Summary of the risk management plan (RMP) for Kanuma (sebelipase alfa)

This is a summary of the risk management plan (RMP) for Kanuma, which details the measures to be taken in order to ensure that Kanuma is used as safely as possible.

Overview of disease epidemiology

Kanuma is a medicine used to treat patients with lysosomal acid lipase deficiency. This is a rare genetic disease caused by the lack of an enzyme called lysosomal acid lipase, which is needed to break down fats within cells. When the enzyme is absent or present only in low levels, fats accumulate in the body's cells, causing symptoms such as growth failure and liver damage. There are two forms of lysosomal acid lipase deficiency, with the disease in infants, also called Wolman disease, being the most severe. In its most severe form, the disease is usually fatal in the first year of life.

The rate of occurrence in infants is estimated to be 1 to 2 per million births and the condition is found in about 1 out of 528,000 infants. The disease that presents in older children and adults is estimated to occur in between 7.7 and 25 people per million.

Summary of treatment benefits

The active substance in Kanuma, sebelipase alfa, is a copy of the enzyme that is lacking in patients with lysosomal acid lipase deficiency. Kanuma is available as a concentrate to be made into a solution for infusion (drip) into a vein.

Kanuma has been studied in 2 main studies in patients with lysosomal acid lipase deficiency. The first study involved 9 infants with growth failure or other evidence of rapidly progressing disease in their first 6 months of life. The study showed that 6 out of the 9 infants given Kanuma survived to 1 year of age. Growth improvements were also observed in all 6 surviving infants.

The second study involved 66 patients (children and adults) and compared Kanuma with placebo (a dummy treatment). The main measure of effectiveness was the proportion of patients who achieved normal levels of a liver enzyme called ALT after 5 months of treatment. High levels of ALT enzymes are a sign of liver damage. In this study, 31% of the patients given Kanuma (11 out of 36) achieved normal levels of ALT enzymes, compared with 7% of the patients given placebo (2 out of 30).

Unknowns relating to treatment benefits

Because of the rarity of the disease, not all patient groups were well represented in the clinical population studied. The clinical trial development programme focused on the population most frequently affected by the disease: infants and children. The efficacy of Kanuma has not been studied in patients older than 65 years of age who are very rarely identified with this disease. There is no evidence to suggest that treatment benefits would be any different in older patients. Only limited data are available for the age range of 2 to 4 years. Also not all ethnic origins were adequately represented in the clinical population studied. However, different ethnic groups are not expected to respond differently to this treatment. No specific studies have been performed in patients with kidney impairment, but reduced kidney function is not expected to affect the way sebelipase alfa is eliminated from the body.

Summary of safety concerns

Risk	What is known	Preventability
Allergic reactions including the risk of severe whole-body reaction (Hypersensitivity reactions including anaphylaxis)	In clinical studies, 21 of 106 (20%) patients treated with Kanuma, 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 an allergic reaction. The reported signs and symptoms included abdominal (tummy) pain, agitation, chills, diarrhoea, eczema, high blood pressure, irritability, fluid build-up and swelling including in the throat, nausea, paleness, itching, fever, rash, rapid heartbeat and vomiting. The majority of reactions occurred during or within 4 hours after the infusion. Three patients experienced signs and symptoms consistent with a severe allergic reaction, including chest discomfort, red eyes, eyelid swelling, difficulty breathing, itchy rash, runny nose, rapid heartbeat and rapid breathing.	In susceptible patients antihistamines and/or corticosteroids will be given before Kanuma infusion. The management of allergic reactions to the infusion may include temporarily interrupting the infusion or lowering the infusion rate. If interrupted, the infusion may be resumed at a slower rate with increases as tolerated. After the first infusion or after any dose increases, the patient should be monitored for an hour for any signs or symptoms of allergic reactions.

