sebelipase alfa (Kanuma™)

Policy # 00508
Original Effective Date: 05/18/2016
Current Effective Date: 06/10/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider sebelipase alfa (Kanuma™)‡ for the treatment of lysosomal acid lipase deficiency to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for sebelipase alfa (Kanuma) for the treatment of lysosomal acid lipase deficiency will be considered when the following criteria are met:

- Patient has a diagnosis of lysosomal acid lipase (LAL) deficiency (Wolman Disease or Cholesteryl Ester Storage Disease [CESD]) confirmed by enzymatic testing; AND
- If the patient has rapidly progressive LAL deficiency presenting within the first 6 months of life, the dose does NOT exceed 5 mg/kg once weekly OR if this is a pediatric or adult patient (not rapidly progressive) with LAL deficiency, the dose does NOT exceed 3 mg/kg every other week.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of sebelipase alfa (Kanuma) when patient selection criteria are not met to be **investigational.***

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Background/Overview

Kanuma is a hydrolytic lysosomal cholesteryl ester and triacylglycerol-specific enzyme indicated for the treatment of patients with a diagnosis of LAL deficiency. Kanuma essentially replaces the enzyme that is deficient in this disease and catalyzes the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol, and fatty acids. In patients with rapidly progressive LAL deficiency presenting within the first 6 months of life, the recommended starting dose is 1 mg/kg as an intravenous infusion once weekly. For patients not receiving an optimal response, the dose should be increased to 3 mg/kg once weekly. For patients with continued suboptimal clinical response, the dose should be further increased to 5 mg/kg once weekly. For patients with pediatric or adult LAL deficiency, the recommended dosage is 1 mg/kg as an intravenous infusion once every other week. For patients with a suboptimal clinical response, the dosage should be increased to 3 mg/kg once every other week. Kanuma is supplied as a single use vial containing 20mg/10mL.

Lysosomal Acid Lipase Deficiency

LAL deficiency is an autosomal recessive lysosomal storage disorder marked by decreased activity or complete loss in activity of the lysosomal acid lipase enzyme. The primary site of action of the LAL enzyme is the lysosome. The LAL enzyme causes the breakdown of lipid particles including low density lipoprotein (LDL). A decrease in the LAL activity leads to an accumulation of lysosomal cholesteryl esters and triglycerides in a variety of cell types, including hepatocytes, adrenal glands, intestines, and cells of monocyte/macrophage lineage throughout the body. The disease typically presents as one of two different phenotypes. The first phenotypic group is an infantile onset, rapidly progressive disease (also known as Wolman Disease) and the second type would be a later onset, slower progressing disease (known as cholesteryl ester storage disease). In infants, LAL deficiency most commonly presents as vomiting, diarrhea, hepatomegaly, and growth retardation and is usually fatal within the first 6 months of life. Rapidly progressing LAL deficiency is estimated to effect 1 in every 500,000 live births. LAL deficiency in children and adults typically presents as hypercholesterolemia, elevated transaminases, and hepatomegaly. The life expectancy of this group is unknown. The incidence in this group varies widely and is thought to range anywhere from 1 in 40,000 individuals to 1 in 130,000 individuals. As of recent, very few cases of the slowly progressing disease have been reported. The disease is thought to be severely underreported as LAL deficiency can be misdiagnosed due to overlap with other conditions including Wilson's disease, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, metabolic syndrome, heterozygous familial hypercholesterolemia, or familial combined hypercholesterolemia. According to a website run by

the manufacturer of Kanuma, the diagnosis can be made clinically in tandem with an enzymatic assay to check LAL activity. LabCorp offers this test under test code 402300. The enzymatic test used in clinical trials was referred to as the dried blood spot test.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Kanuma was approved in December of 2015 for the treatment of lysosomal acid lipase deficiency.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Infants Presenting Within the First 6 Months of Life
A multicenter, open-label, single-arm clinical study of Kanuma was conducted in 9 infants with lysosomal acid lipase deficiency who had growth failure or other evidence of rapidly progressive disease prior to 6 months of age. Patients received Kanuma at 0.35 mg/kg once weekly for the first 2 weeks and then 1 mg/kg once weekly. Due to suboptimal clinical response, doses in all 6 surviving patients were escalated to 3 mg/kg once weekly, between 4 and 88 weeks (median 11 weeks) after starting treatment at 1 mg/kg. In one patient, the dose was escalated to 5 mg/kg once weekly at Week 88 due to decreased growth velocity in a setting of positive neutralizing anti-drug antibodies to Kanuma.

Efficacy of Kanuma was assessed by comparing the survival of 9 Kanuma-treated patients at 12 months of age with an untreated historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. Of the 9 Kanuma-treated infants, 6 patients survived beyond 12 months of age, compared to 0 of 21 patients in the historical cohort, all of whom died by 8 months of age. The median age of the 6 surviving Kanuma-treated patients was 18.1 months (range 12 to 42.2 months).

