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.

*Sebelipase alfa is 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).

Infants (< 6 months of age)

The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL deficiency is 1 mg/kg administered as an intravenous infusion once weekly. Dose escalation to 3 mg/kg once weekly should be considered based on clinical response.

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

Special populations
Renal or 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. See section 5.2.

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

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

Elderly population (≥ 65 years old)
The safety and efficacy of KANUMA 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.

Method of administration
KANUMA is for intravenous use only.

The total volume of the infusion should be administered over approximately 2 hours. A 1-hour infusion may be considered after patient tolerability is established. 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

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).

Excipients
This medicinal product contains 33 mg sodium per vial and 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 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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile
The most serious adverse reactions experienced by 3% of patients in clinical studies were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, mild eyelid oedema, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea and urticaria.

Tabulated list of adverse reactions
The data in Table 1 describe adverse reactions reported in infants who received KANUMA in clinical studies at doses up to 3 mg/kg weekly. The data in Table 2 describe adverse reactions reported in

children and adults who received sebelipase alfa in clinical studies at a dose of 1 mg/kg once every other week.

Adverse reactions are listed by System Organ Class 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported in infants[c] receiving KANUMA

MedDRA System organ class	Frequency[a]	MedDRA preferred term
Immune system disorders	Very common	Eyelid oedema
Psychiatric disorders	Very common	Agitation[b], irritability[b]
Nervous system disorders	Very common	Hypotonia
Cardiac disorders	Very common	Tachycardia[b]
Vascular disorders	Very common	Hypertension, pallor[b]
Respiratory, thoracic and mediastinal disorders	Very common	Respiratory distress, wheezing, cough, rhinitis, nasal congestion, sneezing
Gastrointestinal disorders	Very common	Diarrhoea, gastro-oesophageal reflux disease, retching, vomiting[b]
Skin and subcutaneous tissue disorders	Very common	Urticaria[b], rash[b], eczema[b], pruritis, rash maculo-papular
General disorders and administration site conditions	Very common	Chills, hyperthermia, pyrexia[b], oedema
Investigations	Very common	Body temperature increased, oxygen saturation decreased, blood pressure increased, heart rate increased, respiratory rate increased

[a] Very common = Reported in ≥ 1 patient receiving KANUMA
[b] Reported in ≥ 2 patients receiving KANUMA
[c] Age at first dose: 1 to 6 months

Table 2: Adverse reactions reported in children and adults[d] receiving KANUMA

MedDRA System organ class	Frequency[a]	MedDRA preferred term
Infections and infestations	Common	Urinary tract infection
Immune system disorders	Common	Anaphylactic reaction, eyelid oedema
Metabolism and nutrition disorders	Common	Transient hypercholesterolaemia, transient hypertriglyceridaemia
Psychiatric disorders	Common	Anxiety[c], insomnia
Nervous system disorders	Common	Dizziness
Cardiac disorders	Common	Tachycardia
Vascular disorders	Common	Hyperaemia[e], hypotension
Respiratory, thoracic and mediastinal disorders	Common	Laryngeal oedema[e], dyspnoea[b,c,e],
Gastrointestinal disorders	Common	Diarrhoea[b,e], abdominal pain[b,e], abdominal distension, nausea[b e]

Skin and subcutaneous tissue disorders	Common	Urticaria, rash[c,e] (including rash papular and rash pruritic), pruritus[e], eczema[e]
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Common	Chills, chest discomfort[c,e], oedema, fatigue, infusion site induration, pyrexia
Investigations	Common	Body temperature increased[b,c]
Injury, poisoning and procedural complications	Common	Infusion related reaction[c]

[a] Common = Reported in ≥ 1 patient receiving KANUMA
[b] Reported at the same frequency in patients receiving KANUMA or placebo or more frequently in patients receiving placebo during the double-blind period of LAL-CL02
[c] Reported as part of an adverse reaction in a single patient receiving KANUMA in LAL-CL02
[d] Age at first dose: 4 to 58 years
[e] Reported in ≥ 2 patients receiving KANUMA

Description of selected adverse reactions

Hypersensitivity

Three patients of 106 (3%) patients treated with KANUMA, including 1 of 14 (7%) infants and 2 of 92 (2%) children and adults, in clinical studies experienced signs and symptoms consistent with anaphylaxis. Anaphylaxis occurred during the infusion as late as 1 year after treatment initiation.

