ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

KANUMA 2 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 2 mg sebelipase alfa*.

Each vial of 10 ml contains 20 mg sebelipase alfa.

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

Excipient with known effect
Each vial contains 33 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to slightly coloured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KANUMA is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency.

4.2 Posology and method of administration

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.

Posology

It is important to initiate treatment as early as possible after diagnosis of LAL deficiency.

For instructions on the preventive measures and monitoring of hypersensitivity reactions, see section 4.4. Following the occurrence of a hypersensitivity reaction, appropriate pre-treatment should be considered according to the standard of care (see section 4.4).

Patients with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life
The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL deficiency is either 1 mg/kg or 3 mg/kg administered as an intravenous infusion once weekly, depending on the clinical status of the patient. A higher starting dose of 3 mg/kg should be considered based on the severity of the disease and rapid disease progression.

Dose escalations should be considered based on suboptimal response to 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 persistent 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 should 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 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. Dose escalation to 3 mg/kg once every other week should be considered based on suboptimal response to clinical biochemical criteria, including; e.g., poor growth persistent or deteriorating biochemical markers (e.g., parameters of liver injury (ALT, AST), parameters of lipid metabolism (TC, LDL-c, HDL-c, TG), persistent or worsening organomegaly, and persistent worsening of other symptoms (e.g., gastrointestinal symptoms).

Special populations

Renal impairment
No dosing adjustment is recommended in patients with renal impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of sebelipase alfa (see section 5.2).

Hepatic impairment
No dosing adjustment is recommended in patients with hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of sebelipase alfa (see section 5.2).

Elderly population (≥ 65 years old)
The safety and efficacy of sebelipase alfa in patients older than 65 years have not been evaluated and no alternative dose regimens can be recommended for these patients (see section 5.1).

Overweight patients
The safety and efficacy of sebelipase alfa in overweight patients have not been thoroughly evaluated and therefore no alternative dose regimens can be recommended for these patients at this time.

Paediatric population
Administration of sebelipase alfa to infants with confirmed multiple-organ failure should be at the discretion of the treating physician.

Method of 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 after patient tolerability is established. (For the recommended infusion volumes, see section 6.6.) The infusion period may be extended in the event of dose escalation.

KANUMA should be administered through a 0.2 μm filter (see section 6.6).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Life-threatening hypersensitivity (anaphylactic reaction) to the active substance when attempts to rechallenge are unsuccessful, or to egg or any of the excipients listed in section 6.1, (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions including anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with sebelipase alfa; see section 4.8. Therefore, appropriate medical support must be readily available when sebelipase alfa is administered. If severe reactions occur, the sebelipase alfa infusion should be immediately stopped and appropriate medical treatment should be initiated. The risks and benefits of re-administering sebelipase alfa following a severe reaction should be considered.

Following the first sebelipase alfa infusion, including the first infusion after a dose escalation, patients should be observed for 1 hour in order to monitor for any signs or symptoms of anaphylaxis or a severe hypersensitivity reaction.

The management of hypersensitivity reactions may include temporarily interrupting the infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids. For patients who have experienced allergic reactions during infusion, caution should be exercised upon re-administration. 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.

In cases of severe infusion reactions and in cases of lack or loss of effect, patients should be tested for the presence of antibodies.

This medicinal product may contain traces of egg proteins. Patients with known egg allergies were excluded from clinical studies (see section 4.3).

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In the sebelipase alfa clinical program, patients were routinely tested for anti-sebelipase alfa anti-drug 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 activity has been detected at some postbaseline timepoints in clinical studies (see section 4.8). Overall, no conclusion on the relationship between development of ADAs/NAbs and associated hypersensitivity reactions or suboptimal clinical response can be made.

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. These patients underwent either immunomodulatory therapy alone or in combination with haematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT), resulting in improved clinical response to sebelipase alfa.

Excipients

This medicinal product contains 33 mg sodium per vial equivalent to 1.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult. It is administered in sodium chloride 9 mg/ml (0.9%) solution for infusion (see section 6.6). This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of sebelipase alfa in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid use of sebelipase alfa during pregnancy.

