

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **KANUMA™**

(sebelipase alfa)

Concentrate for Solution for Infusion

2 mg/mL

Enzyme Replacement Therapy

ATC Code: A16AB14

KANUMA™ (sebelipase alfa), indicated for the treatment of infants, children and adults diagnosed with lysosomal acid lipase (LAL) deficiency, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KANUMA™ please refer to Health Canada's Notice of Compliance with conditions - drug products web site: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>

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Submission Control No: 204085

Date of Approval:
December 15, 2017

<p style="text-align: center;">This product has been authorized under the Notice of Compliance with Conditions (NOC/c)</p>

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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KANUMA™

Sebelipase alfa

PART I: HEALTH PROFESSIONAL INFORMATION

KANUMA™ (sebelipase alfa), indicated for the treatment of infants, children and adults diagnosed with lysosomal acid lipase (LAL) deficiency, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KANUMA™ please refer to Health Canada's [Notice of Compliance with conditions - drug products](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php) web site: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Concentrate for Solution for Infusion 2 mg/mL	Trisodium citrate dihydrate, citric acid monohydrate, human serum albumin and Water for Injections. <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

Description

KANUMA (sebelipase alfa) is a recombinant human lysosomal acid lipase (rhLAL). Lysosomal acid lipase (EC 3.1.1.13) is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of cholesteryl esters to free cholesterol and fatty acids and the hydrolysis of triglycerides to glycerol and free fatty acids. It is supplied as a sterile, preservative-free, non-pyrogenic aqueous solution in single-use vials for intravenous infusion. Each mL of solution contains sebelipase alfa (2 mg), citric acid monohydrate (1.57 mg), Human Serum Albumin (10 mg), and trisodium citrate dihydrate (13.7 mg) at pH 5.9.

NOC/c INDICATIONS AND CLINICAL USE

KANUMA™ (sebelipase alfa), is indicated for the treatment of infants, children and adults diagnosed with lysosomal acid lipase (LAL) deficiency.

KANUMA treatment should be supervised by a healthcare professional experienced in the management of patients with LAL deficiency, other metabolic disorders, or chronic liver

diseases. KANUMA should be administered by a trained healthcare professional who can manage medical emergencies.

NOC/c CONTRAINDICATIONS

KANUMA is contraindicated in patients who are diagnosed with life-threatening hypersensitivity to this drug or to any ingredient in the formulation, including any non-medical ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

NOC/c WARNINGS AND PRECAUTIONS

Hypersensitivity reactions, including anaphylaxis: (see **ADVERSE REACTIONS** section).

- Hypersensitivity reactions, including anaphylaxis, have been reported in KANUMA-treated patients. Anaphylaxis has occurred as early as the sixth infusion and as late as 1 year after treatment initiation.
- Due to the potential for anaphylaxis, **appropriate medical support should be readily available when KANUMA is administered.**
- Monitor patients closely during and after every infusion. If anaphylaxis or a severe hypersensitivity reaction occurs, immediately discontinue the infusion and initiate appropriate medical treatment.
- The majority of hypersensitivity reactions occurred during or within 4 hours of the completion of the infusion. The management of hypersensitivity reactions should be based on the severity of the reactions and may include temporarily interrupting the infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids.
- Pre-treatment with antipyretics and/or antihistamines may prevent subsequent reactions in those cases where symptomatic treatment was required
- The benefits and risks of re-administering KANUMA following a severe allergic reaction should be considered.
- Inform patients and/or caregivers of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur.

Hypersensitivity to Eggs or Egg Products

- KANUMA is produced in the egg whites of genetically engineered chickens. Patients with a known history of egg allergies were excluded from the clinical trials. Consider the risks and benefits of treatment with KANUMA in patients with known systemic hypersensitivity reactions to eggs or egg products.

Excipients - sodium

- This medicinal product contains 33 mg sodium per vial and is administered in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration when administering KANUMA to patients on a controlled sodium diet.

Immune

As with all therapeutic proteins, there is potential for immunogenicity. Patients have developed anti-drug antibodies (ADA) to sebelipase alfa during clinical trials (see Immunogenicity in **ADVERSE REACTIONS** section).

Special Population

Pregnant Women

There are no data on sebelipase alfa in pregnant women. The background risk of major birth defects and miscarriage for this lysosomal acid lipase (LAL) deficiency population is unknown. Exercise caution- when considering KANUMA administration.

Nursing Women

There are no data from studies in breast-feeding women. It is not known whether sebelipase alfa is excreted in human milk. Exercise caution-when considering KANUMA administration during breast feeding period.

Fertility

There are no clinical data on the effects of sebelipase alfa on fertility.

