PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrKANUMA®

Sebelipase alfa for injection

2 mg/mL concentrate for solution for infusion

Enzyme Replacement Therapy

Alexion Pharma GmbH
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RECENT MAJOR LABEL CHANGES

4. DOSAGE AND ADMINISTRATION	**2023-09**

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KANUMA® (sebelipase alfa for injection) 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.

1.1 Pediatrics

Pediatrics (0-18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Kanuma in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use. (see ***Section 14: Clinical Trials***)

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

1.2 Geriatrics

Geriatrics (> 65 years of age): The safety and efficacy of Kanuma in patients older than 65 years have not been evaluated and no alternative dosage regimens can be recommended for these patients.

2 CONTRAINDICATIONS

Kanuma is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see ***Section 6 Dosage Forms, Strengths, Composition and Packaging***.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Patients with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life

The recommended starting dose is 1 mg/kg or 3 mg/kg administered as an intravenous (IV) infusion once weekly (qw) , depending on the clinical status of the patient. The higher starting dose of 3 mg/kg qw should be considered based on the severity of the disease and rapid disease progression

Dose escalation should be considered based on suboptimal response to Kanuma based on clinical and biochemical criteria, including, e.g., poor growth (especially mid-upper arm circumference [MUAC]), deteriorating biochemical markers (e.g. liver transaminases, ferritin, C-reactive Protein, and coagulation parameters), persistent or worsening organomegaly, increased frequency of intercurrent infections, and/or persistent worsening of other symptoms (e.g. gastrointestinal symptoms):

- a dose escalation to 3 mg/kg qw should be considered in case of suboptimal clinical response in

patients whose starting dose was 1 mg/kg qw;
- a further dose escalation up to 5 mg/kg qw should be considered in case of suboptimal clinical response.

Further dose adjustments, as a reduction of the dose or an extension of the dose interval, can be made on an individual basis based on achievement and maintenance of therapeutic goals. Clinical studies evaluated doses ranging from 0.35 to 5 mg/kg once weekly, with one patient receiving a higher dose of 7.5 mg/kg once weekly. Doses higher than 7.5 mg/kg have not been studied.

Pediatric and Adult Patients with LAL Deficiency

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 (qow).

Dose escalation to 3 mg/kg qow should be considered based on suboptimal response to Kanuma based on clinical biochemical criteria, including: e.g., poor growth, persistent or deteriorating biochemical markers (e.g., parameters of liver injury [alanine aminotransferase, ALT; aspartate aminotransferase, AST], parameters of lipid metabolism (e.g. total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides [TG]), persistent or worsening organomegaly, and/or persistent worsening of other symptoms (e.g., gastrointestinal symptoms).

4.3 Reconstitution

Dilution is required before use.

- Each vial of Kanuma is intended for single use only.
- Kanuma should 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, colourless to slightly coloured (yellow). Due to the proteinaceous nature of the product, slight flocculation (e.g., thin translucent fibers) may be present in the vialed 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 1). The solution should be mixed gently by inversion and not be shaken.

Table 1: Total Infusion Volumes*

Weight range (kg)	1 mg/kg dose	3 mg/kg dose**	5 mg/kg dose***
	Total infusion volume (mL)	Total infusion volume (mL)	Total Infusion volume (mL)
1-2.9	4	8	12
3-5.9	6	12	20
6-10.9	10	25	50
11-24.9	25	50	150
25-49.9	50	100	250
50-99.9	100	250	500
100-120.9	250	500	600

* 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 who do not achieve an optimal clinical response with a dose of 1 mg/kg.
*** 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 3 mg/kg.

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

4.4 Administration

- Kanuma is for intravenous (IV) 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 beyond 2 hours 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.

4.5 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.

5 OVERDOSAGE

There is very limited information on overdosage with Kanuma. In clinical studies, doses of sebelipase alfa were administered up to 7.5 mg/kg once weekly and no specific signs or symptoms of overdose were identified.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Concentrate for Solution for Infusion 2 mg/mL	Citric Acid Human serum albumin Trisodium citrate dehydrate Water for Injections

Kanuma is supplied in a clear glass vial (Type 1) with a butyl rubber stopper and an aluminum seal with a plastic flip-off cap.

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

Description:

Kanuma 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.

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

7 WARNINGS AND PRECAUTIONS

General

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.

Hypersensitivity reactions, including anaphylactic reactions or anaphylaxis:

- Hypersensitivity reactions, including anaphylactic reactions or 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.

Driving and Operating Machinery

No specific studies have been conducted to assess the direct effect of sebelipase alfa on the ability to drive and use machines. However, adverse effects of sebelipase alfa include dizziness which could affect the ability to drive or use machines.

