

AUSTRALIAN PRODUCT INFORMATION – KANUMA® (SEBELIPASE ALFA *RCE*) CONCENTRATED SOLUTION FOR INTRAVENOUS INFUSION

1 NAME OF THE MEDICINE

Sebelipase alfa *rce*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Kanuma is supplied as a single-use vial containing 20 mg of sebelipase alfa *rce* (2 mg/mL).

For the full list of excipients, see Section 6.1 - List of Excipients.

3 PHARMACEUTICAL FORM

Concentrated solution for intravenous infusion. Kanuma is a clear to slightly opalescent, colourless to slightly coloured solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Kanuma (sebelipase alfa *rce*) is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D).

4.2 DOSE AND METHOD OF ADMINISTRATION

It is important to initiate treatment as early as possible.

Kanuma is for intravenous use only. The total volume of the infusion should be administered over approximately 2 hours. Infusion over 1 hour may be considered after patient tolerability is established. The infusion period may be extended in the event of dose escalation.

For instructions on the preventive measures and monitoring of hypersensitivity reactions, see section 4.4 – *Special Warnings and Precautions for Use; Hypersensitivity reactions, including anaphylaxis.*

Recommended Dose

Infants (< 6 months of age) presenting with LAL-D

The recommended starting dose in infants < 6 months of age presenting with rapidly progressive LAL-D is 1 mg/kg administered as an IV infusion once weekly.

Dose escalations maybe considered based on suboptimal response to clinical and biochemical criteria, including, poor growth, deteriorating biochemical markers (e.g. liver transaminases, ferritin, C-reactive protein, and coagulation parameters), persistent or worsening organomegaly, increased frequency of intercurrent infections, and persistent or worsening of other symptoms (e.g. gastrointestinal symptoms).

A dose escalation to 3 mg/kg should be considered in case of suboptimal clinical response.

A further dose escalation up to 5 mg/kg may be considered in case of persistent 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 1 patient receiving a higher dose of 7.5 mg/kg once weekly (*see Section 5.1 PHARMACODYNAMIC PROPERTIES*). Doses higher than 7.5 mg/kg have not been studied.

Children and adults presenting with LAL-D

The recommended dose in children and adults presenting with LAL-D is 1 mg/kg administered every two weeks as an IV infusion. Dose escalation to 3 mg/kg once every two weeks could be considered based on suboptimal response to clinical and biochemical criteria, including, poor growth, persistent or deteriorating biochemical markers (e.g. liver transaminases, , parameters of lipid metabolism), persistent or worsening organomegaly, and persistent worsening of other symptoms (e.g. gastrointestinal symptoms).

Method of Administration

It is recommended to allow Kanuma vials to reach a temperature between 15°C and 25°C prior to reconstitution to minimize the potential for the formation of sebelipase alfa *rce* protein particles in solution.

Dilute Kanuma with 0.9% sodium chloride 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 with a surface area of greater than 4.5 cm² as available, in order to avoid filter occlusion.

Preparation of the Kanuma infusion

- Determine the number of vials to be diluted for infusion based on the patient’s weight and prescribed dose.
- Dilute the total calculated dose with 0.9% sodium chloride solution for infusion. See Table 1 for recommended infusion volumes by weight range.

Table 1: Recommended Infusion Volumes *

Weight range (kg)	Total infusion volume (mL)		
	1 mg/kg dose	3 mg/kg dose	5 mg/kg dose**
1-10	10	25	50
11-24	25	50	150
25-49	50	100	250
50-99	100	250	500
100-120	250	500	600

* The infusion volume should be based on the prescribed dose and should be prepared to a final Kanuma 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 3 mg/kg

- Mix gently. Do not shake the vials or the prepared infusion.
- Product is for single use in one patient only. Discard any unused portion left in the vial, as the product contains no preservatives.

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°-8°C for not more than 24 hours or up to 8 hours below 25°C.

Special Populations

Patients with renal and hepatic impairment: No dosing adjustment is recommended in patients with renal or hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of sebelipase alfa *rce*.

Adult patients: safety and efficacy data in patients >18 years old are limited.

LAL-D Patient Monitoring Program

Physicians are encouraged to participate and enrol all patients diagnosed with LAL-D in a patient monitoring program.