Pediatrics (0-18 years of age)

Safety and effectiveness of KANUMA have been established in pediatric patients aged 1 month and older. Clinical trials with KANUMA were conducted in 56 pediatric patients (range 1 month to <18 years old).

Administration of KANUMA to infants with confirmed multiple-organ failure should be at the discretion of the treating physician.

Geriatrics (> 65 years of age)

The safety and efficacy of KANUMA in patients older than 65 years have not been evaluated.

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hypersensitivity reactions including anaphylaxis

In clinical trials, 3 of 106 (3%) patients (1 of 14 infants and 2 of 92 children/adults) treated with KANUMA experienced signs and symptoms consistent with anaphylaxis. These patients experienced reactions during infusion with signs and symptoms including chest discomfort, conjunctival injection, dyspnea, generalized and itchy rash, hyperemia, swelling of eyelids, rhinorrhea, severe respiratory distress, tachycardia, tachypnea, and urticaria. Anaphylaxis has occurred as early as the sixth infusion and as late as 1 year after treatment initiation.

In clinical trials, 21 of 106 (20%) KANUMA-treated patients, including 9 of 14 (64%) infants and 12 of 92 (13%) pediatric patients, 4 years and older, and adults, experienced signs and symptoms either consistent with or that may be related to a hypersensitivity reaction. Signs and symptoms of hypersensitivity reactions, occurring in two or more patients, included abdominal pain, agitation, fever, chills, diarrhea, eczema, edema, hypertension, irritability, laryngeal edema, nausea, pallor, pruritus, rash, and vomiting. The majority of reactions occurred during or within 4 hours of the completion of the infusion. Patients were not routinely pre-medicated prior to infusion of KANUMA in these clinical trials.

Transient hyperlipidemia

Consistent with its known mechanism of action, asymptomatic increases in circulating cholesterol and triglycerides have been observed following initiation of treatment. These increases have generally occurred within the first 2 to 4 weeks and improved within a further 8 weeks of treatment.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Patients have developed anti-drug antibodies (ADA) to KANUMA. Some ADA-positive patients were identified to have *in vitro* neutralizing antibodies.

Patients with rapidly progressive LAL deficiency presenting within the first 6 months of life

Four of 7 (57%) infants developed ADA during treatment with KANUMA. Two of the 4 ADA-positive patients were determined to be positive for neutralizing antibodies that inhibit *in vitro* enzyme activity and cellular uptake of the enzyme. At the time of initial ADA positivity, 3 patients were receiving a dosage of 1 mg/kg once weekly and 1 patient was receiving a dosage of 3 mg/kg once weekly. Three of the 4 ADA-positive patients had ADA titers monitored from the initiation of treatment, and developed measureable ADA titers within the first 2 months of exposure. One of the 4 ADA-positive patients had persistent ADA titers. ADA titers decreased to undetectable levels in the remaining 3 patients while receiving continued treatment at a dosage of 3 mg/kg once weekly.

Hypersensitivity reactions occurred in all 4 of the ADA-positive patients, whereas they occurred in only 1 of the 3 ADA-negative patients. None of the patients discontinued treatment. In 1 patient, decreased growth velocity in a setting of neutralizing antibodies to KANUMA was observed.

Children and adult patients with LAL deficiency

Five of 35 (14%) KANUMA-treated children and adult patients who completed the 20-week double-blind period of study treatment developed ADA. All patients were receiving 1 mg/kg once every other week. All 5 ADA-positive patients first developed measurable ADA titers within the first 3 months of exposure. Two of the 5 ADA-positive patients had a measurable ADA titer at only one time point. In the 3 patients with measurable ADA titers at multiple time points, ADA titers decreased to undetectable levels during continued treatment. Two patients developed *in vitro* neutralizing antibodies during the open-label

extension phase after 20 weeks and 52 weeks of treatment with KANUMA, respectively. There is no clear association between the development of ADA and decreased efficacy in children and adult patients treated with KANUMA.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described below reflect exposure to KANUMA in 75 patients who received KANUMA in clinical trials:

- Nine infants (5 males, 4 females) who had growth failure or other evidence of rapidly progressive LAL deficiency presenting within the first 6 months of life received KANUMA for up to 165 weeks (median 60 weeks) at escalating doses ranging between 0.35 mg/kg and 5 mg/kg once weekly. The recommended initial dosage for these patients is 1 mg/kg escalating to 3 mg/kg once weekly (see **DOSAGE AND ADMINISTRATION** section).
- 66 children and adult patients with LAL deficiency aged 4 to 58 years (33 males, 33 females) received KANUMA 1 mg/kg every other week up to 36 weeks.

Table 1 summarizes the most common adverse reactions occurring in $\geq 30\%$ of patients with rapidly progressive LAL deficiency presenting within the first 6 months of life receiving KANUMA.