Immune

As with all therapeutic proteins, there is potential for immunogenicity. In the sebelipase alfa clinical program, patients were routinely tested for anti-sebelipase alfa antidrug antibodies (ADAs) to determine the immunogenicity potential of sebelipase alfa. Patients who tested positive for ADAs were also tested for inhibitory antibody activity. The presence of inhibitory antibody activity has been detected at some postbaseline timepoints in clinical studies (see **Section 8.2 Clinical Trial Adverse Reactions**). Overall, there is no clear relationship between either development of ADAs/inhibitory antibody activity and associated hypersensitivity reactions or suboptimal clinical response.

During clinical trials, a decrease in clinical response associated with the development of inhibitory antibody activity was only observed in 3 patients with a homozygous deletion affecting both alleles of genes Lipase A, lysosomal acid (LIPA) and Cholesterol, 25-Hydroxylase.

Reproductive Health: Female and Male Potential

- **Fertility**

There are no clinical data on the effects of sebelipase alfa on fertility. Animal studies show no evidence of impaired fertility (see **Section 16 Non-Clinical Toxicology**).

7.1 Special Populations

7.1.1 Pregnant Women

There are insufficient data from the use of sebelipase alfa in pregnant women to determine if sebelipase alfa exposure during pregnancy poses any risk to the mother or fetus. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see **Section 16 Non-Clinical Toxicology**). As a precautionary measure, it is preferable to avoid use of Kanuma during pregnancy.

7.1.2 Breast-feeding

There are no data from studies in breast-feeding women. It is not known whether sebelipase alfa is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Kanuma therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

Pediatrics (0-18 years): Safety and effectiveness of Kanuma have been established in pediatric patients aged 1 month and older. Clinical trials with Kanuma were conducted in 88 of 125 pediatric patients (range 1 month to < 18 years old at the time of first dose).

7.1.4 Geriatrics

Geriatrics (>65 years of age): The safety and efficacy of Kanuma in patients older than 65 years have not been evaluated.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The data described below reflect exposure to Kanuma in 125 patients who received Kanuma at doses ranging from 0.35 mg/kg once every other week (qow) to 7.5 mg/kg once weekly (qw) in clinical studies (see Section 14 Clinical Trials). Patients were between 0.5 month and 59 years old (70% were < 18 years old) at the time of first treatment with Kanuma and included 68 males and 57 females.

In infants, the safety of Kanuma was evaluated in an open-label, single-arm, Phase 2/3 study (Study LAL CL03) and in an open-label, Phase 2 study (Study LAL-CL08). In children and adults (3 to 58.8 years), the safety of Kanuma was evaluated in a randomised, placebo-controlled Phase 3 study (Study LAL CL02), an open-label, single-arm, Phase 2 study (LAL-CL01/LAL-CL04), and an open-label, single-arm, Phase 2

study (LAL-CL06). Overall, 102/106 (96.2%) children and adult patients (58 males, 48 females) have received sebelipase alfa at a dosage regimen of 1 mg/kg qow, with a median duration of exposure of 33.199 months (5.98, 59.14 months). The majority of these 102 patients were from Study LAL-CL02 (66/102, 64.7%).

A majority (17/19, 89.5%) of infants (10 males, 9 females) received sebelipase alfa at a dosage regimen of 1 mg/kg qw, with escalating doses ranging between 0.35 mg/kg and 5 mg/kg once weekly. The median duration of exposure was 35.614 months (0.03, 60.19 months).

The most serious adverse reactions experienced by 4% of patients in clinical trials were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival hyperemia, dyspnea, hyperemia, eyelid edema, severe respiratory distress, tachycardia, tachypnea, irritability, flushing, pruritus, urticaria, rhinorrhea, stridor, hypoxia, pallor and diarrhea.

8.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Tabulated list of adverse reactions

Table 3 summarizes the most common adverse reactions occurring in 2 or more patients with rapidly progressive LAL deficiency presenting within the first 6 months of life receiving Kanuma.

Table 3: Most Common Adverse Reactions in Infants with LAL Deficiency

MedDRA System organ class	MedDRA Preferred Term	Kanuma N = 19 n (%)
Immune system disorders	Hypersensitivity[a]	13 (68)
	Anaphylactic reaction[b]	3 (16)
Eye disorders	Eyelid oedema	3 (16)
Cardiac disorders	Tachycardia	10 (53)
Respiratory, thoracic and mediastinal disorders	Respiratory distress	8 (42)
Gastrointestinal disorders	Diarrhea	15 (79)
	Vomiting	15 (79)
Skin and subcutaneous tissue disorders	Rash	7 (37)
	Rash maculo-papular	2 (11)
General disorders and administration site conditions	Hyperthermia	2 (11)
	Pyrexia	15 (79)
Investigations	Body temperature increased	4 (21)
	Oxygen saturation decreased	2 (11)
	Blood pressure increased	2 (11)

	Heart rate increased	3 (16)
	Respiratory rate increased	4 (21)
	Drug specific antibody present	2 (11)

[a]May include: irritability, agitation, vomiting, urticaria, eczema, pruritus, pallor, and drug hypersensitivity
[b]Occurred in 3 infant patients treated in clinical trials. Based on Preferred Term 'anaphylactic reaction' and application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis.