4.3 CONTRAINDICATIONS

Kanuma is contraindicated in patients with a life-threatening hypersensitivity (anaphylactic reaction) to the active substance, to egg, or to any of the excipients (see *section 6.1 – List of Excipients*), when attempts to rechallenge are unsuccessful.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions, including anaphylactic reactions or anaphylaxis

Hypersensitivity reactions, including anaphylactic reactions or anaphylaxis, have been reported in Kanuma-treated patients. In clinical trials, 5 of 125 (4%) patients treated with Kanuma, including 3 of 19 (16%) infants and 2 of 106 (2%) children and adults, experienced serious signs and symptoms consistent with anaphylaxis. These patients experienced reactions during infusion with signs and symptoms including chest discomfort, conjunctival hyperaemia, dyspnoea, hyperaemia, eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea, irritability, flushing, pruritus, stridor, hypoxia, pallor, diarrhoea and urticaria. 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%) paediatric patients, 4 years and older, 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 2 or more patients, included but were not limited to, abdominal pain, agitation, bronchospasm, fever, chills, diarrhoea, eyelid oedema, eczema, face oedema, hypertension, irritability, laryngeal oedema, lip swelling, nausea, oedema, pallor, pruritus, rash, tachycardia, urticaria 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.

Appropriate medical support should be readily available when Kanuma is administered. If anaphylaxis occurs, immediately discontinue the infusion and initiate appropriate medical treatment. Patients should be closely observed during, and after the infusion. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should signs and symptoms occur.

The risks and benefits of re-administering Kanuma following a severe reaction should be considered. For patients who have experienced allergic reactions during infusion, caution should be exercised upon re-administration.

The management of hypersensitivity reactions should be based on the severity of the reaction and may include temporarily interrupting the infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids. If interrupted, the infusion may be resumed at a slower rate with increases as tolerated. Pre-treatment with antipyretics and/or antihistamines may prevent subsequent reactions in those cases where symptomatic treatment was required.

Hypersensitivity to Egg

Sebelipase alfa *rce* is produced in the egg white of transgenic *Gallus* by recombinant DNA technology. 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 life-threatening hypersensitivity (anaphylactic reaction) to egg.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In the Kanuma clinical program, patients were routinely tested for anti-sebelipase alfa *rce* anti-drug antibodies (ADAs) to determine the immunogenicity potential of sebelipase alfa *rce*. Patients who tested positive for ADAs were also tested for inhibitory antibody activity. The presence of inhibitory antibody activity has been detected at some post-baseline timepoints in clinical studies (see *Section 4.8 Adverse Effects (Undesirable effects)*).

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 (see *section 4.8 Adverse Effects (Undesirable effects)*).

Paediatric Use

Eighty-eight of 125 patients (70%) who received Kanuma during clinical studies were in the paediatric and adolescent age range (0.5 months up to 17.6 years) at the time of first dose.

Use in the Elderly

Safety and efficacy of sebelipase alfa *rce* in patients older than 65 years have not been established. Therefore, there is no information available to determine whether patients aged 65 years and over respond differently from younger patients.

Effects on Laboratory Tests

Unknown.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug interaction studies have not been performed with sebelipase alfa *rce*.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No adverse effects on fertility and reproductive performance were observed in male and female rats given IV doses of sebelipase alfa *rce* up to 60 mg/kg administered twice weekly (approximately 122 times the adult human AUC of 1861 ng.h/mL at 1 mg/kg dose administered every two weeks).

Use in pregnancy – Category B1

Sebelipase alfa *rce* administered during the period of organogenesis to rats (on gestation days 6, 9, 12, 15 and 17) and rabbits (on gestation days 7, 10, 13, 16 and 19) at intravenous doses up to 60 and 50 mg/kg, respectively (approximately 122 and 392 times the human AUC of 1861 ng.h/mL at 1 mg/kg dose administered every two weeks, respectively) did not cause any adverse effects on embryofetal development. A pre- and postnatal development study in rats showed no evidence of adverse effects on pre- and postnatal development at intravenous doses (administered on gestation days 6, 9, 12, 15, 18, and 20 and days 4, 7, 10, 14, and 17 postpartum) of sebelipase alfa *rce* up to 60 mg/kg/day (approximately 122 times the human AUC of 1861 ng.h/mL at 1 mg/kg dose administered every two weeks).