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 sebelipase alfa therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on the effects of sebelipase alfa on fertility. Animal studies show no evidence of impaired fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

KANUMA may have a minor influence on the ability to drive and use machines. Adverse events of dizziness have been reported with the use of sebelipase alfa, which could affect the ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The data described below reflect the exposure to sebelipase alfa in 125 patients at doses ranging from 0.35 mg/kg once every other week to 7.5 mg/kg once weekly in clinical studies (see section 5.1), with a treatment duration range from 1 day to 60.5 months (5 years).

Of the 106 children and adults enrolled in clinical studies, 102 (96.2%) have received sebelipase alfa at a dosage regimen of 1 mg/kg once every other week, with a median duration of exposure of 33 months (6, 59 months). The median duration of exposure for the 19 infants enrolled in clinical studies was 35.5 months (1 day to 60 months).

The most serious adverse reactions experienced by 4% of patients in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival hyperaemia, dyspnoea, hyperaemia, eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea, irritability, flushing, pruritus, urticaria, stridor, hypoxia, pallor and diarrhoea.

Tabulated list of adverse reactions

The data in Table 1 describe adverse reactions reported in infants who received sebelipase alfa in clinical studies. The data in Table 2 describe adverse reactions reported in children and adults who received sebelipase alfa in clinical studies.

Adverse reactions are listed by system organ class (SOC) and frequency. Frequencies are defined according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1: Adverse reactions reported in infants receiving sebelipase alfa (N = 19 patients)

MedDRA System organ class	MedDRA Preferred Term	Frequency
Immune system disorders	Hypersensitivity[a] Anaphylactic reaction[b]	Very common
Eye Disorders	Eyelid oedema	Very common
Cardiac disorders	Tachycardia	Very common
Respiratory, thoracic and mediastinal disorders	Respiratory distress	Very common
Gastrointestinal disorders	Vomiting Diarrhoea	Very common
Skin and subcutaneous tissue disorders	Rash Rash maculo-papular	Very common
General disorders and administration site conditions	Pyrexia Hyperthermia	Very common
Investigations	Drug specific antibody present Body temperature increased Oxygen saturation decreased Blood pressure increased Heart rate increased Respiratory rate increased	Very common

[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.

Table 2: Adverse reactions reported in children and adults receiving sebelipase alfa (N = 106 patients)

MedDRA System organ class	MedDRA preferred term	Frequency
Immune system disorders	Hypersensitivity[b]	Very Common
	Anaphylactic reaction[a]	Common

Nervous system disorders	Dizziness	Very common
Cardiac disorders	Tachycardia	Common
Vascular disorders	Hyperaemia Hypotension	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
Gastrointestinal disorders	Abdominal pain Diarrhoea	Very common
	Abdominal distension	Common
Skin and subcutaneous tissue disorders	Rash Rash papular	Common
General disorders and administration site conditions	Fatigue Pyrexia	Very common
	Chest discomfort Infusion site reaction[c]	Common
Investigations	Body temperature increased	Common

[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, laryngeal oedema, nausea, pruritus, urticaria.
[c] Includes: infusion site extravasation, infusion site pain and infusion site urticaria

Description of selected adverse reactions

Hypersensitivity
Five of 125 (4%) patients treated with sebelipase alfa, including 3 of 19 (16%) infants and 2 of 106 (2%) children and adults, in clinical studies experienced serious signs and symptoms consistent with anaphylaxis to sebelipase alfa. Anaphylaxis occurred during the infusion as late as 1 year after treatment initiation.

In clinical studies, 59 of 125 (47%) sebelipase alfa-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, diarrhoea, eyelid oedema, eczema, face oedema, hypertension, irritability, laryngeal oedema, lip swelling, nausea, oedema, 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 hyperlipidaemia
Consistent with its known mechanism of action, asymptomatic increases in circulating cholesterol and triglycerides have been observed following initiation of treatment. These increases have generally occurred within the first 2 to 4 weeks and improved within a further 8 weeks of treatment. See section 5.1.

Immunogenicity
There is potential for immunogenicity (see section 4.4). Patients have developed anti-drug antibodies (ADA) to sebelipase alfa. Compared to children and adults, an increased occurrence of ADA positivity was observed within the infant population (10/19 patients).