Table 4 summarizes the most common adverse reactions that occurred in 2 or more children and adult patients with LAL deficiency receiving Kanuma.

Table 4: Most Common Adverse Reactions in Pediatric and Adult Patients with LAL Deficiency

MedDRA System organ class	MedDRA Preferred Term	Kanuma N=106 n (%)	Placebo* N=30 n (%)
Immune system disorders	Anaphylactic reaction[a]	2 (2)	0
	Hypersensitivity[b]	46 (43)	0
Nervous system disorders	Dizziness	13 (12)	1 (3)
Cardiac disorders	Tachycardia	3 (3)	0
Vascular disorders	Hyperemia	2 (2)	0
	Hypotension	2 (2)	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	7 (7)	1 (3)
Gastrointestinal disorders	Abdominal pain	34 (32)	1 (3)
	Diarrhea	41 (39)	5 (17)
	Abdominal distension	3 (3)	0
Skin and subcutaneous tissue disorders	Rash	9 (8)	3 (10)
	Rash papular	5 (5)	1 (3)
General disorders and administration site conditions	Fatigue	12 (11)	2 (7)
	Pyrexia	45 (42)	6 (20)
	Chest discomfort	4 (4)	0
	Infusion site reaction[c]	5 (5)	0
Investigations	Body temperature increased	6 (6)	1 (3)

[a] Occurred in 2 patients treated in clinical trials. Based on Preferred Term 'anaphylactic reaction' and application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis
[b] May include: chills, eczema, laryngeal oedema, nausea, pruritus, urticaria
[c] Includes: Infusion site extravasation, infusion site pain and infusion site urticaria
*Only study LAL-CL02 contained a comparator arm with a 20-week double-blind treatment period.

Description of selected adverse reactions

Hypersensitivity reactions including anaphylaxis

In clinical trials, 5 of 125 (4%) patients (3 of 19 infants and 2 of 106 children/adults) treated with Kanuma experienced serious signs and symptoms consistent with anaphylaxis to Kanuma. These patients experienced reactions during infusion. Signs and symptoms included chest discomfort, conjunctival hyperaemia, dyspnea, eyelid edema, hyperemia, severe respiratory distress, tachycardia,

tachypnea, irritability, flushing, pruritus, urticaria, rhinorrhea, stridor, hypoxia, pallor and diarrhea. Anaphylaxis has occurred as late as 1 year after treatment initiation.

In clinical trials, 59 of 125 (47%) Kanuma-treated patients, including 13 of 19 (68%) infants and 46 of 106 (43%) children and adults, experienced at least 1 hypersensitivity reaction (selected using a validated, pre-determined set of terms grouped together to identify potential hypersensitivity reactions). Signs and symptoms either consistent with or that may be related to a hypersensitivity reaction, occurring in two or more patients, included but were not limited to abdominal pain, agitation, bronchospasm, chills, diarrhea, eyelid edema, eczema, face edema, hypertension, irritability, laryngeal edema, lip swelling, nausea, edema, pallor, pruritus, pyrexia/body temperature increased, rash, tachycardia, urticaria and vomiting. The majority of reactions occurred during or within 4 hours of the completion of the infusion.

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 general occurred within the first 2 to 4 weeks and improved within a further 8 weeks of Kanuma treatment. (see **Section 10.1 Mechanism of Action**)

Immunogenicity

There is potential for immunogenicity (see **Section 7 Warnings & Precautions**). Among 125 patients with LAL Deficiency enrolled in the clinical studies, 19/125 (15.0%) patients tested positive for anti-drug antibodies (ADAs) at some timepoint after starting treatment with Kanuma. For children and adult patients, ADA positivity was transient with generally low titres of ADAs reported. Persistence of ADA positivity was observed for 10 out of 19 infants and persistence of high titre ADAs was observed for 3 of the 10 infants. Among those 19 patients, 11 (58%) also showed the presence of inhibitory antibody activity (NAbs) at some postbaseline timepoint. There was no clear relationship between development of ADAs/NAbs and associated hypersensitivity reactions or suboptimal clinical response. In clinical studies, 3 patients homozygous for a deletion affecting both alleles of genes Lipase A, lysosomal acid [LIPA] and Cholesterol 25-Hydroxylase developed inhibitory antibody activity associated with a suboptimal clinical response (**Section 7, Warnings & Precautions**). These patients underwent either immunomodulatory therapy alone or in combination with hematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT), resulting in improved clinical response to Kanuma.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

See Clinical Trial Adverse Reactions Section above.

8.5 Post-Market Adverse Reactions

Overall, the safety data collected in the post-marketing setting for sebelipase alfa has been consistent with the safety profile observed during the clinical trial experience. No new safety concerns have been identified.

9 DRUG INTERACTIONS

9.2 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.