Table 1: Most Common Adverse Reactions* in Infants with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life

Adverse Reactions	KANUMA N=9
	n (%)
Diarrhea	6 (67)
Vomiting	6 (67)
Fever	5 (56)
Rhinitis	5 (56)
Anemia	4 (44)
Cough	3 (33)
Nasopharyngitis	3 (33)
Urticaria	3 (33)

*Reported in at least 30% of infant patients receiving KANUMA

Other less common adverse reactions reported in infants with rapidly progressive disease presenting within the first 6 months of life who received KANUMA included hypotonia, decreased oxygen saturation, retching, sneezing, and tachycardia.

Table 2 summarizes the most common adverse reactions that occurred in $\geq 8\%$ of children and adult patients with LAL deficiency receiving KANUMA at a dosage of 1 mg/kg once every other week during the 20-week double-blind treatment period (see **CLINICAL TRIALS** section).

Table 2: Most Common Adverse Reactions* in Pediatric and Adult Patients with LAL Deficiency

Adverse Reactions	KANUMA N = 36	Placebo N = 30
	n (%)	n (%)
Headache	10 (28)	6 (20)
Fever	9 (25)	7 (23)
Oropharyngeal pain	6 (17)	1 (3)
Nasopharyngitis	4 (11)	3 (10)
Asthenia	3 (8)	1 (3)
Constipation	3 (8)	1 (3)
Nausea	3 (8)	2 (7)

* Reported in at least 8% of children and adult patients receiving KANUMA and at a higher incidence than in patients receiving placebo

Other less common adverse reactions reported in children and adult patients who received KANUMA included anxiety and chest discomfort.

DRUG INTERACTIONS

Overview

No interaction studies have been performed. Because it is a recombinant human protein, sebelipase alfa is an unlikely candidate for cytochrome P450 mediated or other drug-drug interactions.

Drug-Lifestyle Interactions

KANUMA has no or negligible influence on the ability to drive and use machines.

NOC/c DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Infants (< 6 months of age) presenting with rapidly progressive LAL deficiency

The recommended starting dose is 1 mg/kg administered as an intravenous infusion once weekly. Dose escalation to 3 mg/kg once weekly should be considered based on clinical response. Doses were escalated to 5 mg/kg weekly in one infant who exhibited suboptimal growth response.

Children and adults

The recommended dose in children and adults who do not present with rapidly progressive LAL deficiency prior to 6 months of age is 1 mg/kg administered as an intravenous infusion once every other week.

Missed Dose

In case of a missed dose, resume the regular schedule as soon as possible. Scheduling of subsequent doses should be determined by the treating physician and the KANUMA dosing regimen.

Administration

- KANUMA is for intravenous use only.
- The total volume of the infusion should be administered over approximately 2 hours.
- A 1-hour infusion may be considered for those patients receiving the 1 mg/kg dose who tolerate the infusion.
- Consider further prolonging the infusion time for patients receiving the 3 mg/kg dose or those who have experienced hypersensitivity reactions.
- Monitor patients during and for 1 hour after every infusion for any signs or symptoms of anaphylaxis or infusion associated reactions.

Dilution is required before use.

- Each vial of KANUMA is intended for single use only.
- KANUMA has to be diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion using aseptic technique.
- The diluted solution should be administered to patients using a low-protein binding infusion set equipped with an in-line, low-protein binding 0.2 µm filter.

Preparation instructions

KANUMA should be prepared and used according to the following steps.

1. The number of vials to be diluted for infusion should be determined based on the patient's weight and prescribed dose.
2. Round up to the next whole vial and remove the required number of vials from the refrigerator to allow them to reach room temperature.
3. It is recommended to allow KANUMA vials to reach a temperature between 15°C and 25°C to minimize the potential for the formation of sebelipase alfa protein particles in solution.
4. The vials should not be left outside the refrigerator longer than 24 hours prior to dilution for infusion. The vials should not be frozen, heated or microwaved and should be protected from light.
5. The vials should not be shaken. Prior to dilution, the solution in the vials should be inspected visually; the solution should be clear to slightly opalescent, colorless to slightly coloured (yellow). Due to the proteinaceous nature of the product, slight flocculation (e.g., thin translucent fibers) may be present in the vialled solution and are acceptable for use.
6. Do not use if the solution is cloudy, or if foreign particulate matter is present.

7. Up to 10 mL of solution should be slowly withdrawn from each vial and diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion. See the recommended total infusion volumes by weight range (Table 3). The solution should be mixed gently by inversion, and not be shaken.

