PART VI: Summary of the risk management plan

Summary of risk management plan for Kanuma (sebelipase alfa)

This is a summary of the risk management plan (RMP) for Kanuma. The RMP details important risks of Kanuma, how these risks can be minimised, and how more information will be obtained about Kanuma's risks and uncertainties (missing information).

Kanuma's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Kanuma should be used.

This summary of the RMP for Kanuma should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Kanuma's RMP.

I. The medicine and what it is used for

Kanuma is authorised for treatment of patients of all ages with lysosomal acid lipase deficiency, which is a genetic disease that leads to liver damage, high blood cholesterol, and other complication due to a build-up of certain types of fats (cholesteryl esters and triglycerides). It contains sebelipase alfa as the active substance and it is given by infusion.

Further information about the evaluation of Kanuma's benefits can be found in Kanuma's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kanuma, together with measures to minimise such risks and the proposed studies for learning more about Kanuma's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Kanuma, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Kanuma is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Kanuma are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kanuma. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Hypersensitivity reactions including anaphylaxis
Important potential risks	Anti-drug antibodies (ADA) development impacting response to drug Use in patients with egg allergy
Missing information	Safety and efficacy in patients older than 65 years of age Safety and efficacy in paediatric population 2-4 years of age Use in pregnant and lactating women Long-term safety and efficacy data

II.B Summary of important risks

Identified risk: Hypersensitivity reactions including anaphylaxis	
Evidence for linking the risk to the medicine	This risk is based on the experience from clinical trials and post-marketing experience as well as known potential of all medicinal products and on the class effect of all therapeutic proteins, including Kanuma (sebelipase alfa).
Risk factors and risk groups	The experience with ERT in lysosomal storage disorder noted that patients with ADAs were more likely to experience hypersensitivity, including anaphylaxis (Kishnani, 2016). However, the pooled data analysis for KANUMA from 6 completed clinical trials did not confirm an association of ADA development with hypersensitivity reactions, including anaphylaxis described in the literature. General risk factors for drug-mediated hypersensitivity associated with infusions in indications outside of lysosomal storage disorder include a previous history of an immediate hypersensitivity reaction, atopy, obstructive lung disease, intravenous delivery of the drug and interrupted administration of the antigen (Miebach, 2009).
Risk minimisation measures	<u>Routine risk minimisation measures</u>: SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 Need for availability of appropriate medical support during administration stated in SmPC section 4.4 Patient observation for one-hour post initial/dose-escalated infusion stated in SmPC section 4.4

	Recommendations for management of hypersensitivity listed in SmPC section 4.4 Recommendation for ADA testing in case of severe infusion-related reactions included in SmPC section 4.4 Restricted medical prescription Additional risk minimisation measures: Guide for healthcare professionals
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The LAL Deficiency Registry See section II.C of this summary for an overview of the post-authorisation development plan.

Kishnani PS, Dickson PI, Muldowney L, Lee JJ, Rosenberg A, Abichandani R, Bluestone JA, Burton BK, Dewey M, Freitas A, Gavin D, Griebel D, Hogan M, Holland S, Tanpaiboon P, Turka LA, Utz JJ, Wang YM, Whitley CB, Kazi ZB, Pariser AR. Immune response to enzyme replacement therapies in lysosomal storage diseases and the role of immune tolerance induction. Mol Genet Metab. 2016; 117(2): 66-83.

Miebach E. Management of infusion-related reactions to enzyme replacement therapy in a cohort of patients with mucopolysaccharidosis disorders. Int J Clin Pharmacol Ther 2009; 47 Suppl 1: S100-6

Potential risk: ADA development impacting response to drug	
Evidence for linking the risk to the medicine	This potential risk is based on the known potential of all medicinal products and on the class effect of all therapeutic proteins, including Kanuma (sebelipase alfa).
Risk factors and risk groups	The absence or presence of the mutant enzyme protein (i.e. cross-reactive immunologic material negative or positive, respectively) in patients with lysosomal storage disease primarily determines the immunologic response to enzyme replacement therapy. No data were identified for the distribution of cross-reactive immunologic material or other risk factors for ADA development in patients with lysosomal acid lipase deficiency. In Study LAL-CL08, patients who completely lack the ability to produce both enzymes showed the highest levels of ADAs and neutralising antibodies, most likely related to the lack of enzyme and immune intolerance. Two patients who completely lack the ability to produce both enzymes underwent successful bone marrow and haematopoietic stem cell transplantation, resulting in a decrease in ADAs and neutralising antibodies attributed to the presence of enzyme, which in turn lowered the need for higher doses of sebelipase alfa.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 Recommendation for ADA testing in case of severe infusion-related reactions is included in SmPC section 4.4. Restricted medical prescription Additional risk minimisation measures:

	Guide for healthcare professionals
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The LAL Deficiency Registry See section II.C of this summary for an overview of the post-authorisation development plan.

Potential risk: Use in patients with egg allergy	
Evidence for linking the risk to the medicine	Sebelipase alfa (active ingredient of Kanuma) is produced in egg white of transgenic hens. Subjects with known egg allergies have been excluded from clinical trials and as such, the data on use of Kanuma in this patient population and the potential outcomes is limited.
Risk factors and risk groups	Studies suggest that egg allergy is more common in children than in adults and that many children will develop a tolerance for eggs as they age towards adulthood (Savage, 2007).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 2, 4.3, and 4.4 PL section 2 Additional risk minimisation measures: None

Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. J Allergy Clin Immunol. 2007;120:1413–7.

Missing information: Safety and efficacy in patients older than 65 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The LAL Deficiency Registry See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Safety and efficacy in paediatric population 2-4 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The LAL Deficiency Registry

Missing information: Safety and efficacy in paediatric population 2-4 years of age	
	See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in pregnant and lactating women	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.6 and 5.3 PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The LAL Deficiency Registry See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety and efficacy data	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The LAL Deficiency Registry See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

The LAL Deficiency Registry

Purpose of the study:

The objective of the LAL Deficiency Registry is to use uniform methodology to collect longitudinal data over an extended period to provide information that can be used to:

- Further understand the disease, its progression and any associated complications.
- Evaluate the long-term effectiveness and safety of sebelipase alfa.
- Evaluate the long-term effectiveness of other potential therapeutic and supportive interventions.
- Evaluate information on sebelipase exposure in patient populations for which limited information is available, including paediatric patients 2 to 4 years in age, adults > 65 years in age, and patients who are pregnant or lactating

- Improve care through evidence-based patient management.
- Understand the relationship between lysosomal acid lipase deficiency, access to care (e.g. access to relevant clinical specialists with specific disease monitoring and/or management strategies), and clinical outcomes.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Kanuma.