9.3 Drug-Behavioural Interactions

No specific studies have been conducted to assess the direct effect of sebelipase alfa on the ability to drive and use machines. (See **Section 7, Warnings & Precautions**)

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

LAL Deficiency is a rare disease associated with significant morbidity and mortality, which affects individuals from infancy through adulthood. 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. LAL Deficiency presenting in infants is a medical emergency with rapid disease progression over a period of weeks that is typically fatal within the first 6 months of life.

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 a variety of cell populations, organs and organ systems, among them hepatocytes and macrophages. In the liver, this accumulation leads to hepatomegaly, increased hepatic fat content, transaminase elevation signaling chronic liver injury, and progression to fibrosis, cirrhosis, and complications of end-stage liver disease. In the spleen, LAL Deficiency results in splenomegaly, anemia, and thrombocytopenia. 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, associated with increased liver fat content and transaminase elevations. In addition to liver disease, patients with LAL Deficiency experience increased risk for cardiovascular disease and accelerated atherosclerosis. The enzyme deficiency also leads to reduced generation of free cholesterol, which results in increased production of apoB-containing lipoproteins and reduced

HDL-C particle formation.

Lipid-modifying agents such as HMG-CoA reductase inhibitors or PCSK9 inhibitors may lead to reductions in LDL-C in patients with LAL Deficiency but do not impact the associated liver disease progression as these agents do not address the underlying enzyme deficiency.

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL), which 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. Replacement of LAL enzyme activity leads to reductions in liver fat content and transaminases, and enables metabolism of cholesteryl esters and triglycerides in the lysosome, leading to reductions in LDL-C and non- HDL-C, triglycerides, and increases in HDL-C. Improvement in growth occurs as a result of substrate reduction in the intestine.

In a rat disease model of LAL Deficiency that recapitulates many aspects of the human disease, improvements in serum transaminases and reduction in hepatomegaly, improvement in liver pathology including reduction in liver fibrosis, restoration of normal growth, and prolonged survival were observed following treatment with sebelipase alfa.

10.2 Pharmacodynamics

In clinical trials, after initiation of dosing with Kanuma, breakdown of accumulated lysosomal

lipid led to initial increases in circulating cholesterol and triglycerides within the first 2 to 4 weeks of treatment. Improvements in dyslipidemia related to LAL Deficiency were seen within a further 8 weeks of treatment with Kanuma and were accompanied by improvements in ALT by Week 4 that were maintained through Week 20 in all patients treated with Kanuma. These improvements were maintained until Week 260 for infants and Week 256 for children and adults treated 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.

10.3 Pharmacokinetics

Children and Adults

The pharmacokinetics of Kanuma in children and adults were determined using a population pharmacokinetic analysis of 71 patients with LAL Deficiency who received intravenous infusion of Kanuma across 3 clinical studies (LAL-CL02, LAL-CL04, and LAL-CL06) (Table 5). Based on a non-compartmental analysis of data, the pharmacokinetics of sebelipase alfa are nonlinear with a greater than dose-proportional increase in exposure observed between the 1 and 3 mg/kg doses. No accumulation is seen at 1 mg/kg (once weekly or once every other week) or 3 mg/kg once weekly.

Table 5: Summary of Pharmacokinetic Parameters for Repeated Administrations of 1 mg/kg Sebelipase Alfa in Patients With LAL Deficiency by Age Group

Parameter	Children Age 2 to < 18 years (N = 44) Mean (CV%)	Adults ≥ 18 years (N = 24) Mean (CV%)
CL (L/h)	26.2 (50.7)	37.7 (39.4)
Q (L/h)	1.57 (40.1)	1.68 (38.8)
Vc (L)	3.91 (53.6)	6.45 (95.1)
V_{ss} (L)	9.89 (21.2)	12.4 (49.3)
$t_{½\beta}$ (h)	3.51 (61.1)	3.05 (46.7)

Note: Data for children are from Studies LAL-CL02 and LAL-CL06, and data for adults are from Studies LAL-CL02, LAL-CL04, and LAL-CL06.
CL = clearance; PK = pharmacokinetic(s); Q = peripheral clearance; $t_{½\beta}$ = terminal elimination half-life; Vc = central volume of distribution; V_{ss} volume of distribution at steady-state.

Predicted exposure parameters of sebelipase alfa from clinical trials are presented by age group in Table 6.

Table 6: Summary of Exposure Parameters of Sebelipase Alfa by Age Group in Patients With LAL Deficiency Based on Simulations

Parameter Statistic	Children (Age 2 < 18 years) 1 mg/kg (N = 44)	Adults (Age ≥ 18 years) 1 mg/kg (N = 24)	Overall 1 mg/kg (N = 72)
AUC_{ss} (ng × h/mL) Mean (CV%)	1560 (57.0)	2070 (41.4)	1670 (55.4)
$C_{max,ss}$ (ng/mL) Mean (CV%)	746 (56.7)	993 (39.5)	799 (54.8)

Note: Data for children are from Studies LAL-CL02 and LAL-CL06, and data for adults are from Studies LAL-CL02, LAL-CL04, and LAL-CL06.
AUC_{ss} = area under the curve under steady state; $C_{max,ss}$ = maximum concentration under steady state; CV = coefficient of variation; LAL = lysosomal acid lipase.

