1 Tradename

LysaKare® 25 g/25 g solution for infusion

2 Description and composition

Pharmaceutical form

Solution for infusion.

Clear, colorless solution, free from visible particles.

pH: 5.1 to 6.1

Osmolality: 420 to 480 mOsm/kg

Active substances

One 1,000 mL infusion bag contains 25 g of L-arginine hydrochloride (equivalent to 20.7 g arginine) and 25 g of L-lysine hydrochloride (equivalent to 20 g lysine).

Excipients

Water for injection.

3 Indications

LysaKare is indicated for reduction of renal radiation exposure during peptide-receptor radionuclide therapy (PRRT) with lutetium (^{177}Lu) oxodotreotide in adults.

4 Dosage regimen and administration

LysaKare is indicated for administration during PRRT with lutetium (^{177}Lu) oxodotreotide. It should therefore only be administered by a healthcare provider experienced in the use of PRRT.

Please refer to full prescribing information of lutetium (^{177}Lu) oxodotreotide.

Dosage regimen

General target population

Adults

The recommended treatment regimen in adults consists of infusion of a full bag of LysaKare concomitantly with lutetium (^{177}Lu) oxodotreotide. The dose of LysaKare should not be decreased even if the dose of lutetium (^{177}Lu) oxodotreotide is reduced.

Antiemetics

Pre-treatment with an antiemetic is recommended to prevent nausea and vomiting. Antiemetics should be administered with sufficient lead time prior to the start of LysaKare. In case of severe nausea or vomiting during the infusion of LysaKare despite administration of a preventive antiemetic, an antiemetic of a different pharmacological class can be administered.

Please refer to the full prescribing information of the antiemetic for administration instructions.

Special populations

Renal impairment

Due to the potential for clinical complications related to volume overload and an increase in serum potassium associated with the use of LysaKare, this medicinal product should not be administered in patients with creatinine clearance <30 mL/min. Care should be taken with LysaKare use in patients with creatinine clearance between 30 and 50 mL/min, due to a potential increased risk of transient hyperkalemia in these patients (see section 6 Warnings and precautions).

Hepatic impairment

The use of arginine and lysine has not been specifically studied in patients with severe hepatic impairment (see section 6 Warnings and precautions).

Pediatric patients (below 18 years)

The safety and efficacy of LysaKare in pediatric patients (below 18 years) have not been established. No data are available.

Geriatric patients (65 years or above)

There are limited data on the use of LysaKare in patients 65 years of age or above.

Elderly patients are more likely to have decreased renal function, and care should therefore be taken in determining eligibility based on creatinine clearance (see section 6 Warnings and precautions).

Method of administration

For intravenous (IV) use only.

To achieve optimal renal protection, LysaKare should be administered as a 4-hour infusion (250 mL/hour) and must be initiated 30 minutes prior to administration of lutetium (^{177}Lu) oxodotreotide.

Infusion of LysaKare and lutetium (^{177}Lu) oxodotreotide through a separate venous access in each of the patient's arms is the preferred method. However, if two intravenous lines are not possible due to poor venous access or institutional/clinical preference, LysaKare and lutetium (^{177}Lu) oxodotreotide may be infused through the same line via a three-way valve, taking into consideration flow rate and maintenance of venous access.

5 Contraindications

None.

6 Warnings and precautions

Please refer to the prescribing information of lutetium (^{177}Lu) oxodotreotide for warnings related to lutetium (^{177}Lu) oxodotreotide.

Hyperkalemia

A transient increase in serum potassium levels occurs in most patients receiving LysaKare, with maximum serum potassium levels reached approximatively 4 to 5 hours after the start of the infusion and usually returning to normal levels within 24 hours after the start of the amino acid solution infusion. Serum potassium level increases are generally mild and transient. Patients with reduced creatinine clearance may be at increased risk for transient hyperkalemia (see section 6 Warnings and precautions, Renal impairment).

Serum potassium levels must be tested before each administration of LysaKare. In case of hyperkalemia, the patient's history of hyperkalemia and concomitant medication should be checked. Hyperkalemia must be corrected accordingly before starting the LysaKare infusion (see section 12 Clinical studies).

In case of clinically significant hyperkalemia, patients should be retested prior to LysaKare infusion to confirm that hyperkalemia has been successfully corrected (see section 12 Clinical studies). Patients should be monitored closely for signs and symptoms of hyperkalemia, e.g. dyspnea, weakness, numbness, chest pain and cardiac manifestations (conduction abnormalities and cardiac arrhythmias). An electrocardiogram (ECG) should be performed prior to discharging the patient.

Vital signs should be monitored during the infusion regardless of baseline serum potassium levels. Patients should be encouraged to remain hydrated and to urinate frequently before, on the day of and the day after administration (e.g. 1 glass of water every hour) to facilitate elimination of excess serum potassium.