In clinical studies, 21 of 106 (20%) KANUMA-treated patients, including 9 of 14 (64%) infants and 12 of 92 (13%) children and adults, experienced signs and symptoms either consistent with or that may be related to a hypersensitivity reaction. These reported signs and symptoms occurring in two or more patients included abdominal pain, agitation, chills, diarrhoea, eczema, hypertension, irritability, laryngeal oedema, 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

Patients have developed anti-drug antibodies (ADA) to sebelipase alfa. Based on the limited data currently available the development of ADA seems to occur more frequently in infants.'

In LAL-CL03, 4 of 7 evaluable infants (57%) developed ADA during treatment with KANUMA. At the time of initial ADA positivity, 3 patients were receiving a dose of 1 mg/kg once weekly and 1 patient was receiving a dose of 3 mg/kg once weekly. Most patients who developed ADA did so within the first 2 months of exposure. ADA titres decreased to undetectable levels during continued treatment in 3 of the 4 patients. Two patients were determined to be positive for antibodies that inhibit *in vitro* enzyme activity and cellular uptake of the enzyme. In a separate study in infants, one of five evaluable patients developed antibodies that inhibit *in vitro* enzyme activity and cellular uptake of the enzyme.

In LAL-CL02, 5 of 35 evaluable children and adults (14%) who were administered KANUMA during the 20-week double-blind period of the study developed ADA. All patients were receiving 1 mg/kg once every other week. Those patients who developed ADA did so within the first 3 months of

exposure. ADA titres decreased to undetectable levels during continued treatment in all patients. Two patients were positive at only a single time point. No patients developed antibodies that inhibited *in vitro* enzyme activity and one patient developed antibodies that inhibited cellular uptake of the enzyme *in vitro*.

The association between the development of ADA to sebelipase alfa and reductions in treatment effect or the occurrence of adverse reactions has not been determined.

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 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: not yet assigned

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 the liver, this accumulation leads to hepatomegaly, increased hepatic fat content, transaminase elevation signaling chronic liver injury, and progression to fibrosis, cirrhosis, and complications of end stage liver disease. In the spleen, LAL deficiency results in splenomegaly, anemia, and thrombocytopenia. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. Dyslipidemia is common with elevated LDL and triglycerides and low HDL, 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 internalized 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 low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol,

triglycerides, and increases in HDL cholesterol. Improvement in growth occurs as a result of substrate reduction in the intestine.

Clinical studies

Infants presenting with LAL deficiency

LAL-CL03 was a multicentre, open-label, single-arm study of KANUMA in 9 patients with LAL deficiency with growth failure or other evidence of rapidly progressive disease prior to 6 months of age. Patients also had rapidly progressive liver disease and severe hepatosplenomegaly. The age range at study entry was 1-6 months. Patients received sebelipase alfa at 0.35 mg/kg once weekly for the first 2 weeks and then 1 mg/kg once weekly. 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. A further dose escalation to 5 mg/kg once weekly was allowed.

Efficacy was assessed by comparing the survival experience of KANUMA-treated patients who survived past 12 months of age in LAL-CL03 with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics. In LAL-CL03, 6 of 9 KANUMA-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). 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 once weekly 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. Dose escalation to 3 mg/kg once weekly was associated with additional improvements in weight gain, lymphadenopathy and serum albumin. 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.

One infant was treated with 5 mg/kg once weekly in LAL-CL03; no new adverse reactions were reported at this dose. In the absence of more clinical data, this dose is not recommended.

Children and adults with LAL deficiency

LAL-CL02 was a multicentre, double-blind, placebo-controlled study in 66 children and adults with LAL deficiency. Patients were randomised to receive KANUMA at a dose of 1 mg/kg (n = 36) or placebo (n = 30) once every other week for 20 weeks in the double-blind period. The age range at randomisation was 4-58 years old (71% were < 18 years old). For study entry, patients were required to have ALT levels of ≥1.5 X upper limit of normal (ULN). 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 old.

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	KANUMA (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 KANUMA; n = 29 for placebo).

[c] Evaluated in patients with MEGE-MRI assessments performed (n = 32 for KANUMA; n = 25 for placebo).