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

Distribution: 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 (Vz) parameter decreased with increasing dose and ranged from 22.0mL/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 Vz at higher doses indicates that more sebelipase alfa was in the systemic circulation at the higher doses.

Metabolism: 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).

Elimination: 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.

Duration of Effect: 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 and Conditions

Geriatrics: Sebelipase alfa has not been investigated in patients aged 65 years or older.

Ethnic origin: There is limited information on sebelipase alfa pharmacokinetics in non-Caucasian ethnic groups.

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.

Immunogenicity

Antidrug antibody (ADA) has been observed in LAL-D patients (see **Section 8.2 Clinical Trial Adverse Reactions**). For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported. No apparent correlation of antibody development to altered sebelipase alfa pharmacokinetics was observed.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C to 8°C). Unopen 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).

12 SPECIAL HANDLING INSTRUCTIONS

Do not freeze or shake. Protect from light.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: sebelipase alfa

Chemical name: recombinant human lysosomal acid lipase (rhLAL)

Molecular formula: $C_{1968}H_{2945}N_{507}O_{551}S_{15}$; 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 Inactivation

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.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Table 7: Summary of patient demographics for completed clinical trials in LAL-D

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex Gender

LAL-CL02	Phase III, multi-center, randomized, 20 weeks double-blind, placebo-controlled, followed by open-label extension	Intravenous infusion, 1 mg/kg every other week Duration: Double-blind period- 20 weeks Open-label period- up to 234 weeks	66 subjects (36 in treatment group, 30 in placebo group enrolled.	16.6 years[2] (range: 4 -58)	33 M 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 Duration of treatment: Up to 5 years	9 subjects enrolled.	3.0 months[3] (range: 1.1 - 5.8)	5 M 4 F
LAL-CL04	Phase II open-label extension study for adult subjects who successfully completed dose-ranging study Study LAL-CL01	Intravenous infusion 0.35, 1, or 3 mg/kg qw for 4 weeks; 1 or 3 mg/kg qow thereafter Duration of treatment: Up to 5 years	8 subjects	15.6 years[4] (4.1, 42.4)	6 M 2 F

LAL-CL06	Phase II, multi-center, open-label	Intravenous infusion 1 mg/kg qow, dose escalation to 3 mg/kg qow, and subsequently to 3 mg/kg qw Duration of treatment: Up to 144 weeks	31 subjects	16.9 years[3] (3.0, 54.8)	19 M 12 F
LAL-CL08	Phase II, open-label, multi-center repeat dose in infants with rapidly progressive LAL-D	Intravenous Infusion Starting dose 1 mg/kg qw; dose escalation to 3 mg/kg qw , and further to 5 mg/kg or 7.5 mg/kg qw Duration of treatment: Up to 3 years	10 subjects	2.7 months[3] (0.5, 4.1)	5 M 5 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.
(4) Age at time of diagnosis

Infants presenting with LAL Deficiency

Study LAL-CL03

LAL-CL03 was a multicenter, open-label, single-arm study of Kanuma in 9 patients under 24 months of age with a confirmed diagnosis of LAL Deficiency and growth failure with onset before 6 months of age. Patients also had rapidly progressive liver disease and severe hepatosplenomegaly. The median age of patients at the time of initiation of dosing was 3.0 months (range = 1 to 6 months). The median duration of exposure to sebelipase alfa was 55.6 months per patient (range = 0.03 to 60 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 occurred as early as 1 month and up to 20 months after starting treatment at 1 mg/kg. Two of these 6 patients were subsequently dose escalated to 5 mg/kg once weekly, as allowed by the study protocol.

Study LAL-CL08

Study LAL-CL08 was a multicentre, open-label study of Kanuma in 10 infants ≤ 8 months of age with confirmed diagnosis of rapidly progressive LAL Deficiency requiring urgent intervention, including but not restricted to marked abdominal distension and hepatomegaly, failure to thrive, disturbance of coagulation, severe anemia, and/or a sibling with a rapidly progressive course of LAL Deficiency.

The median age of the study patients on the date of their first infusion of sebelipase alfa was 3 months (range: 0.5 to 4months). Eight (80%) patients completed the study. The median duration of exposure was 34months (range: 1to 37 months). Two (20%) patients were considered early terminated due to death. All 10 patients received a starting dose of 1 mg/kg qw. The 9 patients who survived beyond Week 4 each received a dose escalation to 3 mg/kg qw, and 7 of these patients received a subsequent dose escalation to 5 mg/kg qw, as allowed per study protocol. One patient received a further dose escalation to 7.5 mg/kg qw. Two patients had a subsequent dose reduction, which occurred after successful transplant procedures; one patient received a BMT and the other patient received a HSCT.