In case hyperkalemia symptoms develop during LysaKare infusion, appropriate corrective measures must be taken. In case of severe symptomatic hyperkalemia, discontinuation of LysaKare infusion should be considered, taking into consideration the risk-benefit of renal protection versus acute severe hyperkalemia.

Renal impairment

The use of arginine and lysine has not been specifically studied in patients with renal impairment. Arginine and lysine are substantially excreted and reabsorbed by the kidney, and their efficacy in the reduction of renal radiation exposure is dependent on this. Due to the potential for clinical complications related to volume overload and an increase in serum potassium associated with the use of LysaKare, this medicinal product should not be administered in patients with creatinine clearance <30 mL/min. Care should be taken with LysaKare use in patients with creatinine clearance between 30 and 50 mL/min, due to a potential increased risk of transient hyperkalemia. Kidney function (creatinine and creatinine clearance) should be tested before each LysaKare infusion.

Hepatic impairment

The use of arginine and lysine has not been studied in patients with severe hepatic impairment. Hepatotoxicity has been observed in patients receiving complex amino acid solutions administered as part of total parenteral nutrition (TPN) protocols , therefore, care should be taken with LysaKare use in patients with severe hepatic impairment defined as either total bilirubinemia >3 times the upper limit of normal or a combination of albuminemia <30 g/L and international normalized ratio (INR) >1.5. Liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin, bilirubin) should be tested before each LysaKare infusion.

Heart failure

Due to the potential for clinical complications related to volume overload, care should be taken with LysaKare use in patients with severe heart failure defined as class III or IV in the New York Heart Association (NYHA) classification.

Patients with severe heart failure defined as class III or IV in the NYHA classification should only be treated with LysaKare after careful benefit-risk assessment, taking into consideration the volume and osmolality of Lysakare solution.

Metabolic acidosis

Metabolic acidosis has been observed with complex amino acid solutions administered as part of total parenteral nutrition (TPN) protocols. Shifts in acid-base balance alter the balance of extracellular-intracellular potassium and the development of acidosis may be associated with rapid increases in plasma potassium. Metabolic acidosis was also observed with LysaKare based on laboratory parameters only, which usually resolved within 24 hours of administration, and without clinical symptoms.

7 Adverse drug reactions

Summary of the safety profile

The clinical safety of LysaKare is based on publications of studies with amino acid solutions that had the same composition as LysaKare with regard to amino acid content. These studies included over 900 patients receiving more than 2,500 doses of arginine and lysine, as well as patients receiving commercially available complex amino acid solutions, during PRRT with various radiolabeled somatostatin analogs.

There are limited safety data on the use of arginine and lysine solutions for infusion without concomitant administration of PRRT, which also includes the use of antiemetics as pre-medication and often the concomitant use of short acting somatostatin analogs.

The most common adverse reactions related to the amino acid solutions are nausea (approximately 25%) and vomiting (approximately 10%). Cases of hyperkalaemia have also been reported (see section 6 Warnings and precautions). These adverse reactions are mostly mild to moderate.

In a Phase IV multicenter open-label study using LysaKare without concomitant administration of PRRT, no new adverse drug reactions were identified, and the safety profile remains consistent with the safety profile as presented based on literature and clinical practice.

Tabulated summary of adverse drug reactions

The adverse reactions (Table 7-1) from publications are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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 7-1 Adverse drug reactions

Adverse drug reaction	Frequency category
Metabolism and nutrition disorders	
Hyperkalaemia	Not known
Nervous system disorders	
Dizziness	Not known
Headache	Not known
Vascular disorders	
Flushing	Not known
Gastrointestinal disorders	
Nausea	Very common
Vomiting	Very common
Abdominal pain	Not known

8 Interactions

No interaction studies have been performed.

No interaction with other medicinal products is expected since there is no information that other medicinal products are re-absorbed by the same kidney re-absorption mechanism.

9 Pregnancy, lactation, females and males of reproductive potential

Please refer to the prescribing information of lutetium (^{177}Lu) oxodotreotide for pregnancy, lactation and female and male contraception recommendations related to lutetium (^{177}Lu) oxodotreotide.

9.1 Pregnancy

Risk summary

There are no adequate and well-controlled studies with LysaKare in pregnant women and no animal reproduction studies have been conducted.

9.2 Lactation

Risk summary

There are no data regarding the effects of LysaKare on the breast-fed child or on milk production. Arginine and lysine, being naturally occurring amino acids, are present in human milk.

9.3 Females and males of reproductive potential

Infertility

There are no data on the effects of LysaKare on fertility.

