of LAL deficiency at six months of age and older) for treatment with sebelipase alfa. The panellists indicated that genetic testing, in general, is increasingly accessible and timely in receiving results; this would apply to targeted sequencing of the LIPA gene. Therefore, requiring genetic testing as part of the initiation criteria would not have a clinically meaningful impact on treatment access for patients.

The panellists agreed that patients who are at least six months of age with a confirmed diagnosis of LAL deficiency (as confirmed by two documented pathogenic mutations in the LIPA gene and documented biochemical evidence of deficient LAL activity) and who have at least one of the clinical signs and/or symptoms listed in Table 1 should receive sebelipase alfa. However, the panellists stated that patients whose liver manifestations have progressed to the point where they are experiencing increased portal vein pressures, or de novo evidence of portal hypertension on ultrasound and Doppler, or new clinical presentation of portal hypertension (e.g., esophageal varices), or severe hepatic dysfunction (Child-Pugh class C), or end-stage liver disease, treatment with sebelipase alfa is not likely to provide benefit. Therefore, treatment with sebelipase alfa should not be initiated in patients who are at least six months of age and present at these points in their disease.

The panellists noted that LAL deficiency in patients with onset at six months of age and older (i.e., noninfantile onset) is variable in how it manifests and progresses. Given the rarity and variable spectrum of LAL deficiency in older patients, it may be misdiagnosed for a more common condition with similar clinical manifestations, such as non-alcoholic steatohepatitis or dyslipidemia. The initiation criteria listed in Table 1 increases the likelihood of reimbursement for patients who truly have LAL deficiency and who may benefit from treatment with sebelipase alfa.

The panellists agreed that 12 months was an appropriate interval for the initial authorization of reimbursement based on the need for a minimum 12-month period to be able to observe the effects of sebelipase alfa on clinical outcomes (such as reduced hepatomegaly).

Recommended Continuation Criteria

The panellists agreed that six months was an appropriate interval for the reassessment of treatment effects with sebelipase alfa following the initial 12-month authorization. They also agreed that there was no need to specify an earlier time point for assessment following treatment initiation as sebelipase alfa would be discontinued if the patient was not receiving benefit or was experiencing clinically important adverse effects.

The panellists stated that the rapidly progressive and life-limiting nature of the infantile onset form of LAL deficiency (i.e., in patients with onset of clinical manifestations before six months of age) would require life-long treatment with sebelipase alfa for survival. Therefore, treatment in this subpopulation of patients would not stop if the patient continued to live, unless he or she experienced an adverse event requiring treatment discontinuation, as described in the discontinuation criteria.

Recommended Discontinuation Criteria

The panellists agreed that adverse events related to anaphylactic reactions, hypotension, or fever would constitute clinically important adverse reactions requiring discontinuation of therapy with sebelipase alfa in all patients regardless of age of onset.

In patients with LAL deficiency onset at age six months and older, the panellists agreed that sebelipase alfa is unlikely to provide benefit for those whose condition had progressed to end-stage organ failure. In addition, the panellists agreed that a less than 10% improvement from baseline in ALT or AST, worsening liver fibrosis, failure to thrive and to meet growth standards in children and adolescents, 15% increases in spleen and/or liver volume, and signs of portal hypertension would all indicate that the patient is not adequately responding to treatment with sebelipase alfa. The panellists discussed whether changes from baseline in blood low-density lipoprotein – cholesterol levels would be a reasonable criterion; however, it was decided that lack of improvement in blood low-density lipoprotein – cholesterol levels would not be a sufficiently sensitive or specific clinical criterion to stop treatment in part because most patients would receive other therapies for dyslipidemia that would make it difficult to discern the effects of sebelipase alfa on this marker.

Recommended Administration Criteria

The panellists agreed that patients should be under the care of a specialist with experience in the diagnosis and management of LAL deficiency. However, administration of sebelipase alfa would not need to be done by the specialist.

Additional Guidance

The panellists discussed the need for collecting more data regarding the epidemiology of LAL deficiency and the longer-term effects of sebelipase alfa. The rarity of LAL deficiency would require not only a Canada-wide registry, but linkages globally for clinically important outcome assessments. As well, it would be necessary to establish a network of Canadian experts in the diagnosis and management of LAL deficiency with access to specialized clinic data. A LAL deficiency network should be comprised of hepatologists, lipidologists, metabolic geneticists, and liver pathologists who have experience with LAL deficiency. This approach could be used to ensure that only the appropriate patient population is treated with sebelipase alfa and that clinically important outcomes related to treatment are collected.