Children and adults with LAL Deficiency

Study LAL-CL02

Study 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. The mean age at randomization was 16.6 years, range 4-58 years (36% were <12 years old and 71% were <18 years old). For study entry, patients were required to have ALT levels of ≥1.5 X upper limit of normal (ULN). 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. Of the 32 patients who had a liver biopsy at study entry, 100% had fibrosis and 31% had cirrhosis. The age range of patients with biopsy evidence of cirrhosis was 4-21 years.

Study LAL-CL01/LAL-CL04

LAL-CL01 was a dose-ranging study followed by open-label safety and extension study LAL-CL04 in adult patients with liver dysfunction due to LAL-D. Eight of nine patients transitioned from Study LAL-CL01 after 4 weeks of treatment (0.35 mg/kg qw, 1 mg/kg qw, or 3 mg/kg qw) to Study LAL-CL04 (1 mg/kg qow or 3 mg/kg qow), with 5 patients receiving a dose of 1 mg/kg qow and 3 patients receiving a dose of 3 mg/kg qow for a duration of up to 5 years.

Study LAL-CL06

LAL-CL06 was a multicenter, open-label study in 31 children and adults with LAL Deficiency and was designed to include patients who may have been ineligible for previous clinical studies due to age, disease progression, previous treatment by hematopoietic stem cell or liver transplantation, less common disease manifestations, or disease characteristics that precluded participation in a placebo-controlled study. At least 4 patients in the study were to be between the age of 2 and 4 years. The study consisted of a screening period of up to 45 days, a treatment period of up to 96 weeks and an expanded treatment period of up to 48 weeks (for a total of up to 144 weeks of treatment). The median duration of exposure to sebelipase alfa was 33.15 months (range: 14 to 33.5 months).

Twenty-eight of the 31 patients completed the 96-week treatment period (1 patient discontinued treatment at Week 61 due to withdrawal of consent, 1 patient at Week 64 due to pregnancy and 1 patient at Week 76 due to transition to commercial therapy). Twenty-five of the 28 patients who completed the 96-week treatment period continued to receive treatment with sebelipase alfa during the extended treatment period. All 31 patients received sebelipase alfa at a starting dose of 1 mg/kg qow. Thirteen of the 31 patients received dose escalations as allowed by the study protocol. Eleven of these 13 patients had an initial dose escalation from 1 mg/kg qow to 3 mg/kg qow, and 4 of these patients had a further dose escalation to 3 mg/kg qw.

Study Results

Infants presenting with LAL Deficiency

Study LAL-CL03

Efficacy was assessed by comparing the survival experience of Kanuma-treated patients who survived beyond 12 months of age in LAL-CL03 with a historical cohort of untreated infants 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%). With continued treatment until 48 months of age, 1 additional patient died at age 15 months.

Kanuma resulted in improvements in alanine aminotransferase (ALT) / aspartate aminotransferase (AST) levels (indicating a decrease in liver injury) and in weight gain; improvements were noted within the first several weeks of treatment and were maintained through the end of the study. From baseline to Week 240 (Month 60), the mean reductions for ALT and AST were -43.5 U/L and -45.25U/L, respectively. From baseline to Week 240, mean weight-for-age percentile improved from 12.74% to 43.17% and mean serum albumin levels increased from 26.9 g/L to 31.98 g/L. Dose escalation to 3 mg/kg once weekly was associated with additional improvements in weight gain, lymphadenopathy and serum albumin.

Study LAL-CL08

The percentages (95% confidence intervals [CIs]) of patients surviving to 12, 18, 24, and 36 months of age were 90% (55.5%, 99.7%), 80% (44.4%, 97.5%), 80% (44.4%, 97.5%), and 75% (34.9%, 96.8%), respectively. Two patients were <36 months of age at the time of study completion and were excluded from the analysis for survival to 36 months. Reductions in AST, gamma glutamyltransferase (GGT), and total bilirubin and increases in serum albumin were observed in the overall study population, with median changes from baseline to last assessment of -34.5 U/L, -66.67 IU/L, -63.64 µmol/L, and 33.33 g/L, respectively.

Height and weight increased gradually. Median changes from baseline in Z-scores for weight for height (WFH) were decreases through Week 4. Starting from Week 24, there were consistent improvements. At Week 144, the median change (range) in Z-scores for WFH was 3.07 (-1.0, 5.3) from baseline.

Children and adults with LAL Deficiency

Study LAL-CL02

The following endpoints were assessed: normalization of ALT, normalization of AST, decrease in LDL-cholesterol, decrease in non-HDL-cholesterol, decrease in triglycerides, increase in HDL-cholesterol,

decrease in liver fat content assessed by multi-echo gradient echo (MEGE) MRI, decrease in liver volume assessed by MRI, and improvement in hepatic steatosis measured by morphometry.