There is insufficient data from the use of Kanuma in pregnant women to determine if sebelipase alfa *rce* exposure during pregnancy poses any risk to the mother or fetus. Pregnant and lactating women were excluded from Kanuma clinical trials. As a precautionary measure, it is preferable to avoid the use of Kanuma during pregnancy.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No specific studies have been conducted to assess the direct effect of Kanuma on the ability to drive and use machines. However, adverse effects of Kanuma include dizziness which could affect the ability to drive or use machines. See *section 4.8 Adverse Effects (Undesirable Effects)*.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The data described below reflect exposure of Kanuma in 125 patients who received Kanuma at dosages ranging from 0.35 mg/kg every two weeks to 7.5 mg/kg weekly in clinical studies. Patients were between 0.5 months and 59 years old (70% were < 18 years old) at the time of first treatment with Kanuma.

In infants, the safety of Kanuma was evaluated in an open-label, single arm Phase 2/3 study (*Study LAL-CL03*; weekly doses of 0.35, 1, 3, and 5 mg/kg) , see *Section 5.1 Clinical Trials*) and in an open-label, Phase 2 study (*Study LAL-CL08*; starting dose of 1 mg/kg weekly with potential sequential dose escalations when dose escalation criteria were met, to 3 mg/kg weekly, 5 mg/kg weekly, and 7.5 mg/kg weekly). Fifteen of nineteen infants received dose escalations as allowed by the study protocol from 1 mg/kg to 3 mg/kg administered weekly. Among these patients, nine patients had a further dose escalation to 5 mg/kg weekly, and one of these patients received a further dose escalation to 7.5 mg/kg weekly. Four of nineteen infants died for reasons unrelated to Kanuma prior to a protocol-defined dose escalation to 3 mg/kg once weekly.

In children and adults, the safety of Kanuma was evaluated in a randomised placebo-controlled Phase 3 study (*Study LAL-CL02*; doses of 1 mg/kg every two weeks during the double blind phase and doses of 1 and 3 mg/kg every two weeks during the extension phase); an open-label, single-arm, Phase 1/ 2 study in adults (*Study LAL-CL01*; doses of 0.35 mg, 1 mg, or 3 mg/kg weekly for four weeks, followed by a period when patients were off treatment with Kanuma before entering an extension period (*Study LAL-CL04*) during which patients resumed the previous dosage for another four weeks and then switched to a regimen of 1 or 3 mg/kg every two weeks; and an open-label, Phase 2 study in children and adults (≥ 8 months) (*Study LAL-CL06*; dose of 1 mg/kg every two weeks, with potential dose escalations up to 3 mg/kg weekly when subjects met dose escalation criteria). Twenty-three of 106 children and adults received dose escalations as allowed by the study protocol from 1 mg/kg to 3 mg/kg administered every two weeks, and four of these patients had a further dose escalation to 3 mg/kg weekly.

Overall, 102/106 (96.2%) children and adult patients have received Kanuma administered at a dosage regimen of 1 mg/kg every 2 weeks, with a median duration of exposure of 33 months (6,59 months). The majority of these 102 patients were from *Study LAL-CL02* (66/102, 64.7%). The median duration of exposure for the nineteen infants enrolled in clinical trials was 35.6 months (1 day, 60 months).

The most serious adverse reactions experienced by 4% of patients in clinical trials were signs and symptoms consistent with anaphylaxis, see *section 4.4 – Special Warnings and Precautions for Use; Hypersensitivity reactions including anaphylaxis*.

Tabulated list of adverse reactions

Table 2 below summarises the most common adverse reactions occurring in $\geq 30\%$ of patients with rapidly progressive LAL-D presenting in the first 6 months of life receiving Kanuma.

Table 2: Adverse Reactions Reported in $\geq 30\%$ of Infants Receiving Kanuma in Completed Clinical Studies

Adverse Reactions	Kanuma* n=19
Preferred Term	n (%)
Diarrhoea	15 (79)
Vomiting	15 (79)
Pyrexia	15(79)
Hypersensitivity ^a	13(68)
Rhinitis	10 (53)
Tachycardia	10 (53)
Respiratory distress	8(42)
Anaemia	7 (37)
Device related infection	9(47)
Cough	11(58)
Nasopharyngitis	9 (47)

*Includes pooled studies LAL-CL08 and LAL-CL03. These studies did not contain comparator arms and therefore comparator data is not displayed.

^aMay include: irritability, agitation, vomiting, urticaria, eczema, pruritus, pallor, and drug hypersensitivity.

Table 3 below summarises the adverse reactions that occurred in $\geq 8\%$ of children or adults receiving Kanuma.