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 sebelipase alfa (9 children and adult patients and 10 infants). For children and adult patients with LAL

Deficiency, ADA positivity was transient with generally low titers of ADAs reported. Persistence of ADA positivity was observed for all 10 infants and persistence of high titer 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies, doses of sebelipase alfa were explored up to 7.5 mg/kg once weekly and no specific signs or symptoms were identified following the higher doses. For management of adverse reactions, see sections 4.4 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Enzymes; ATC code: A16AB14

Lysosomal acid lipase (LAL) deficiency

LAL deficiency is a rare disease associated with significant morbidity and mortality, which affects individuals from infancy through adulthood. 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. LAL deficiency 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 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, anaemia, and thrombocytopenia. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. Dyslipidaemia is common, with elevated low-density lipoprotein cholesterol (LDL-C) and triglycerides and low high-density lipoprotein cholesterol (HDL-C), associated with increase liver fat content and transaminase elevations. In addition to liver disease, patients with LAL deficiency experience increased risk for cardiovascular disease and accelerated atherosclerosis.

Mechanism of action

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

Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalised into lysosomes. Sebelipase alfa catalyses 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.

Clinical studies

Infants presenting with LAL deficiency

Study LAL-CL03

LAL-CL03 was a multicentre, open-label, single-arm study of sebelipase alfa 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 months (range = 1 to 6 months). The median duration of exposure to sebelipase alfa was 55.6 months per patient (range = 1 day to 60 months). Patients received sebelipase alfa at 0.35 mg/kg once weekly (qw) for the first 2 weeks and then 1 mg/kg once weekly. Based on clinical response, 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 qw for 6 patients. Two of these 6 patients were subsequently dose escalated to 5 mg/kg once weekly, as allowed by the study protocol.

Efficacy was assessed by comparing the survival experience of sebelipase alfa-treated patients who survived past 12 months of age in Study LAL-CL03 with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics. In LAL-CL03, 6 of 9 sebelipase alfa-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment until 48 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%).

Sebelipase alfa 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 -45.25 U/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

Study LAL-CL08 was a multicentre, open-label study of sebelipase alfa 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 anaemia, 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 4 months). Eight (80%) patients completed the study. The median duration of exposure was 34 months (range: 1 to 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. 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

Study LAL-CL02 was a multicentre, double-blind, placebo-controlled study in 66 children and adults with LAL deficiency. Patients were randomised to receive sebelipase alfa at a dose of 1 mg/kg (n = 36) or placebo (n = 30) once every other week (qow) for 20 weeks in the double-blind period. The mean age range at randomisation was 16.5 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-cholesterol > 190 mg/dl at study entry, and 24% of patients with LDL-cholesterol > 190 mg/dl 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.

The following endpoints were assessed: normalisation of ALT, decrease in LDL-cholesterol, decrease in non-HDL-cholesterol, normalisation of AST, decrease in triglycerides, increase in HDL-cholesterol, decrease in liver fat content assessed by multi-echo gradient echo magnetic resonance imaging (MEGE-MRI), and improvement in hepatic steatosis measured by morphometry.

A statistically significant improvement in multiple endpoints was observed in the sebelipase alfa-treated group as compared to the placebo group at the completion of the 20-week double-blind period of the study, as shown in Table 3. The absolute reduction in mean ALT level was -57.9 U/l (-53%) in the sebelipase alfa-treated group and -6.7 U/l (-6%) in the placebo group.

Table 3: Primary and secondary efficacy endpoints in 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 sebelipase alfa-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.

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 (up to 130 weeks) at a sebelipase alfa dose of 1 mg/kg once every other week. In patients who had received sebelipase alfa 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. Twelve (12) of 66 patients in the open label period were dose escalated to 3 mg/kg once every other week 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 sebelipase alfa-treated patients during the double-blind period, initiation of treatment with sebelipase alfa during the open-label period produced rapid 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

In a separate open-label study (LAL-CL01/LAL-CL04) in adult patients with LAL deficiency, 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 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. Increases in serum transaminases and LDL-cholesterol and decreases in HDL-cholesterol were observed during the period in which patients were off treatment with sebelipase alfa.

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 haematopoietic 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 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.