Table 3: Total infusion volumes*

Weight range (kg)	1 mg/kg dose	3 mg/kg dose**
	Total infusion volume (mL)	Total infusion volume (mL)
1-10.9	10	25
11-24.9	25	50
25-49.9	50	100
50-99.9	100	250
100-120.9	250	500

* The infusion volume should be based on the prescribed dose and should be prepared to a final sebelipase alfa concentration of 0.1-1.5 mg/mL.

** For patients with LAL deficiency presenting within the first 6 months of life who do not achieve an optimal clinical response with a dose of 1 mg/kg.

8. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

There is very limited information on overdosage with KANUMA. In clinical studies, doses of sebelipase alfa were administered up to 5 mg/kg once weekly in one infant and no specific signs or symptoms of overdose were identified.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Lysosomal acid lipase (LAL) deficiency

LAL deficiency is an autosomal recessive lysosomal storage disorder characterized by a genetic defect resulting in a marked decrease or loss in activity of the lysosomal acid lipase (LAL) enzyme.

The primary site of action of the LAL enzyme is the lysosome, where the enzyme normally causes the breakdown of lipid particles including LDL-c.

Deficient LAL enzyme activity results in the lysosomal accumulation of cholesteryl esters and triglycerides. In the liver, this accumulation leads to increased hepatic fat content, and progression to fibrosis, cirrhosis, and complications of end stage liver disease. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. Dyslipidemia due

to impaired degradation of lysosomal lipid is common with elevated LDL and triglycerides and low HDL.

Mechanism of Action

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL).

Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids.

Pharmacodynamics

In clinical trials, after initiation of dosing with KANUMA, breakdown of accumulated lysosomal lipid led to initial increases in LDL-c and triglycerides within the first 2 to 4 weeks of treatment. In general, following increases in LDL-c and triglycerides, these parameters decreased to below pre-treatment values within 8 weeks of treatment with KANUMA.

In all patients with elevated alanine aminotransferase (ALT) values at baseline (82 of 84 patients in clinical trials), reductions in ALT values were observed, generally within 2 weeks after initiation of treatment with KANUMA. Treatment interruption resulted in increases in LDL-c and ALT values and decreases in HDL-c.

Pharmacokinetics

Children and Adults

Mean pharmacokinetic parameters for sebelipase alfa for 65 children (≥ 4 years to < 18 years) and adult patients who received intravenous infusion of KANUMA at 1 mg/kg once every other week in Study LAL-CL02 were estimated using a population pharmacokinetic model, and are summarized in Table 4.

Table 4: Mean (SD) Population Pharmacokinetics Parameters Following Administration of Sebelipase Alfa in children and adult patients receiving 1 mg/kg once every other week

PK Parameters	LAL-CL02 – Children and Adults 1 mg/kg qow					
	4-11 years old N=24		12-17 years old N=23		≥ 18 years old N=18	
	Week ^a 0	Week 22	Week ^a 0	Week 22	Week ^a 0	Week 22
AUC _{SS} (ng·h/mL)	1134 (990)	942 (388)	1436 (606)	1454 (699)	1989 (991)	1861 (599)
C _{max} (ng/mL)	572 (422)	490 (205)	736 (323)	784 (480)	1076.9 (556)	957.0 (303)
T _{max} (h)	1.2 (0.5)	1.3 (0.6)	1.2 (0.6)	1.1 (0.3)	1.4 (0.6)	1.3 (0.6)

CL (L/h)	28.8 (9.1)	31.1 (7.1)	35.1 (10.1)	37.4 (12.4)	36.4 (10.0)	38.2 (12.5)
V _c (L)	3.3 (2.5)	3.6 (3.0)	5.0 (2.4)	5.4 (2.4)	5.5 (1.7)	5.3 (1.6)
t _{1/2} (min)	6.2 (5.5)	5.4 (4.3)	5.7 (4.2)	6.6 (3.7)	5.8 (4.7)	6.6 (3.7)

^aWeek 22 for placebo patients reset to Week 0, i.e. first week of active treatment

AUC_{ss} = area under the plasma concentration time curve at steady-state; CL = clearance; C_{max} = maximum concentration; qow = once every other week; qw = once weekly; t_{1/2} = half-life; T_{max} = time to maximum concentration; V_c = central volume of distribution a Week 22 for placebo patients reset to Week 0, i.e. first week of active treatment

The pharmacokinetic profile of sebelipase alfa was nonlinear with a greater than dose-proportional increase in exposure between 1 and 3 mg/kg based on non-compartmental analysis of data from 9 adults in Study LAL-CL01/LAL-CL04. No accumulation was observed following once weekly or once every other week dosing.

Absorption, Distribution, Metabolism, Excretion

As sebelipase alfa is administered intravenously, characterization of absorption is not applicable.