At the completion of the 20-week double-blind period of the study, a statistically significant improvement in multiple efficacy endpoints was observed in the Kanuma-treated group as compared to the placebo group, as shown in Table 8. Normalization of ALT was achieved in 31% (11/36) of Kanuma-treated patients and 7% (2/30) placebo patients. LDL-cholesterol normalization (<130 mg/dL) was achieved in 40.6% (13/32) of Kanuma-treated patients and 6.7% (2/30) of placebo patients with abnormal baseline LDL-cholesterol (≥130 mg/dL) at the end of the 20-week double-blind period.

Table 8: Efficacy Endpoints in Study LAL-CL02

Endpoint	**Sebelipase alfa (n = 36)**	**Placebo (n = 30)**	**P-value[d]**
Primary Endpoint			
Normalisation of ALT[a]	31%	7%	0.0271
Secondary Endpoints			
LDL-cholesterol, mean % change from baseline	-28%	-6%	< 0.0001
Non-HDL-cholesterol, mean % change from baseline	-28%	-7%	< 0.0001
Normalisation of AST[b]	42%	3%	0.0003
Triglycerides, mean % change from baseline	-25%	-11%	0.0375
HDL-cholesterol, mean % change from baseline	20%	-0.3%	< 0.0001
Liver fat content[c], mean % change from baseline	-32%	-4%	< 0.0001

[a] Proportion of patients who achieved normalisation defined as 34 or 43 U/l, depending on age and gender.
[b] Proportion of patients who achieved normalisation defined as 34-59 U/l, depending on age and gender. Evaluated in patients with abnormal baseline values (n = 36 for sebelipase alfa; n = 29 for placebo).
[c] Evaluated in patients with MEGE-MRI assessments performed (n = 32 for sebelipase alfa; n = 25 for placebo).
[d] P-values are from Fisher's exact test for normalisation endpoints and Wilcoxon rank-sum test for all other endpoints.

Paired liver biopsies at Baseline and Week 20 were available in a subset of patients (n = 26). Of patients with paired liver biopsies, 63% (10/16) of Kanuma-treated patients had improvement in hepatic steatosis (at least ≥ 5% reduction) as measured by morphometry compared to 40% (4/10) of placebo patients. This difference was not statistically significant.

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

Patients who participated in Study LAL-CL02 were eligible to continue treatment in an open-label periods of the study. 66 patients entered the first open-label period during which all patients received Kanuma at a dosage regimen of 1 mg/kg once every other week. In patients who had received Kanuma during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels.

Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period of the study. Consistent with what was observed in Kanuma-treated patients during the double-blind period, initiation of treatment with Kanuma during the open-label period produced improvements in ALT levels and in lipid parameters including LDL-cholesterol and HDL-cholesterol levels.

Improvements in ALT levels and in lipid parameters (LDL-cholesterol and HDL-cholesterol levels) were maintained during the open-label expanded treatment period for up to 256 weeks (5 years), with overall mean treatment duration of 42.5 months.

Study LAL-CL01/LAL-CL04

Improvements in serum transaminase and lipid levels were sustained through the 260-week treatment period. Increases in serum transaminases and LDL-cholesterol and decreases in HDL-cholesterol were observed during the period in which patients were off treatment with Kanuma.

Study LAL-CL06

Serum transaminases (ALT/AST) were elevated at Baseline in approximately 75% of patients, and approximately half of the patients had levels > 1.5 x ULN. Reductions in ALT and AST were evident by Week 4 and were sustained during long-term treatment with sebelipase alfa, with mean changes from Baseline to Week 144 of -40.3 U/L (-32.0%) and -42.2 U/L (34.2%), respectively.

Transient increases in total cholesterol, non-HDL-C, and LDL-C were observed shortly after initiation of treatment (Week 4), and then levels dropped to below baseline by the next assessment at Week 8. This observation is consistent with mobilization of accumulated lipid substrates from the affected tissues and has been observed in previous clinical studies of sebelipase alfa. Continued long-term therapy with sebelipase alfa produced an improvement in the serum lipid profile, with mean changes from Baseline to Week 144 in LDL-C, triglycerides, and non-HDL-C of -54.2 mg/dL, -47.5 mg/dL, and -63.7 mg/dL, respectively, and mean percent changes of -31.2%, -19.1%, and -30.3%, respectively. An increase in HDL-C levels was observed, with a mean increase from Baseline to Week 144 of 10.2 mg/dL and a mean percent increase of 39.7%.

Liver biopsy data in children and adult population

In Studies LAL-CL02 and LAL-CL06 liver biopsies were evaluable for Ishak Fibrosis Scores for 59 patients at baseline and 38 patients at Month 12 (meaning after 12 months of exposure to sebelipase alfa). There were 36 patients who had Ishak scores at both baseline and Month 12.