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

Liver biopsy is the accepted standard for histologic assessment of liver disease activity and fibrosis, despite such limitations as sampling variability, potential complications of an invasive technique, and subjective scoring.

Liver biopsies from 59 patients enrolled in Studies LAL-CL02 and LAL-CL06 were assessed by an independent pathologist at a central facility, who was blinded to assessment timepoint and treatment assignment. All biopsies were evaluated semi-quantitatively for histologic features such as Ishak Fibrosis Score, portal inflammation, lobular inflammation, macrovesicular steatosis, and microvesicular steatosis. Computer-assisted morphometry was used to quantify percent steatosis, fibrogenic cells, collagen, and macrophages.

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).

Paediatric population

Eighty-eight of 125 patients (70%) who received sebelipase alfa during clinical studies were in the paediatric and adolescent age range (1 month up to 18 years) at the time of first dose. Currently available data are described sections 4.8 and 5.1.

LAL deficiency registry

Medical or healthcare professionals are encouraged to participate and enrol all patients diagnosed with LAL deficiency in the LAL deficiency registry..

5.2 Pharmacokinetic properties

The pharmacokinetics of sebelipase alfa in children and adults were determined using a population pharmacokinetic analysis of 102 patients with LAL deficiency who received intravenous infusions of sebelipase alfa across 4 clinical studies LAL-CL02, LAL-CL03, LAL-CL04 and LAL-CL06 (Table 4).
Predicted pharmacokinetic and exposure parameters of sebelipase alfa from clinical trials are presented by age group in Table 4.

Table 4: Mean (SD) Predicted Pharmacokinetic and Exposure Parameters following Repeated Administration of 1 mg/kg Sebelipase Alfa in Patients With LAL Deficiency by Age Group

Parameter	Age < 4 years (N = 5)	Age 4 to < 12 years (N = 32)	Age 12 to < 18 years (N=34)	≥ 18 years (N = 31)
CL (L/h)	17.2 (7.07)	22.8 (11.2)	32.7 (10.8)	37.6 (13.8)
Q (L/h)	1.96 (0.963)	1.41 (0.633)	1.61 (0.551)	1.54 (0.594)
Vc (L)	2.06 (1.22)	2.72 (1.43)	4.06 (2.01)	6.01 (5.43)
Vss (L)	6.13 (1.22)	6.79 (1.43)	8.13 (2.01)	10.1 (5.43)
$t_{½\beta}$ (h)	1.88 (0.69)	2.71 (1.63)	2.18 (1.28)	2.24 (1.05)
AUCss (ng × h/mL)	521 (174)	1410 (774)	1610 (658)	2060 (793)
Cmax,ss (ng/mL)	247 (80.6)	679 (370)	786 (315)	997 (367)

Note: Estimates are derived from data from Studies LAL-CL02, LAL-CL03, 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; $t_{½\beta}$ = terminal elimination half-life; Vc = central volume of distribution; Vss = Volume of distribution at steady state

Linearity/non-linearity

No conclusion on the linearity of sebelipase alfa 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.

Special populations

During the covariate analysis of the population pharmacokinetics model for sebelipase alfa, age, sex and enzyme maturation were found to not have a significant influence on CL (drug clearance) and V_c

(central volume of distribution) of sebelipase alfa. Body weight and body surface area are significant covariates on CL. Sebelipase alfa has not been investigated in patients aged 65 years or older.

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

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

Immunogenicity

As with all therapeutic proteins, there is the potential for the development of immunogenicity (see section 4.8).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity in rats and monkeys, or fertility, embryo-foetal and peri- and postnatal development in rats and rabbits. Chronic toxicity studies in juvenile cynomolgous monkeys showed no toxicity at doses up to 3 times the recommended dose in infants and 10 times the recommended dose in adults/children. No adverse findings were observed in rat and rabbit embryofoetal development studies at doses up to at least 10 times the adult/children recommended dose and in rat fertility and peri- postnatal development studies at doses up to 10 times the adult/children recommended dose.

Studies to evaluate the mutagenic and carcinogenic potential of sebelipase alfa have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid monohydrate
Human serum albumin
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials: 2 years.