After multiple-dose once weekly (qw) administration of sebelipase alfa in 9 adult subjects with LAL Deficiency in Study LAL-CL01, the median apparent volume of distribution (V_z) parameter decreased with increasing dose and ranged from 22.0 mL/kg at 3 mg/kg (n=3), 70.0 mL/kg at 1 mg/kg (n=3), and 788.2 mL/kg at 0.35 mg/kg (n=3). The lower V_z at higher doses indicates that more sebelipase alfa was in the systemic circulation at the higher doses.

As a fully-human recombinant human LAL enzyme, sebelipase alfa is expected to be metabolized in the same manner as other endogenous proteins (degraded into small peptides and amino acids via catabolic pathways).

The plasma elimination of sebelipase alfa was rapid at all doses, with no consistent changes over time. After multiple-dose administration at 1 and 3 mg/kg in Study LAL-CL01 (qw administration) and extension study LAL-CL04 (once every other week [qow] administration), the median terminal elimination half-life (t_{1/2}) ranged between 6.6 and 15.4 minutes with the 1 mg/kg dose and between 6.6 and 12.7 minutes with the 3 mg/kg dose. After multiple-dose qw and qow administration of the 1 and 3 mg/kg doses in these studies, the median CL ranged between 541 and 900 mL/kg at the 1 mg/kg dose and was lower (108 to 165 mL/kg) at the 3 mg/kg dose.

There is limited information on the impact of anti-drug antibodies on sebelipase alfa pharmacokinetics.

Infants (<6 months of age)

The pharmacokinetic profile in infants cannot be characterized due to limited pharmacokinetic data (n=4).

Special populations

Hepatic Insufficiency: Sebelipase alfa is a protein and is expected to be metabolically degraded through peptide hydrolysis. Consequently, impaired liver function is not expected to affect the pharmacokinetics of sebelipase alfa. There is a lack of data in patients with severe hepatic impairment.

Renal Insufficiency: Renal elimination of sebelipase alfa is considered a minor pathway for clearance. There is a lack of data in patients with renal impairment.

STORAGE AND STABILITY

Store in a refrigerator (2°C to 8°C). Do not freeze or shake. Protect from light.

Unopened vials are stable for 2 years. Do not use beyond the expiration date stamped on the carton.

KANUMA contains no preservatives; therefore, product should be used immediately after dilution. If immediate use is not possible, the diluted product may be stored up to 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F).

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

KANUMA is supplied as a sterile, preservative-free, non-pyrogenic aqueous concentrate for solution for infusion in single-use vials for intravenous use. Each vial contains 20 mg of sebelipase alfa* in 10 mL. Each mL of solution contains sebelipase alfa (2 mg), citric acid monohydrate (1.57 mg), human serum albumin (10 mg), and trisodium citrate dihydrate (13.7 mg) at pH 5.9.

**Sebelipase alfa is produced in egg white of transgenic Gallus by recombinant DNA (rDNA) technology.*

Packaging:

KANUMA is supplied in a clear glass vial (Type I) with a butyl rubber stopper, and an aluminum seal with a plastic flip-off cap.

KANUMA is available in 20 mg/10 mL (2 mg/mL) solution in single-use vials.

PART II: SCIENTIFIC INFORMATION

KANUMA™ (sebelipase alfa), indicated for the treatment of infants, children and adults diagnosed with lysosomal acid lipase (LAL) deficiency, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KANUMA™, please refer to Health Canada's Notice of Compliance with conditions - drug products web site:
<http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/notices-avis/conditions/index-eng.php>

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: sebelipase alfa

Chemical name: recombinant human lysosomal acid lipase (rhLAL)

Molecular formula and molecular mass: C₁₉₆₈H₂₉₄₅N₅₀₇O₅₅₁S₁₅; 43 kDa (excluding the mass of the carbohydrates).

Physicochemical properties: Sebelipase alfa is a glycoprotein with an approximate mass of 43 kDa (excluding the mass of carbohydrates). The amino acid sequence for sebelipase alfa is the same amino acid sequence for human LAL. The recombinant protein contains 6 N-linked glycosylation sites.

Product Characteristics

KANUMA (sebelipase alfa) is a recombinant human lysosomal acid lipase (rhLAL). Lysosomal acid lipase (EC 3.1.1.13) is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of cholesteryl esters to free cholesterol and fatty acids and the hydrolysis of triglycerides to glycerol and free fatty acids.

KANUMA is supplied as a sterile, preservative-free, non-pyrogenic aqueous solution in single-use vials for intravenous infusion. Each vial contains 20 mg of sebelipase alfa in 10 mL. Each mL of solution contains sebelipase alfa (2 mg), citric acid monohydrate (1.57 mg), human serum albumin (10 mg), and trisodium citrate dihydrate (13.7 mg) at pH 5.9.