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Following initiation of treatment with Kanuma 1 mg/kg once weekly, weight-for-age z-scores improved in 3 of 5 surviving patients with growth failure, and all 6 surviving patients demonstrated improvements in weight-for-age z-scores following dose escalation to 3 mg/kg once weekly.

Across this study and another study in infants with rapidly progressive LAL Deficiency, 9 patients received successive dose escalations up to 5 mg/kg once weekly due to suboptimal clinical response. Of the 9 patients whose Kanuma dose was escalated to 5 mg/kg once weekly, 6 were alive at their last follow up at 3 years, and 2 were alive at their last follow up at 5 years.

Of these 9 patients, 6 experienced normalization of ALT and/or AST which had remained abnormal on the lower Kanuma dose.

Pediatric and Adult Patients
The safety and efficacy of Kanuma were assessed in 66 pediatric and adult patients with lysosomal acid lipase deficiency, aged 4 to 58 years (71% were less than 18 years old), in a multicenter, double-blind, placebo-controlled trial. Patients were randomized to receive Kanuma at a dosage of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. Sixty-two of the 66 (94%) patients had lol density lipoprotein cholesterol (LDL-c) of 130 mg/dL or greater at study entry. The majority of patients (58%) had LDL-c above 190 mg/dL at study entry, and 24% of patients with LDL-c above 190 mg/dL remained on lipid lowering medications.

At the completion of the 20-week double-blind period of the trial, a statistically significant improvement in percent change from baseline in LDL-c was observed in the Kanuma-treated group as compared to the placebo group (mean difference and 95% C.I.: -22%, [-33%, -15%]; $p<0.0001$). LDL-c of less than 130 mg/dL was achieved in 13 of 32 (41%; 95% C.I.: [24%, 58%]) Kanuma-treated patients and in only 2 of 30 (7%; 95% C.I.: [0%, 16%]) placebo-treated patients with baseline LDL-c of 130 mg/dL or greater. A statistically significant improvement in percent change from baseline at 20 weeks was also observed in the Kanuma-treated group compared to the placebo group for other parameters related to lysosomal acid lipase deficiency, including decreases in non-high density lipoprotein cholesterol (non-HDL-c) (mean difference and 95% C.I.: -21%, [-30%, -15%]; $p<0.0001$) and triglycerides (mean difference and 95% C.I.: -14%, [-28%, -1%]; $p=0.0375$), and increases in high density lipoprotein cholesterol (HDL-c) (mean difference and 95% C.I.: 20%, [12%, 26%]; $p<0.0001$). The effect of Kanuma on cardiovascular morbidity and mortality has not been established.

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Patients treated with Kanuma had larger reductions from baseline in ALT values and liver fat content (measured by MRI), compared to patients treated with placebo. The significance of these findings as they relate to progression of liver disease in lysosomal acid lipase deficiency has not been established.

Pediatric and adult patients who participated in the randomized, placebo-controlled trial were eligible to continue treatment in an open-label extension. Sixty-five of the 66 patients entered the open-label extension and were treated with Kanuma at a dosage of 1 mg/kg once every other week. During the open-label extension, patients treated with Kanuma for up to 36 weeks demonstrated improvements in lipid parameters, including LDL-c and HDL-c levels, and ALT

Across two studies in children and adults with LAL Deficiency, 23 of 97 patients received dose escalations from the protocol-defined starting dose of 1 mg/kg every other week. Before being escalated to 3 mg/kg every other week, patients were on 1 mg/kg every other week for a median of 19 months (range 6 to 33 months), and most dose escalations were initiated in response to an increase in serum transaminase levels, an increase in serum lipids, or a decrease in weight for age (WFA) z-scores in children. Of the 23 patients whose Kanuma dose was escalated to 3 mg/kg every other week, 20 were children. After the dose escalation, 14 of the 23 patients experienced normalization of one or more of the following biomarkers which had remained abnormally high on the lower Kanuma dose: serum transaminases, triglycerides, and/or LDL-c.

References

1. Kanuma [package insert]. Alexion Pharmaceuticals. Cheshire, Connecticut. Updated November 2021.
2. Kanuma Drug Evaluation. Express Scripts.
3. LADLSource.com. Alexion Pharmaceuticals.

Policy History

Original Effective Date: 05/18/2016
Current Effective Date: 06/10/2024
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. New policy.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

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05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. No change to coverage.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. No change to coverage.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. No change to coverage.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. No change to coverage.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. No change to coverage.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Updated the patient selection criteria and the background/rationale sections to include updated dosing per the revised FDA package insert.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J2840 Delete code effective 06/01/2023: J3490
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.