After dilution: Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2°C to 8°C, or up to 12 hours below 25 °C.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would normally not be longer than 24 hours at 2 °C to 8 °C, or up to 12 hours below 25 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear glass vial (Type I) with a siliconised butyl rubber stopper, and an aluminium seal with a plastic flip-off cap, containing 10 ml of concentrate.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Each vial of KANUMA is intended for single use only. KANUMA has to be diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion using aseptic technique.
The diluted solution should be administered to patients using a low-protein binding infusion set equipped with an in-line, low-protein binding 0.2 µm filter, with a surface area of greater than 4.5 cm^2 as available in order to avoid filter occlusion.

Preparation of the sebelipase alfa infusion

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

a. The number of vials to be diluted for infusion should be determined based on the patient's weight and prescribed dose.
b. It is recommended to allow KANUMA vials to reach a temperature between 15 °C and 25 °C prior to dilution to minimise the potential for the formation of sebelipase alfa protein particles in solution. 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.
c. The vials should not be shaken. Prior to dilution, the concentrate in the vials should be inspected visually; the concentrate should be clear to slightly opalescent, colourless to slightly coloured (yellow). Due to the proteinaceous nature of the medicinal product, slight flocculation (e.g., thin translucent fibres) may be present in the vial concentrate and is acceptable for use.
d. Do not use if the concentrate is cloudy, or if foreign particulate matter is present.
e. Up to 10 ml of concentrate should be slowly withdrawn from each vial and diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion. See Table 5 for recommended total infusion volumes by weight range. The solution should be mixed gently, and not be shaken.

Table 5: Recommended 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 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.

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

7. MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1033/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 2015
Date of latest renewal: 23 April 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Fujifilm Diosynth Biotechnologies USA Inc
6051 George Watts Hill Drive
Research Triangle Park
North Carolina
NC 27709
UNITED STATES

Alexion Pharma International Operations Limited (APIOL)
Alexion Athlone Manufacturing Facility (AAMF)
Monksland Industrial Estate
Monksland
Athlone
Roscommon
N37 DH79
IRELAND

Name and address of the manufacturer responsible for batch release

Almac Pharma Services Ltd.
Seagoe Industrial Estate
Craigavon
Co Armagh
BT63 5UA
United Kingdom

Alexion Pharma International Operations Limited
College Business and Technology Park
Blanchardstown Road North
Dublin 15
D15 R925
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any

subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Kanuma in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational material is aimed to encourage healthcare professionals to enrol patients in the prospective disease and clinical outcome registry of patients with Lysosomal Acid Lipase (LAL) Deficiency to monitor for efficacy and safety of Kanuma (LAL Deficiency Registry), with particular regard to hypersensitivity reactions, including anaphylaxis, and anti-drug antibodies (ADA) development impacting response to drug.

The MAH shall ensure that in each Member State where Kanuma is marketed, all healthcare professionals who are expected to use Kanuma have access to the educational material. The physician's educational material should contain:

- Summary of Product Characteristics
- Guide for healthcare professionals

The guide for healthcare professionals shall contain the following key elements:

- Warning and precautions on the the risk of hypersensitivity including anaphylaxis or ADA development, with particular reference to symptoms, time to onset and severity.
- Information on how to manage patients experiencing severe hypersensitivity reactions including anaphylaxis.
- Details on how to monitor for potential ADA formation following initiation of treatment with Kanuma, particularly in patients on Kanuma who experience clinically important hypersensitivity reactions or potential loss of clinical response.
- Information to healthcare professionals that it is the responsibility of the MAH to provide the test for the monitoring of ADA positive patients including the modalities for requesting the test.

- Information on the ongoing LAL Deficiency Registry, including the importance of enrolling patients, also those not treated with Kanuma, and the modalities for participation.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): LAL Deficiency Registry: Non-interventional, multicentre, prospective disease and clinical outcome registry of patients with Lysosomal Acid Lipase Deficiency to further understand the disease, its progression and any associated complication, and to evaluate the long-term efficacy (normalisation of hepatic function) and safety of Kanuma (in particular hypersensitivity reactions, including anaphylaxis, and anti-drug antibodies development potentially impacting response to drug) according to agreed protocol.	Interim reports expected every 2 years Final study report expected in Jan 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

KANUMA 2 mg/ml concentrate for solution for infusion
sebelipase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of concentrate contains 2 mg sebelipase alfa. Each vial contains 20 mg sebelipase alfa in 10 ml of solution.