Viral Clearance Studies

The viral safety of sebelipase alfa is confirmed by a combination of selection and qualification of vendors, raw material testing, process validation for viral removal and inactivation capacity, and routine in-process testing.

NOC/c CLINICAL TRIALS

An overview of KANUMA (sebelipase alfa) clinical trial in LAL-D population is summarized in Table 5.

Table 5: Overview of sebelipase alfa clinical trials in LAL Deficiency population

Study #	Trial design	Dosage and route of administration	Study subjects (n = number)	Mean age (Range)	Gender
LAL-CL02	Phase III, multi-center, randomized, 20 weeks double-blind, placebo-controlled, followed by open-label up to 130 weeks	Intravenous infusion. 1 mg/kg every other week	66 subjects (36 in treatment group, 30 in placebo group) enrolled. Open label period: ongoing	16.1 years ² (range: 4 - 58)	33M 33 F
LAL-CL03	Phase II / III, open-label, multi-center, single arm Dose escalation study. Infants with rapidly progressive LAL-D presenting with growth failure within the first 6 months of life	Intravenous infusion. 0.35 mg/kg/week (1 subject at 0.2 mg/kg) Escalate to 1 mg/kg/week, or 3 mg/kg/week based on clinical responses	9 subjects enrolled. Clinical trial: ongoing	3.0 months ³ (range: 1.1 - 5.8)	5 M 4 F

M = male; F = female; HSCT= Hematopoietic stem cell transplantation

- (1) Age at Enrollment. Demographics and baseline characteristics were collected in LAL-CL01 and not collected again in LAL-CL04.
 (2) Age at randomization
 (3) Age of subjects at the time of initiation of treatment with sebelipase alfa.

Infants presenting with LAL deficiency

LAL-CL03 was a multicenter, open-label, single-arm study of KANUMA in 9 patients with LAL deficiency with growth failure or other evidence of rapidly progressive disease prior to 6 months of age. The age range at study entry was 1-6 months. Patients received sebelipase alfa at 0.35 mg/kg once weekly for the first 2 weeks and then 1 mg/kg once weekly. Due to suboptimal clinical response, all 6 surviving patients received dose escalation to 3 mg/kg once weekly which occurred between 4 and 88 weeks (median 11 weeks) after starting treatment at 1 mg/kg. One patient, who had a suboptimal growth response at 3 mg/kg in association with the presence of neutralising antibodies, received a dose increase to 5 mg/kg qw.

Efficacy was assessed by comparing the proportion of 9 KANUMA-treated patients who survived beyond 12 months of age in LAL-CL03 with a historical cohort of 21 untreated infants with similar age presenting with LAL deficiency with similar clinical characteristics. In LAL-CL03, 6 of 9 KANUMA-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%) compared to the historical cohort, of which none of 21 patients survived beyond 8 months of age (0% 12-month survival, 95% CI: 0% to 16%).

Following initiation of treatment with KANUMA 1 mg/kg once weekly, 5 of the 6 surviving patients were dose escalated to 3mg/kg once weekly prior to 52 weeks. All 6 surviving patients demonstrated improvements in weight-for-age percentiles by week 52.

With continued treatment beyond 12 months of age, 1 additional patient died at age 15 months. The median age of the 5 surviving KANUMA-treated patients was 20.4 months (range 15.7 to 42.2 months), based on a data cutoff date of 10 June 2014.

Children and adults with LAL deficiency

LAL-CL02 was a multicenter, double-blind, placebo-controlled study in 66 children and adults with LAL deficiency. Patients were randomized to receive KANUMA 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. Patients were stratified for potential confounders (age, ALT levels and use of lipid lowering medications). After completing the double-blind period, each patient was to begin open label treatment with KANUMA at a dose of 1 mg/kg during the extension period. The age range at randomization was 4-58 years old (71% were < 18 years old). For study entry, patients were required to have ALT levels of ≥ 1.5 X upper limit of normal (ULN) (based on age and gender specific normal ranges of the central lab performing the assay) on two consecutive measurements at least 1 week apart. The majority of patients (58%) had LDL-cholesterol >4.9 mmol/L (>190 mg/dl) at study entry, and 24% of patients with LDL-cholesterol >4.9 mmol/L were on lipid lowering medicinal products.

Results for select efficacy endpoints evaluated during the 20-week double-blind period are shown in Table 6.