Table 3: Adverse Reactions Reported in $\geq 8\%$ Children or Adults Receiving Kanuma

Adverse Reactions	Kanuma* n=106	Placebo** n=30
Preferred Term	n (%)	n (%)
Headache	47(44)	6(20)
Hypersensitivity ^a	46 (43)	0
Pyrexia	45 (42)	6(20)
Diarrhoea	41(39)	5(17)
Abdominal pain	34(32)	1(3)
Oropharyngeal pain	21(20)	1(3)
Nasopharyngitis	52(49)	3(10)
Constipation	12(11)	1(3)
Nausea	19(18)	2(7)
Dizziness	13(12)	1(3)
Fatigue	12(11)	2(7)
Rash	9(8)	3(10)

*Includes pooled studies LAL-CL01/LAL-CL04, LAL-CL02 and LAL-CL06.

**Only study LAL-CL02 contained a comparator arm with a 20-week double-blind treatment period.

^a The incidence of "hypersensitivity" was calculated based on the number of patients with Preferred Term(s) that met the SMQ for hypersensitivity (narrow).

Less common adverse reactions

Adverse reactions that occurred in Infants at rates less than 30% included (presented by SOC [italicized] and PT):

- *Infections and infestations*
 - Catheter site infection
- *Immune system disorder*
 - Anaphylactic reaction^b
- *Eye disorder*
 - Eyelid oedema
- *Skin and subcutaneous disorders*
 - Rash maculo-papular
- *General disorders and administration site conditions*
 - Hyperthermia
- *Investigations*
 - Body temperature increased
 - Respiratory rate increased
 - Heart rate increased
 - Blood pressure increased
 - Drug specific antibody present
 - Oxygen saturation decreased

^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.

Adverse reactions that occurred in Children or Adults at rates less than 8% included (presented by SOC [italicized] and PT);

- *Immune system disorder*
 - Anaphylactic reaction^c
- *Cardiac disorder*
 - Tachycardia
- *Vascular disorders*
 - Hyperaemia
 - Hypotension
- *Respiratory, thoracic and mediastinal disorders*
 - Dyspnoea

- *Gastrointestinal disorders*
 - Abdominal distention

- *Skin and subcutaneous disorders*
 - Rash
 - Rash papular
- *General disorders and administration site conditions*
 - Asthenia
 - Chest discomfort
 - Infusion site reaction
- *Investigations*
 - Body temperature increased

^c 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

Description of selected adverse reactions

Transient hyperlipidaemia

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

Immunogenicity

There is potential for immunogenicity, (*see section 4.4 Special Warnings and Precautions for Use*).

Among 106 children and adults with LAL deficiency enrolled in the clinical studies, 9/106 (8%) patients were reported with ADA positivity and 2/106 (2%) of patients tested positive for NABs that inhibited enzyme activity and/or cellular uptake. Among 19 infants with LAL deficiency enrolled in the clinical studies, 10/19 (53%) patients were reported with ADA positivity and 9/19 (47%) patients tested positive for NABs that inhibited enzyme activity and/or cellular uptake.

Overall, there is 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 (*see section 4.4 Special Warnings and Precautions for Use*). 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.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

The maximum dose of Kanuma used in clinical trials was 7.5 mg/kg/week. No specific signs or symptoms were identified following the higher doses.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lysosomal Acid Lipase Deficiency (LAL-D) is a rare disease associated with significant morbidity and mortality affecting individuals from infancy through to adulthood. LAL-D 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.

LAL-D is an autosomal recessive lysosomal storage disorder characterised by a genetic defect resulting in a marked decrease or loss in activity of the lysosomal acid lipase (LAL) enzyme. Deficient LAL enzyme activity results in progressive complications due to the lysosomal accumulation of cholesteryl esters and triglycerides in multiple organs, including the liver, spleen, intestine, and the walls of blood vessels. The resulting lipid accumulation in the liver 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, anaemia, and thrombocytopenia. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. In parallel, dyslipidemia due to impaired degradation of lysosomal lipid is common with elevated low-density lipoprotein cholesterol (LDL-c) and triglycerides, and low high-density lipoprotein cholesterol (HDL-c). In addition to liver disease, patients with LAL-D experience increased risk for cardiovascular disease and accelerated atherosclerosis.