[d] P-values are from Fisher's exact test for normalisation endpoints and Wilcoxon rank-sum test for all other endpoints.

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

Open-label period
Sixty-five of 66 patients entered the open-label period (up to 130 weeks) at a KANUMA dose of 1 mg/kg once every other week. In patients who had received KANUMA during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels. Four (4) of 65 patients in the open label period were dose escalated to 3 mg/kg once every other week based on clinical response.

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-cholesterol and HDL-cholesterol levels.

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 104-week treatment period.

Paediatric population
Fifty-six of 84 patients (67%) who received sebelipase alfa during clinical studies (LAL-CL01/LAL-CL04, LAL-CL02 and LAL-CL03) were in the paediatric and adolescent age range (1 month up to 18 years).

The European Medicines Agency has deferred the obligation to submit the results of studies with KANUMA in one or more subsets of the paediatric population in LAL deficiency (see section 4.2 for information on paediatric use).

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

Children and adults
The pharmacokinetics of sebelipase alfa in children and adults were determined using a population pharmacokinetic analysis of 65 patients with LAL deficiency who received intravenous infusions of KANUMA at 1 mg/kg once every other week in LAL-CL02. Twenty-four patients were aged 4-11 years, 23 were aged 12-17 years, and 18 were aged ≥ 18 years (Table 4). Based on a non-compartmental analysis of data from adults (LAL-CL01/LAL-CL-04), the pharmacokinetics of sebelipase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure observed between the 1 and 3 mg/kg dosages. No accumulation was seen at 1 mg/kg (once weekly or once every other week) or 3 mg/kg once weekly.

Table 4: Mean Population Pharmacokinetic Parameters

Pharmacokinetic Parameter	Study LAL-CL02 – Children and Adults 1 mg/kg once every other week					
	4-11 years old N=24		12-17 years old N=23		≥ 18 years old N=18	
	Week 0	Week 22*	Week 0	Week 22*	Week 0	Week 22*
AUC_{ss} (ng·hr/mL)	1133.8	941.6	1436.4	1453.6	1989.3	1861.0
C_{max} (ng/mL)	571.7	489.6	736.4	783.6	1076.9	957.0
T_{max} (hr)	1.2	1.3	1.2	1.1	1.4	1.3
CL (L/hr)	28.8	31.1	35.1	37.4	36.4	38.2
V_c (L)	3.3	3.6	5.0	5.4	5.5	5.3
$T_{1/2}$ (hr)	0.1	0.1	0.1	0.1	0.1	0.1

* Week 22 for placebo patients reset to Week 0, i.e. first week of active treatment
AUC_{ss} = Area under the plasma concentration time curve at steady-state
C_{max} = Maximum concentration
T_{max} = Time to maximum concentration
CL = Clearance
V_c = Central volume of distribution
$T_{1/2}$ = Half-life

Infants (< 6 months of age)
In LAL-CL03, sebelipase alfa was eliminated from the systemic circulation with a median $T_{1/2}$ of 0.1 hr (range: 0.1-0.2) at the 3 mg/kg once weekly dose (n = 4). The difference in exposures to sebelipase alfa between the once weekly 0.35 mg/kg and 3 mg/kg groups was more than dose proportional, with a 8.6-fold increase in dose resulting in a 9.6-fold increase in exposure for AUC and a 10.0-fold increase for C_{max}.

Linearity/non-linearity
Based on these data, the pharmacokinetics of sebelipase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure observed between the 1 and 3 mg/kg dose.

Special populations
During the covariate analysis of the population pharmacokinetics model for sebelipase alfa, age, body weight, and sex were not found to have a significant influence on CL and V_c of sebelipase alfa.

Sebelipase alfa has not been investigated in patients 2 to 4 years of age or patients aged 65 years or older.

There is limited information of 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.

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

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

Trisodium citrate dihydrate
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 reconstitution to minimize 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 solution in the vials should be inspected visually; the solution should be clear to slightly opalescent, colourless to slightly coloured (yellow). Due to the proteinaceous nature of the product, slight flocculation (e.g., thin translucent fibres) may be present in the vialed solution and is acceptable for use.
d. Do not use if the solution is cloudy, or if foreign particulate matter is present.
e. Up to 10 ml of solution should be slowly withdrawn from each vial and diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion. See 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 (1 mg/kg dose)*

Weight range (kg)	Total infusion volume (ml)
1-10	10
11-24	25
25-49	50
50-99	100
100-120	250

* 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.