Table 6: Efficacy endpoints in LAL-CL02

Endpoint	KANUMA (n = 36)	Placebo (n = 30)	Treatment Effect Estimates and 95% CI	P-value ^b
LDL-cholesterol, mean % change from baseline ^a	-28.5%	-5.8%	-22.7% (-31.9, -13.5)	< 0.0001
Non-HDL-cholesterol, mean % change from baseline ^a	-28.1%	-6.3%	-21.8% (-29.3, -14.3)	< 0.0001
Triglycerides, mean % change from baseline ^a	-26.0%	-9.1%	-16.9% (-31.5, -2.3)	0.0238
HDL-cholesterol, mean % change from baseline ^a	19.9%	0.5%	19.4% (12.0, 26.9)	< 0.0001

^aTreatment effects and corresponding 95% confidence intervals are based on a ANCOVA model where age at randomization, baseline ALT and use of lipid-lowering medications are fixed factors and the baseline parameter value is a covariate.

^bThe type I error rate was controlled using a fixed sequence procedure.

The effect of Kanuma on cardiovascular morbidity and mortality has not been established.

Patients treated with KANUMA had larger percentage 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 LAL deficiency has not been established.

Open-label period

Sixty-five of 66 patients entered the open-label period at a KANUMA dose of 1 mg/kg once every other week. Four (4) of 65 patients in the open label period were dose escalated to 3 mg/kg once every other week based on clinical response.

During the open-label extension period, patients treated with KANUMA for up to 36 weeks showed improvements in the efficacy endpoints evaluated during the double-blind period.

NON-CLINICAL TOXICOLOGY

General Toxicology

In repeat-dose toxicity studies conducted in rats and Cynomolgus monkeys, no sebelipase alfa-related adverse effects were observed following once weekly intravenous administration of sebelipase alfa. In 4-week studies, the no-observed-adverse-effect level (NOAEL) was 50 mg/kg body weight in both rats and Cynomolgus monkeys, equivalent to AUC values 267- and 310-fold greater than the human AUC value of 1387 ng•h/mL (at 1 mg/kg body weight once every other week), respectively. In a 6-month study conducted in Cynomolgus monkeys, the NOAEL was 30 mg/kg body weight, equivalent to an AUC value 766-fold greater than the human AUC value. In all studies, the NOAEL was the highest dose tested.

In safety pharmacology studies, no respiratory adverse effects in rats or cardiovascular adverse effects in monkeys were observed following single intravenous doses of sebelipase alfa of up to 50 mg/kg body weight. In addition, no CNS adverse effects were observed in rats following once weekly intravenous administration for 4 weeks at doses up to 50 mg/kg body weight.

Carcinogenicity and Genotoxicity

Studies to evaluate the carcinogenic or genotoxic potential of sebelipase alfa have not been performed.

Reproductive and Developmental Toxicity

In reproductive and developmental toxicity studies, intravenous administration of sebelipase alfa did not result in adverse effects on fertility and reproductive performance in male and female rats (twice weekly dosing), embryo-fetal development in rats (dosing on gestation days [GD] 6, 9, 12, 15, and 17) and rabbits (dosing on GD 7, 10, 13, 16, and 19), or on pre- and post-natal development in rats (dosing on GD 6, 9, 12, 15, 18, and 20 and on post-natal days 4, 7, 10, 14, and 17) at up to the highest doses tested. The NOAEL for reproductive toxicity in rats was 60 mg/kg body weight. The NOAEL for embryo-fetal toxicity was 60 mg/kg body weight in rats and 50 mg/kg body weight in rabbits. The NOAEL for pre- and post-natal developmental toxicity, including reproductive toxicity in the F1 generation, in rats was 60 mg/kg body weight. The AUC values in these studies were 164- and 526-fold greater in rats and rabbits, respectively, than the human AUC value.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

KANUMA™ is indicated for the treatment of infants, children and adults diagnosed with lysosomal acid lipase (LAL) deficiency.

It has been approved *with conditions*. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

KANUMA™
Sebelipase alfa for Intravenous Use (2 mg/mL)

This leaflet is a summary and will not tell you everything about Kanuma. Talk to your healthcare professional if you have any questions about KANUMA.

Read this carefully before you start receiving your medicine, even if you have taken it before. Some of the information may have changed. Keep this pamphlet since you may need to refer to it after starting treatment with Kanuma.

What is KANUMA used for?

KANUMA contains the active substance sebelipase alfa. Sebelipase alfa is similar to the naturally occurring enzyme lysosomal acid lipase (LAL), which the body uses to breakdown fats. It is used to treat infants, children and adults with lysosomal acid lipase deficiency (LAL deficiency).

LAL deficiency is a genetic disease that leads to liver damage, high blood cholesterol, and other complications due to a build-up of certain types of fats (cholesteryl esters and triglycerides).

How does KANUMA work?

KANUMA contains the active substance sebelipase alfa which is similar to the naturally occurring enzyme lysosomal acid lipase (LAL). It works by breaking down the build-up of fat in tissues and organs.