Sebelipase alfa *rce* is taken up by cells and is subsequently internalised into lysosomes where it catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. Binding of glycans present on sebelipase alfa *rce*, to cell surface receptors is implicated in the cellular uptake of sebelipase alfa *rce*. Treatment with sebelipase alfa *rce* restores LAL enzyme activity in LAL-D cells, enabling hydrolysis of cholesteryl esters and triglycerides in the lysosome. Sebelipase alfa *rce* treatment restored hepatic LAL activity and lead to reductions in the fat content of the liver and spleen; reductions in serum transaminases, LDL-c, non-HDL-c, and triglycerides; and increases in serum HDL-c. Improvement in growth was associated with LAL substrate reduction in the intestine.

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. In open-label studies, some infants showed sustained improvement for up to 260 weeks, and some children and adults showed sustained improvement for up to 256 weeks. Treatment interruption resulted in increases in LDL-c and ALT values and decreases in HDL-c.

Clinical trials

Infants presenting with LAL Deficiency

Study LAL-CL03

Study LAL-CL03 was a multicentre, open-label, single-arm study of Kanuma in 9 patients with LAL-D with growth failure, or other evidence of rapidly progressive disease prior to 6 months of age. Patients had rapidly progressive liver disease and severe hepatosplenomegaly. The age range at study entry was 1-6 months. Patients received Kanuma at 0.35 mg/kg per week for the first 2 weeks, and then 1 mg/kg per week. Based on clinical response, dose escalation to 3 mg/kg per week occurred as early as 1 month and up to 20 months after starting treatment at 1 mg/kg. A further dose escalation to 5 mg/kg per week was allowed.

Efficacy was assessed by comparing the survival experience of Kanuma-treated patients who survived past 12 months of age in *Study LAL-CL03* with a historical cohort of untreated infants presenting with LAL-D with similar clinical characteristics. In *Study LAL-CL03*, 6 of the 9 Kanuma-treated infants survived beyond 12 months (67% 12-month survival; 95% CI: 30% to 93%). With continued treatment beyond 12 months of age, 1 additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond 8 months of age (0% 12-month survival, 95% CI: 0% to 16%).

Kanuma at doses up to 1 mg/kg per week resulted in improvements in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and weight gain within the first several weeks of treatment. From baseline to week 48, the mean reductions for ALT and AST were -34.0 U/l and -44.5 U/l, respectively. From baseline to week 48, mean weight-for-age percentile improved from 12.74% to 29.83% and mean serum albumin levels increased from 26.7 g/l to 38.7 g/l. Dose escalation to 3 mg/kg per week was associated with additional improvements in weight gain, lymphadenopathy and serum albumin.

Children and adults with LAL Deficiency

Study LAL-CL02

Study LAL-CL02 was a multicentre, double-blind, placebo-controlled study in 66 children and adults with LAL-D. Patients were randomised to receive a Kanuma dose of 1 mg/kg (n = 36) or placebo (n = 30) every two weeks for 20 weeks in the double-blind period. The median age at randomisation was 13.5 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-c > 4.91 mmol/L at study entry, and 24% of patients with LDL-c > 4.91 mmol/L were on lipid lowering medications. 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.

Randomisation was stratified by 1) age at randomisation (<12 years old; ≥12 years old); 2) ALT level at screening (<3 x ULN; ≥3 x ULN); and 3) use of lipid lowering medications (yes; no). The following endpoints were assessed: normalisation of ALT, decrease in LDL-c, decrease in non-HDL-c, normalisation of AST, decrease in triglycerides, increase in HDL-c, decrease in liver fat content assessed by multi-echo gradient echo magnetic resonance imaging (MEGE-MRI), and improvement in hepatic steatosis measured by morphometry.

Through an exploratory analysis, a statistically significant improvement in multiple endpoints was observed in the Kanuma-treated group as compared to the placebo group at the completion of the 20-week double-blind period, as shown in Table 4. Normalisation of ALT was achieved in 31% (11/36) of Kanuma-treated patients and 7% (2/30) of placebo patients. LDL-c normalisation (<3.36 mmol/L) was achieved in 40.6% (13/32) of Kanuma-treated patients and 6.7% (2/30) of placebo patients with abnormal baseline LDL-c (≥3.36 mmol/L).

Patients treated with Kanuma had larger reductions from baseline in ALT values and liver fat content (measured by MRI) compared to patients treated with placebo. The absolute reduction in mean ALT level was -57.9 U/l (-53%) in the Kanuma-treated group and -6.7 U/l (-6%) in the placebo group.