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

7. MARKETING AUTHORISATION HOLDER

Synageva BioPharma Limited
1A Local Board Road
Watford
Hertfordshire WD17 2JP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1033/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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

Name and address of the manufacturer responsible for batch release

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

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**

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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 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, the measures described below:

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 yearly within PSURs Final study report expected in Jan 2027
Study LAL-CL08: an open-label, Phase 2 study in infants with rapidly progressive LAL Deficiency to explore long-term safety and efficacy data. The efficacy objectives are assessment of hepatic function overtime up to 3 years and survival at 12 months. The safety objectives should focus on hypersensitivity reactions, particularly anti-drug antibodies development impacting response to drug.	Final study report expected in December 2018

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 vial contains 20 mg sebelipase alfa in 10 ml of solution (2 mg/ml)

3. LIST OF EXCIPIENTS

Excipients:
Trisodium citrate dihydrate (see leaflet for further information)
Citric acid monohydrate
Human serum albumin
Water for injections

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.

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

Synageva BioPharma Ltd.
1A Local Board Road
Watford
Hertfordshire WD17 2JP
United Kingdom.

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

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
2. What you need to know before you are given KANUMA
3. How KANUMA is given
4. Possible side effects
5. How to store KANUMA
6. Contents of the pack and other information

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. **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.

- 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 and breast-feeding
You should not be given KANUMA if you are pregnant unless clearly necessary. It is not known whether sebelipase alfa passes into breast milk; therefore it is recommended that you stop breast-feeding or using KANUMA treatment while breast-feeding.

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

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

3. How KANUMA is given

The dose you or your child receives is based on your or your child's body weight. The recommended dose is 1 mg per kg body weight once every other week through a drip into a vein. For patients who have signs and symptoms of the disease when they are infants, the recommended starting dose is 1 mg/kg once weekly. 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. Dose adjustments may be considered based on how well you or your child responds to treatment. 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, swelling of the throat, rapid breathing, fast heartbeat, chest discomfort, mild swelling of eyelids, red eyes, runny nose, flushing, and hives. **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 side effects reported in infants (1 to 6 months old) are:

eyelid swelling	agitation	high blood pressure
decreased muscle tone	difficulty breathing	wheezing
paleness	stuffy or swollen nose	sneezing
cough	heartburn (reflux diseases)	dry heaving
diarrhoea	hives	rash
vomiting	itching	raised rash
red swollen skin	fever	swelling
chills	rapid breathing	not enough oxygen in the blood
fast heartbeat	irritability	

Common side effects reported in children and adolescents (4 to 18 years old) and adults are:

severe allergic reaction (anaphylactic reaction)	infection of the urinary system	swelling of the eyelids
temporary increased cholesterol or triglyceride (fats) levels in the blood	fast heartbeat	anxiety
sleeplessness	dizziness	low blood pressure
redness in face	shortness of breath	swelling of the throat
diarrhoea	stomach ache	stomach bloating
nausea	hives	rash
itching	red swollen skin	increased menstrual bleeding
shivers	chest discomfort	swelling
tiredness	hardened area around the infusion site	fever

Frequency, type and severity of adverse reactions in children are the same as 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 (2 mg/ml).
- The other ingredients are trisodium citrate dihydrate (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. It is a solution that is clear to slightly opalescent, and colourless to slightly coloured.

Pack sizes: 1 vial containing 10 ml of concentrate.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Synageva BioPharma Limited
1A Local Board Road
Watford
Hertfordshire WD17 2JP
United Kingdom

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

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 reconstitution to minimize 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 solution in the vials should be inspected visually; the solution should be clear to slightly opalescent, colourless to slightly coloured (yellow). Due to the proteinaceous nature of the product, slight flocculation (e.g., thin translucent fibres) may be present in the vialed solution and is acceptable for use.
d. Do not use if the solution is cloudy, or if foreign particulate matter is present.
e. Up to 10 ml of solution should be slowly withdrawn from each vial and diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion. See 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)*

Weight range (kg)	Total infusion volume (ml)
1-10	10
11-24	25
25-49	50
50-99	100
100-120	250

* 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.

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