Part VI: Summary of the risk management plan

Summary of risk management plan for LysaKare (2.5% lysine arginine amino acid solution in sterile water)

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

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

This summary of the RMP for LysaKare 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 LysaKare's RMP.

I. The medicine and what it is used for

LysaKare is indicated for use as a renal protective agent during Peptide Receptor Radionuclide Therapy (PRRT) with Radiolabeled Somatostatin Analogs (RSAs). It contains 2.5% lysine arginine solution in sterile water as the active substance and it is given by intravenous route 250 mL/h for a total of 4 hours.

Further information about the evaluation of LysaKare’s benefits can be found in LysaKare’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/lysakare.

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

Important risks of LysaKare, together with measures to minimise such risks are outlined below.

- Specific information, such as warnings, precautions, in the package leaflet and SmPC addressed to patients and healthcare professionals;

Together, these measures constitute *routine risk minimisation* measures.

II.A List of important risks and missing information

Important risks of LysaKare 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 LysaKare. 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	Hyperkalaemia
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk Hyperkalaemia	
Evidence for linking the risk to the medicine	In PRRT, amino acid solutions are used as co infusion with RSA. Majority of the publications described about the active substances, L-lysine and L-arginine which are positively charged amino acids that competitively inhibit the proximal tubular reabsorption of the radiopeptide to reduce the kidney retention of the radiolabelled compound, thus reducing the radiation exposure to the kidney. Few publications report hyperkalaemia as an adverse effect of co infused amino acids. A frequently cited mechanism for these findings is that acidosis causes potassium to move from cells to extracellular fluid (plasma) in exchange for hydrogen ions. There are several potential mechanisms described in the literature for the increased serum potassium associated with infusions of any cationic amino acids. These include the direct displacement of intracellular potassium by the cationic amino acids, and a shift of intracellular potassium to the cell exterior secondary to increased production of ketonic bodies in an acidic environment (Barone et al 2004) Hyperkalaemia associated with lysine may be caused by the ketogenic characteristics of lysine that lowers intracellular pH causing an outwardly directed potassium flux (Lapa et al 2014b). Lastly, diarrhea is one of the common symptoms in small bowel and pancreatic NETs (Basuroy et al 2018). Dehydration in these patients due to diarrhea may lead to hypotension and decreased tissue perfusion leading to metabolic acidosis with subsequent elevation of potassium (Leslie et al 2018) However, the doses of the amino acids vary in each of the publication. A common observation noted was that the higher the doses of Lysine and Arginine, the patients are more prone to experience Hyperkalaemia. The levels of hyperkalaemia observed in some patients were severe (as reported) and required correction and close monitoring. In the proposed LysaKare formulation with 2.5% solution, the instances of increased serum potassium levels reported in the literature are transient and generally mild; serum

	potassium returns to normal levels in 24h and it is not associated with clinically relevant symptoms.
Risk factors and risk groups	Patients with existing hyperkalaemia Patients with reduced creatinine clearance < 30 mL/min: The use of arginine and lysine has not been specifically studied in patients with renal impairment. Arginine and lysine are substantially excreted and re-absorbed by the kidney, and its efficacy in the reduction of renal radiation exposure is dependent on this. Due to potential for clinical complications related to volume overload, use of LysaKare in patients with creatinine clearance < 30 mL/min is not recommended. Patients with cardiac insufficiency are known to have problems with fluid overload when receiving intravenous fluids. Thus, large volume infusions associated with parenteral amino acid formulations are not recommended in patients with cardiac insufficiency for their approved indications. Patients with severe hepatic impairment who could develop potential metabolic overload Elderly patients who are likely to have reduced renal function are at risk, care should be taken in determining eligibility based on creatinine clearance
Risk minimisation measures	Routine risk minimisation measures beyond adverse reactions reporting and signal detection. Hyperkalaemia specific follow up questionnaire to allow a sound medical assessment of cases reporting Hyperkalaemia. Sections in SmPC: 4.4 Special warnings and precautions for use 4.8 Undesirable effects <u>Additional pharmacovigilance activities</u>: A Category 3 post-authorization safety study to assess the effect of LysaKare administration on potassium blood levels concentration up to 24h compared to baseline Additional risk minimisation measures None

Important potential risk

None

Missing information

None

II.C Post-authorisation development plan

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

Not applicable

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

Not applicable.