Table 4: Primary and secondary 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-c, mean % change from baseline	-28%	-6%	< 0.0001
non-HDL-c, 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-c, mean % change from baseline	20%	-0.3%	< 0.0001
Liver fat content ^c , mean % change from baseline	-32%	-4%	< 0.0001

Table 4: Primary and secondary efficacy endpoints in Study LAL-CL02

Endpoint	Sebelipase alfa (n = 36)	Placebo (n = 30)	P-value ^d
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low-density lipoprotein cholesterol (LDL-c); high-density lipoprotein cholesterol (HDL-c); alanine aminotransferase (ALT); aspartate aminotransferase (AST).

^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 $\geq 5\%$ reduction) as measured by morphometry compared to 40% (4/10) of placebo patients (Table 5). This difference was not statistically significant. Five of the 10 (50%) placebo patients with paired biopsies worsened from baseline compared to one of 16 (6%) in the Kanuma-treated patients (p=0.0184).

Table 5: Change from Baseline to Last Visit in the Double-Blind Treatment Period in Liver Histopathology

Result at Last Visit in the Double-Blind Treatment Period	Sebelipase Alfa (n = 19) n (%)	Placebo (n = 13) n (%)	Difference (%)	P-value ^a
N	16	10		
Endpoint improved from Baseline ^b	10 (63)	4 (40)	23	0.4216
Endpoint unchanged from Baseline ^b	5 (31)	1 (10)	21	0.3524
Endpoint worsened from Baseline ^b	1 (6)	5 (50)	-44	0.0184
Overall distribution of results ^c	0.0454			

^a Fisher's exact test for treatment differences between the percentage of sebelipase alfa – placebo subjects.

^b P-value for this row compares proportion of subjects with this result vs any other result.

^c P-value for this row compares distribution of 3 possible results across treatment groups.

Open-label period

Patients who participated in Study LAL-CL02 were eligible to continue treatment in an open-label period of the study. Sixty-five of 66 patients entered the open-label period

(up to 130 weeks) at a dose of 1 mg/kg Kanuma every two weeks. 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-c and HDL-c levels. Twelve of 66 patients in the open label period were dose escalated to 3 mg/kg (per fortnight) based on clinical response.

Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period. 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 rapid improvements in ALT levels and in lipid parameters including LDL-c and HDL-c levels (refer to Figure 1 and Figure 2).

Figure 1: Mean Change from Baseline in ALT Values over Time in Study LAL-CL02

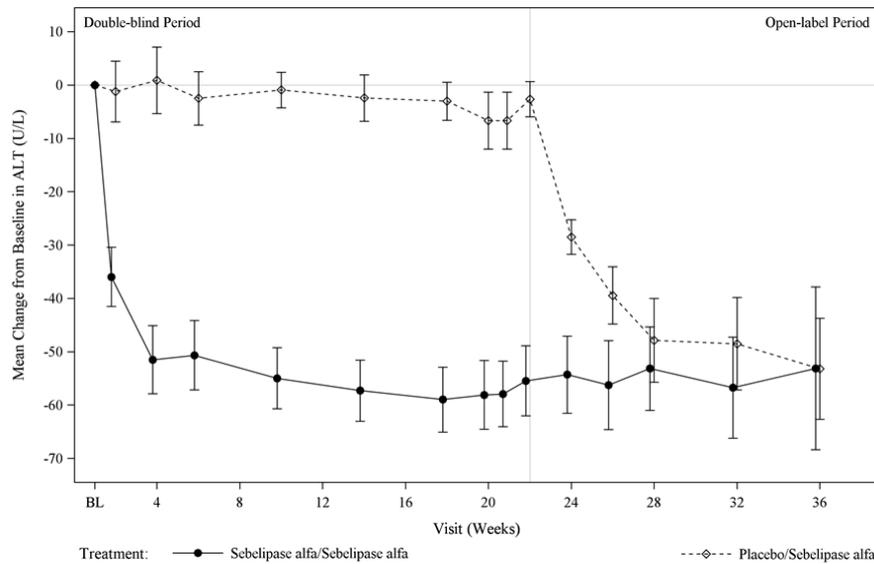
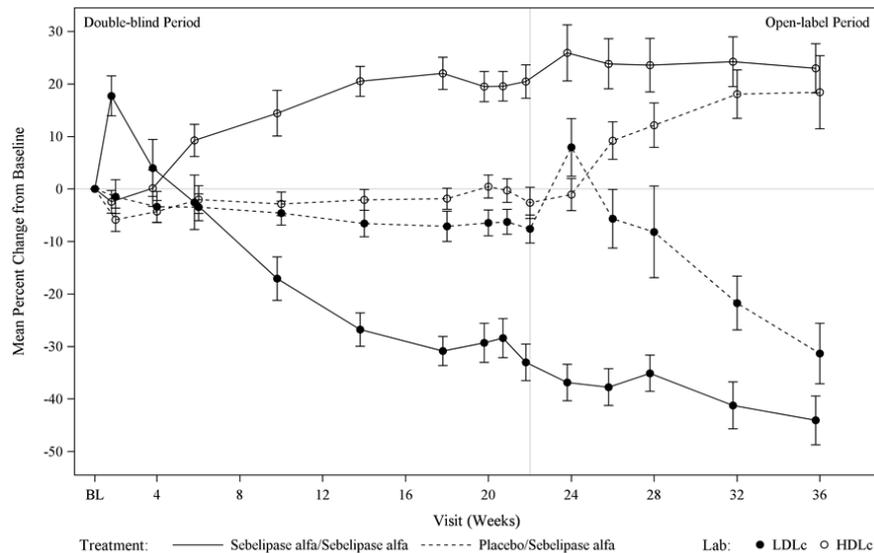