At baseline, 3 of 59 patients (5%) had Ishak scores of 0 (no fibrosis) and 15 (25%) patients had Ishak scores of 6, indicating established or advanced cirrhosis. Ishak scores improved by Month 12, when 9 of 38 patients (24%) had Ishak scores of 0 and 7 patients (18%) had Ishak scores of 6. Overall, 31 of 36 patients (86.1%) had Ishak scores that had improved or did not progress at Month 12. There were 10 patients (28%) with a ≥ 2 point reduction in Ishak scores from baseline to Month 12, including changes from stage 2 to stage 0, from stage 3 to stages 1 and 0, from stage 5 to stage 0 (> 3-point reduction), and from stage 6 to stages 4 and 3. Globally, these 10 patients with a ≥ 2-point reduction in Ishak stage scores had also substantial improvements in other study-related assessments, such as reduction in ALT, LDL-C, HDL-C, and non-HDL-C over the same time period.

Based on eligibility criteria, patients in Study LAL-CL06 generally were expected to have more cirrhosis and intractable disease than patients in Study LAL-CL02, due to more advanced liver disease at baseline. The liver biopsy findings in Studies LAL-CL02 and LAL-CL06 were consistent with each other. At baseline, in both studies, the majority of patients had microvesicular steatosis (57 of 59, 97%), including 45 of 59 patients (76%) with a score 4 (scale of 0-4, with severe is defined as 4 and equivalent to > 66% hepatocyte involvement/replacement), as expected with the underlying disease. At Month 12, the percentage of patients with severe microvesicular steatosis were decreased, with 17 of 38 patients (45%) having > 66% hepatocyte involvement/replacement (score 4).

16 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:
Studies to evaluate the carcinogenic potential of sebelipase alfa have not been performed.

Genotoxicity:
Studies to evaluate the genotoxic potential of sebelipase alfa have not been performed.

Reproductive and Developmental Toxicology:
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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

KANUMA®
sebelipase alfa for injection

Read this carefully before you start taking **Kanuma** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **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 patients 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: Citric acid monohydrate, Human serum albumin, Trisodium citrate dehydrate, Water for injection

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 Kanuma or its ingredients have occurred.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Kanuma. Talk about any health conditions or problems you may have, including if you:
- 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
- you or your child is on a controlled sodium diet

Other warnings you should know about:
<u>Hypersensitivity including anaphylaxis</u>
- 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.

Driving and using machines
Kanuma may have a minor influence on the ability to drive and use machines. Adverse effects of sebelipase alfa include dizziness which could affect the ability to drive or use machines.

Anti-drug antibodies
The development of blood proteins against Kanuma, also called anti-drug antibodies, may occur during the treatment. Talk to your doctor if you feel that Kanuma is no longer working as well for you.

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

How to take Kanuma:
Your doctor or nurse will give Kanuma to you or 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 or 3 mg/kg once weekly. Dose adjustments may be considered based on how well you or your child responds to treatment.

Overdose:
There is very limited information on overdosage with Kanuma.

If you think you, or a person you are caring for, have taken too much Kanuma, contact a 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?
These are not all the possible side effects you may feel when taking Kanuma. If you experience any side effects not listed here, contact your healthcare professional.

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		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Stomachache	**√**		
COMMON			
Anaphylactic reaction (severe allergic reaction)[a]		**√**	
Hypersensitivity[b]		**√**	

[a] Occurred in 2 patients treated in clinical studies. Based on Preferred Term 'anaphylactic reaction' and application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis.
[b] May include: chills, eczema, swelling of the throat, nausea, itching, and hives.

Other very common (≥ 1/10) adverse reactions reported in children and adult patients who received Kanuma included dizziness, diarrhea, tiredness and fever.

Other common (≥ 1/100 to < 1/10) adverse reactions reported in children and adult patients who received Kanuma included fast heartbeat, skin redness, low blood pressure, shortness of breath, stomach bloating, rash, raised rash, chest discomfort, reaction at the infusion site, and body temperature increased.

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		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Difficulty breathing		**√**	
Hypersensitivity[a]		**√**	
Anaphylactic reaction (severe allergic reaction)[b]		**√**	
Diarrhea		**√**	
Vomiting		**√**	
Body temperature increased		**√**	
Fever		**√**	
Development of blood proteins		**√**	

[a] May include: irritability, agitation, vomiting, urticaria, eczema, pruritus, pallor, and drug hypersensitivity
[b] Occurred in 3 infant patients treated in clinical studies. Based on Preferred Term 'anaphylactic reaction' and application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis.

Other very common (≥ 10%) side effects occurring in infants include: swelling of eyelids, fast heartbeat, rash, raised rash, decreased oxygen in the blood, blood pressure increased, and rapid breathing.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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 www.alexion.com, or by calling 1-844-MAP-PAM2 (1-844-627-7262)

This leaflet was prepared by Alexion Pharma GmbH.
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