Important potential risks

Important potential risk	What is known
Development of antibodies	In clinical trials, some patients developed antibodies against the active

against sebelipase alfa (Anti-drug antibody development impacting response to the medicine)	substance in Kanuma, sebelipase alfa. The effects of these antibodies on treatment response or adverse events are not well understood at this time but are being investigated in post-approval studies.
Use in patients with egg allergy	Kanuma is a protein that is produced from the egg white of hens. Patients with known egg allergies were not included in clinical trials. Therefore, Kanuma must not be used in patients with a life-threatening allergy to eggs.

Missing information

Missing information	**What is known**
Safety and efficacy in patients older than 65 years of age	The safety and efficacy of Kanuma in patients older than 65 years of age have not been evaluated and no alternative dose schedule can be recommended for these patients.
Safety and efficacy in children aged 2 to 4 years	The data from the clinical trials in this age group of children are limited.
Use in pregnant and breastfeeding women	There are no data from the use of Kanuma in pregnant women. Animal studies do not indicate direct or indirect harmful effects in pregnancy. As a precautionary measure, it is preferable to avoid use of Kanuma during pregnancy. There are no data from studies in breastfeeding women. It is not known whether sebelipase alfa passes into human milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Kanuma therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
Long-term safety and efficacy data	Long-term safety and efficacy data are currently not available. The longest exposure is currently approximately 2.5 years. However, information is planned to be gathered through the observational registry which is proposed to monitor long-term efficacy and safety of Kanuma in paediatric and adult patients for a period of up to 10 years.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Kanuma can be found on www.swissmedicinfo.ch.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures are for the following risks:

Allergic reactions including the risk of acute severe whole-body reaction and development of antibodies against sebelipase alfa

Risk minimisation measure: Educational material
Objective and rationale: To inform healthcare professionals of the risks of allergic reactions and the development of antibodies against the medicine
Description: All healthcare professionals who are expected to use Kanuma should be provided with educational material to inform them of: • the risks of allergic reactions and the development of antibodies against the medicine; • how to manage patients experiencing severe allergic reactions; • how to monitor for the potential development of antibodies against the medicine (the test for monitoring antibodies will be provided by the company that markets Kanuma); • the observational registry and the importance of enrolling patients.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
LAL-CL06: a single-arm phase 2 study in a broad population of children and adults with LAL deficiency who are not eligible for other currently enrolling investigational studies of sebelipase alfa	Efficacy and safety; pharmacokinetic.	Safety and efficacy in a paediatric population 2-4 years of age. Anti-drug antibody development impacting response to treatment.	Ongoing	June 2017
LAL-CL08: an open-	Efficacy and safety;	Long-term safety and	Ongoing	December 2018

label, phase 2 study in infants with rapidly progressive LAL deficiency	pharmacokinetic.	efficacy data. Anti-drug antibody development impacting response to treatment.		
An observational disease and clinical outcomes registry of patients with lysosomal acid lipase (LAL) deficiency (Wolman disease and cholesteryl ester storage disease) and carriers of the disorder	The objective of the LAL deficiency registry is to use uniform methodology to collect longitudinal data over an extended period to provide information to: - Further understand the disease, its progression and any associated complication. - Evaluate the long-term efficacy and safety of sebelipase alfa. - Evaluate the long-term effectiveness of other potential therapeutic and supportive interventions. - Improve care through evidence-based patient management. - Understand the relationship between LAL deficiency and access to care.	Hypersensitivity reactions including anaphylaxis. ADA development impacting response to treatment. Safety and efficacy in patients older than 65 years of age. Safety and efficacy in a paediatric population 2-4 years of age. Use in pregnant or breastfeeding women. Long-term safety and efficacy data.	Planned	Interim reports will be aligned with PSUR submissions. The registry is scheduled to run 10 years; the final report will be submitted 12 months after completion of the registry period.

Studies which are a condition of the marketing authorisation

Study LAL-CL08 and the above-mentioned registry are conditions of the marketing authorisation of Kanuma.

Summary of changes to the risk management plan over time

Not applicable.