Figure 2: Mean Percent Change in Lipid Levels over Time in Study LAL-CL02



Study LAL-CL01/LAL-CL04

In a separate open-label study in adult patients with LAL-D (*Study LAL-CL01/LAL-CL04*; Kanuma dosage of 0.35, 1, and 3 mg/kg per week for 4 weeks, followed by a period off treatment before entering an extension period receiving fortnightly dose of 1 or 3 mg/kg), improvements in serum transaminase and lipid levels were sustained through the 260-week treatment period. Eight of nine patients transitioned from *Study LAL-CL01* after four weeks of treatment (0.35 mg/kg weekly, 1 mg/kg weekly, or 3 mg/kg weekly) with five patients receiving a dose of 1 mg/kg every two weeks and three patients receiving a dose of 3 mg/kg every two weeks. Five patients contributed results at 260 weeks. Increases in serum transaminases and LDL-c and decreases in HDL-c were observed during the period in which patients were off treatment with Kanuma.

5.2 PHARMACOKINETIC PROPERTIES

No conclusion on the linearity of sebelipase alfa *rce* pharmacokinetics can be made due to limited data at higher exposures. No drug accumulation is observed following 1 mg/kg or 3 mg/kg once every other week dosing, although observations for the drug accumulation at 3mg/kg every other week are based on a limited number of patients. Accumulation following once weekly dosing is not expected based on relatively rapid drug clearance.

The pharmacokinetics of sebelipase alfa *rce* in children and adults were determined using a population pharmacokinetic analysis of 102 patients with LAL-D who received intravenous infusions of Kanuma across 4 clinical studies (*LAL-CL02, LAL-CL03, LAL-CL04 and LAL-CL06* refer to **Error! Reference source not found.**). Four patients were below 2 years old, 33 were 2 to 11 years old, 34 were 12 to 17 years old, and 31 were adults (18 years and over). The pharmacokinetic profiles of sebelipase alfa *rce* were similar between adolescents and adults. The $T_{1/2}$ was similar across all age groups.

Table 6: Mean (SD) Population PK Model-based Predicted Pharmacokinetic and Exposure Parameters of Sebelipase Alfa in Paediatric and Adult Patients With LAL Deficiency by Age Group

	<2 years (N=4)	≥2 to <12 years (N=33)	≥12 to <18 years (N=34)	Adults (N=31)	Overall (N=102)
PK Parameters					
CL (L/h)	15.0 (5.87)	22.9 (11.0)	32.7 (10.8)	37.6 (13.8)	30.3 (13.4)
Q (L/h)	2.11 (1.05)	1.41 (0.623)	1.61 (0.551)	1.54 (0.594)	1.54 (0.616)
Vc (L)	1.52 (0.275)	2.77 (1.43)	4.06 (2.01)	6.01 (5.43)	4.14 (3.56)
Vss (L)	5.59 (0.275)	6.83 (1.43)	8.13 (2.01)	10.1 (5.43)	8.20 (3.56)
t1/2α (h)	0.0663 (0.0184)	0.102 (0.0838)	0.0915 (0.0504)	0.124 (0.119)	0.104 (0.0867)
t1/2β (h)	1.80 (0.769)	2.69 (1.61)	2.18 (1.28)	2.24 (1.05)	2.35 (1.33)
Exposure Parameters (assuming 1 mg/kg dose)					
AUC_{ss} (ng.h/mL)	508 (198)	1390 (776)	1610 (658)	2060 (793)	1630 (803)
C_{max,ss} (ng/mL)	240 (91.1)	666 (371)	786 (315)	997 (367)	790 (382)

Note: Data for infants (< 2 years) are from Study LAL-CL03, data for children (> 2 to < 18 years) are from Studies LAL-CL02 and LAL-CL06, and data for adults (> 18 years) are from Studies LAL-CL02, LAL-CL04, and LAL-CL06.