3. LIST OF EXCIPIENTS

Excipients:
Sodium citrate
Citric acid monohydrate
Human serum albumin
Water for injections
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 10 ml
20 mg/10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use after dilution.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1033/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

KANUMA 2 mg/ml sterile concentrate
sebelipase alfa
IV use after dilution

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg/10 ml

6. OTHER

Store in a refrigerator
Do not freeze.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

KANUMA 2 mg/ml concentrate for solution for infusion
sebelipase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you or your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What KANUMA is and what it is 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 of all ages 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 KANUMA works
This medicine is an enzyme replacement therapy. This means that it replaces the missing or defective LAL enzyme in patients with LAL deficiency. This medicine works by lowering the build-up of fat that causes medical complications, including impaired growth, liver damage and heart complications. It also improves blood levels of fats, including elevated LDL (bad cholesterol) and triglycerides.

2. What you need to know before KANUMA is given

You must not be given KANUMA
- If you or your child has experienced life-threatening allergic reactions to sebelipase alfa that cannot be managed when you or your child receives the medicine again, or to egg or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
- If treated with KANUMA, you or your child may experience a side effect while you or your child is being given the medicine or during the hours following the infusion (see section 4). This is known as an infusion reaction which can sometimes be severe, and may include an

allergic reaction that could be life-threatening and require medical treatment. The first time that you or your child are given KANUMA you should be observed by a healthcare professional for 1 hour to watch for any signs of an infusion reaction. **If you or your child experiences a severe infusion reaction like this, seek immediate medical attention**. If you or your child has an infusion reaction you or your child may be given additional medicines to treat or help prevent future reactions. These medicines may include antihistamines, fever-reducing medicines and/or corticosteroids (a type of anti-inflammatory medicines).
If the infusion reaction is severe, your doctor may stop KANUMA infusion and start giving you or your child appropriate medical treatment.

- The development of blood proteins against KANUMA, also called anti-drug antibodies, may occur during the treatment. Talk to your doctor if you experience decreased efficacy with KANUMA
- This medicine may contain egg proteins. If you or your child has an egg allergy or a history of allergies to eggs, tell your doctor or nurse (see **You must not be given KANUMA**).

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

Pregnancy
There are no data from the use of sebelipase alfa in pregnant women. As a precautionary measure, you should not be given KANUMA if you are pregnant.

Breast-feeding
It is not known whether sebelipase alfa passes into breast milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking KANUMA, considering the benefit of breast-feeding to the baby and the benefit of KANUMA to the mother.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

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.

KANUMA contains sodium
This medicine, when diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion for intravenous administration contains 33 mg sodium (main component of cooking/table salt) at the recommended dose. This is equivalent to 1.7% of the recommended maximum daily dietary intake of sodium for an adult. Tell your doctor if you or your child is on a controlled sodium diet.

3. How KANUMA is given

The dose you or your child receives is based on your or your child's body weight.

Infants (< 6 months of age)
For patients who have signs and symptoms of the disease when they are infants, the recommended starting dose is 1 mg/kg or 3 mg/kg once weekly. Dose adjustments may be considered based on how well your child responds to treatment.

Children and adults
The recommended dose is 1 mg per kg body weight once every other week through a drip into a vein. Dose adjustments may be considered based on how well you or your child responds to treatment.

Each infusion will take approximately 1 to 2 hours. You or your child may be monitored by your doctor or nurse for an additional hour after the infusion. KANUMA should be started at as young an age as possible and is intended for long-term use.

Your doctor or nurse will give KANUMA to you or your child by an infusion (drip) into a vein. The medicine will be diluted before being given to you or your child.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects were seen while patients were being given the medicine or shortly after (infusion reactions). The most serious side effects may include an allergic reaction (seen very commonly [may affect more than 1 in 10 people] in infants younger than 6 months old, or commonly [may affect up to 1 in 10 people] in children and adults) with symptoms including difficulty breathing, rapid breathing, fast heartbeat, chest discomfort, mild swelling of eyelids, red eyes, runny nose, flushing, hives, itching, diarrhoea, paleness, wheezing, low blood oxygen, skin redness and irritability. **If you or your child experiences symptoms like these, seek immediate medical attention.** If you or your child has an infusion reaction you or your child may be given additional medicines to treat or help prevent future reactions. If the infusion reaction is severe, your doctor may stop the infusion of KANUMA in the vein and start giving appropriate medical treatment.