What are the ingredients in KANUMA?

Medicinal ingredients: Sebelipase alfa

Non-medicinal ingredients: Trisodium citrate dehydrate, Citric acid monohydrate, Human serum albumin, Water for injections

KANUMA comes in the following dosage forms:

KANUMA is a concentrated solution to be diluted before use.

KANUMA is supplied in a clear glass vial (Type I) with a butyl rubber stopper, and an aluminum seal with a plastic flip-off cap, containing 10 mL of concentrate.

Do not use KANUMA if:

- Your doctor determined that life-threatening allergic reactions to sebelipase alfa KANUMA or its ingredients have occurred.

Warnings and precautions**Hypersensitivity including anaphylaxis**

- In clinical trials, KANUMA has caused hypersensitivity, some of which were severe. The symptoms include abdominal pain, agitation, fever, chills, diarrhea, dry flaky skin, swelling, high blood pressure, irritability, nausea, swelling of the throat, pale skin, itchy skin, rash, and vomiting. The majority of these reactions occurred during or within 4 hours of the completion of the infusion.
- Anaphylaxis/life-threatening allergic reaction: If you/your child develop signs and symptoms of a severe reaction including chest discomfort, red eyes, difficulty breathing, generalized and itchy rash, excess blood to parts of the body, swelling of eyelids, runny nose, fast heartbeat, rapid breathing and hives, seek immediate medical attention.
- Tell your doctor if you have had a severe allergic reaction to eggs or egg products, as people with a known history of egg allergies were excluded from clinical trials.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given KANUMA. Talk about any health conditions or problems you may have, including if:

- your infant has confirmed multiple-organ failure
- you are pregnant or think you may be pregnant or are planning to have a baby
- you are nursing

Other medicines and KANUMA

Tell your doctor if you or your child are using, have recently used or might use any other medicines.

Driving and using machines

KANUMA has no or negligible influence on the ability to drive and use machines.

KANUMA contains sodium

Each 10 mL vial contains 33 mg sodium. Tell your doctor if you or your child is on a controlled sodium diet.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How KANUMA is given?

Your doctor or nurse will give KANUMA to you or your child by an infusion (drip) into a vein. The medicine will be diluted before being given to you or your child. Each infusion will take approximately 2 hours. You or your child may be monitored by your doctor or nurse for an additional 2 hours after the infusion.

Usual dose:

The dose you or your child receives is based on your or your child's body weight. The recommended dose is 1 mg per kg body weight once every other week intravenously. For infants with signs and symptoms of rapidly deteriorating disease, the recommended starting dose is 1 mg/kg once weekly. Dose adjustments may be considered based on how well you or your child responds to treatment.

Overdose:

The consequences of an overdose are not known with KANUMA.

If you think you were given too much KANUMA contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Contact your physician immediately if you miss a dose of KANUMA. Your physician will decide when you should receive your next dose.

What are possible side effects from using KANUMA?

Like all medicines, KANUMA can cause side effects, although not everybody gets them. If you experience any side effects not listed here, contact your healthcare professional.

The table below summarizes most **SERIOUS** common side effects that occurred in infant patients (< 6 months of age) with LAL-D receiving KANUMA.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
VERY COMMON		
Difficulty breathing		√
Swelling of the throat		√
Rapid breathing		√
Fast heartbeat		√
Chest discomfort		√
Mild swelling of eyelids/red eyes		√
Redness		√
Hives		√
LESS COMMON		
Decreased muscle tone		√
Not enough oxygen in the blood		√
Irregular heartbeat		√

Other common ($\geq 30\%$) side effects occurring in infants include: diarrhea, vomiting, fever, runny nose, stuffy nose, anemia, and cough.

The table below summarizes the common **SERIOUS** side effects that occurred in children and adult patients with LAL-D receiving KANUMA.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
COMMON		
Difficulty breathing		√
Swelling of the throat		√
Rapid breathing		√
Fast heartbeat		√
Chest discomfort		√
Swelling of eyelids/red eyes		√
Redness		√
Hives		√
LESS COMMON		
Anxiety		√

Other common adverse reactions reported in children and adult patients who received KANUMA included fever, stuffy nose, headache, mouth and throat pain, constipation, weakness and nausea.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store in a refrigerator (2°C to 8°C). Protect from light.

DO NOT FREEZE.

Do not use beyond the expiration date stamped on the carton.

Keep out of reach and sight of children.

If you want more information about KANUMA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website <http://alexion.com>, or by calling 1-844-MAP-PAM2 (1-844-627-7262).

This leaflet was prepared by Alexion Pharma GmbH.

Date of Preparation: December 7, 2017