AUC_{ss} = area under the serum concentration-time curve at steady state; CL = clearance; C_{max,ss} = maximum observed serum concentration under steady state conditions; PK = pharmacokinetic(s); Q = peripheral clearance; t_{1/2β} = terminal elimination half-life; V_c = central volume of distribution; V_{ss} = volume of distribution at steady state

The volume of distribution was low, consistent with limited distribution of sebelipase alfa *rce* into tissues. However, the pharmacology of sebelipase alfa *rce* and results of pharmacodynamic studies in vitro and in LAL-D rats are consistent with the fraction of sebelipase alfa *rce* that is taken up by cells distributing into a variety of tissues.

Special Populations

During the covariate analysis of the population pharmacokinetics model for sebelipase alfa *rce*, age, sex and enzyme maturation were found not to have a significant influence on CL (drug clearance) and V_c (Central volume of distribution) of sebelipase alfa *rce*. Body weight and body surface area are significant covariates on CL. Sebelipase alfa *rce* has not been investigated in patients 65 years of age or older.

There is limited information on the impact of anti-drug antibodies on sebelipase alfa *rce* pharmacokinetics. As with all therapeutic proteins, there is the potential for the development of immunogenicity. Nineteen of 125 (15%) patients with LAL Deficiency had at least 1 postbaseline antidrug antibody (ADA) positive result, 10 of which were infants. Among children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titres of ADAs reported. In the absence of additional treatment, e.g. immunomodulation, ADA positivity appeared to be persistent in infants. There was no observed impact of anti-drug antibody development on sebelipase alfa *rce* pharmacokinetics.

Renal and hepatic impairment

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

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted to assess the genotoxic potential of sebelipase alfa *rce*.

Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of sebelipase alfa *rce*.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sodium citrate
citric acid monohydrate
albumin
water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Do not use beyond the expiration date (EXP) stamped on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Kanuma vials must be stored in a refrigerator (2 to 8° C, Do not freeze) in the original packaging in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

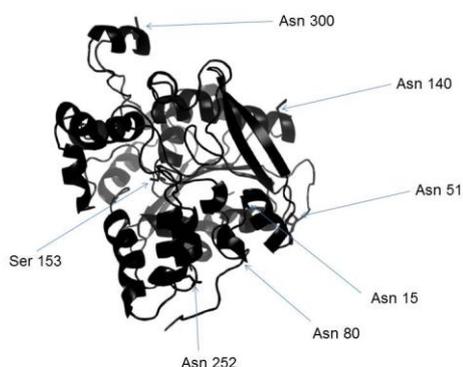
Single unit 20mg carton. Contains one 10mL vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any unused portion left in the vial, as the product contains no preservatives. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

CAS registry number: 1276027-63-4

Sebelipase alfa *rce* is a recombinant human lysosomal acid lipase (rhLAL) produced by recombinant DNA technology and purified from the egg white of genetically engineered chickens {transgenic Gallus}. Purified sebelipase alfa *rce* is a monomeric glycoprotein containing 6 N-linked glycosylation sites with a molecular weight of approx. 55 kDa.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Alexion Pharmaceuticals Australasia Pty Ltd
Suite 401. Level 4. Building A
20 Rodborough Rd
Frenchs Forest NSW 2086

Medical enquiries: 1800 788 189

9 DATE OF FIRST APPROVAL

18 May 2017

10 DATE OF REVISION

14 October 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Replace sebelipase alfa with Kanuma where appropriate to refer to the drug product and not the active ingredient
4.4	Update to figures and descriptions of signs and symptoms of Anaphylaxis and Hypersensitivity; Added section on Immunogenicity
4.8	Increased information for Immunogenicity updated to include integrated data set from updated tables to present AEs
5.0	Updated to include information following integrated results from the completed clinical studies