Very Common (may affect more than 1 in 10 people) side effects reported in infants (1 to 6 months old) are:
Hypersensitivity (irritability, agitation, vomiting, urticaria, eczema, pruritus, pallor and drug hypersensitivity), severe allergic reactions (anaphylactic reactions)
Eyelid swelling
Fast heartbeat
Difficulty breathing
Diarrhoea, vomiting
Rash, raised rash
Fever
Decreased oxygen in the blood, blood pressure increased, rapid breathing, development of blood proteins

Very Common (may affect 1 in 10 people or more) side effects reported in children and adolescents (4 to 18 years old) and adults are:
Hypersensitivity (chills, eczema, laryngeal oedema, nausea, pruritus and urticaria)
Dizziness
Stomach ache, diarrhoea
Tiredness, fever

Common (may affect up to 1 in 10 people) side effects reported in children and adolescents (4 to 18 years old) and adults are:
Severe allergic reaction (anaphylactic reaction),
Fast heartbeat
Skin redness, low blood pressure
Shortness in breath
Stomach bloating
Rash, red swollen skin
Chest discomfort, reaction at the infusion site

Frequency, type and severity of adverse reactions in children are similar to those in adults.

Reporting of side effects
If you or your child gets any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store KANUMA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C). Do not freeze. Do not shake. Store in the original package in order to protect from light.

For diluted solutions, immediate use is recommended. If not used immediately, the diluted solution may be stored up to 24 hours at 2 °C to 8 °C or up to 12 hours below 25 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What KANUMA contains
- The active substance is sebelipase alfa. Each ml of concentrate contains 2 mg sebelipase alfa. Each vial contains 20 mg of sebelipase alfa in 10 ml.
- The other ingredients are sodium citrate (see section 2 under 'KANUMA contains sodium'), citric acid monohydrate, human serum albumin, and water for injections.

What KANUMA looks like and contents of the pack
KANUMA is supplied as a concentrate for solution for infusion (sterile concentrate). It is a solution that is clear to slightly opalescent, and colourless to slightly coloured.

Pack size: 1 vial containing 10 ml of concentrate.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
France

Manufacturer:
Almac Pharma Services
Seagoe Industrial Estate
Craigavon BT63 5UA
United Kingdom

Alexion Pharma International Operations Limited
College Business and Technology Park
Blanchardstown Road North

Dublin 15
D15 R925
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Alexion Europe SAS
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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Each vial of KANUMA is intended for single use only. KANUMA has to be diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion using aseptic technique.
The diluted solution should be administered to patients using a low-protein binding infusion set equipped with an in-line, low-protein binding 0.2 µm filter, with a surface area of greater than 4.5 cm^2 as available in order to avoid filter occlusion.

Preparation of the sebelipase alfa infusion

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

a. The number of vials to be diluted for infusion should be determined based on the patient's weight and prescribed dose.
b. It is recommended to allow KANUMA vials to reach a temperature between 15 °C and 25 °C prior to dilution to minimise the potential for the formation of sebelipase alfa protein particles in solution. 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.
c. The vials should not be shaken. Prior to dilution, the concentrate in the vials should be inspected visually; the concentrate should be clear to slightly opalescent, colourless to slightly coloured (yellow). Due to the proteinaceous nature of the medicinal product, slight flocculation (e.g., thin translucent fibres) may be present in the vial concentrate and is acceptable for use.
d. Do not use if the concentrate is cloudy, or if foreign particulate matter is present.
e. Up to 10 ml of concentrate should be slowly withdrawn from each vial and diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion. See Table 1 for recommended total infusion volumes by weight range. The solution should be mixed gently, and not be shaken.

Table 1: Recommended infusion volumes*

	1 mg/kg dose	3 mg/kg dose	5 mg/kg dose**
Weight range (kg)	**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 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.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.