10 Overdosage

In the event of over-hydration or solute overload, elimination should be promoted by forced diuresis and frequent bladder voiding.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: All other therapeutic products, detoxifying agents for antineoplastic treatment, ATC code: V03AF11.

Mechanism of action (MOA)

Arginine and lysine undergo glomerular filtration and, via competition, interfere with renal resorption of lutetium (^{177}Lu) oxodotreotide, reducing the radiation dose delivered to the kidney.

Pharmacokinetics (PK)

Arginine and lysine are naturally occurring amino acids that follow physiological pharmacokinetic steps and biochemical processes after infusion.

Absorption

LysaKare is intended for intravenous use, and is therefore 100% bioavailable.

Distribution

Transient elevations in plasma arginine and lysine are observed after intravenous administration, whereupon the highly water-soluble amino acids are quickly distributed throughout tissues and body fluid.

Biotransformation/metabolism

Like other naturally occurring amino acids, arginine and lysine serve as building blocks in protein anabolism and as precursors for several other products, including nitric oxide, urea, creatinine, and acetyl-coenzyme A.

Elimination

Arginine and lysine are rapidly distributed. Based on a study with 30 g arginine infused over 30 minutes, plasma elimination of amino acids follows at least a biphasic or triphasic decline, with levels returning to baseline within 6 hours post-dose. Initial rapid clearance is through glomerular filtration in the kidney in the first 90 minutes post-infusion. Remaining amino acid is removed by non-renal clearance.

Pediatric patients (below 18 years)

No pharmacokinetic data are available on the use of arginine and lysine at the same dose as LysaKare and for the same indication in pediatric patients.

12 Clinical studies

Clinical efficacy and safety for arginine and lysine are based on published literature of studies using solutions with the same arginine and lysine content as LysaKare.

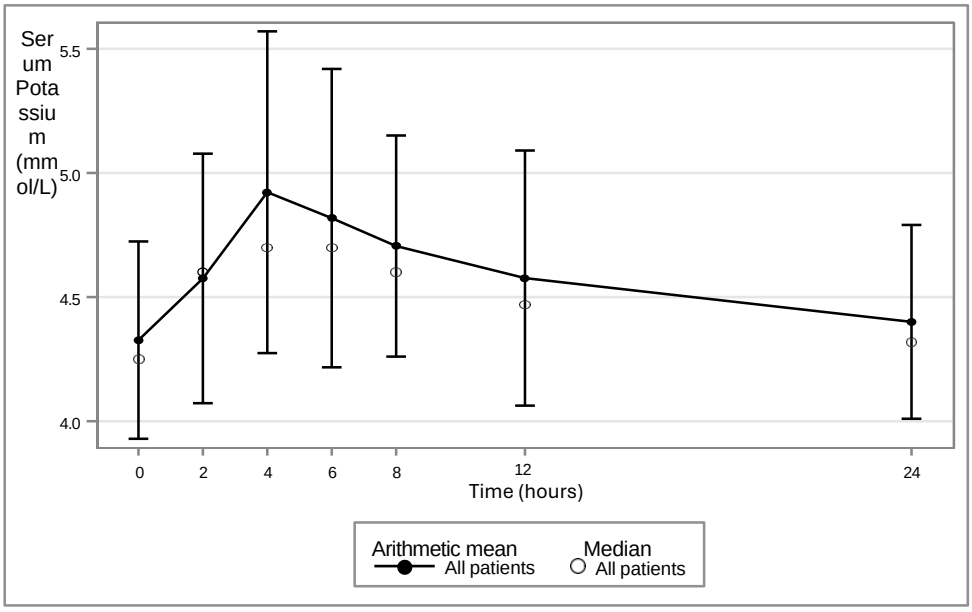
The toxicities that are observed following administration of PRRT are directly due to the radiation- absorbed dose to organs. The kidneys are the critical organs for lutetium (^{177}Lu) oxodotreotide toxicity and the dose limiting organ if amino acids are not administered to reduce renal uptake and retention.

A dosimetry study including 6 patients showed that a 2.5% lysine-arginine amino acid solution reduced renal radiation exposure by about 47% as compared to no treatment, without having an effect on tumor uptake of lutetium (^{177}Lu) oxodotreotide. This reduction in renal radiation exposure mitigates the risk for radiation-induced renal injury.

Based on a publication of the largest study using arginine and lysine in the same quantities as LysaKare, the average kidney absorbed dose, as determined by planar imaging dosimetry, was 20.1±4.9 Gy, which is below the established threshold for increased risk of renal toxicities of 23 Gy.

A Phase IV multicenter open label study was conducted to assess the effect of LysaKare on serum potassium concentrations and characterization of the safety profile. A total of 41 patients with somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumours (GEP-NET) who were eligible for lutetium (^{177}Lu) oxodotreotide treatment, received LysaKare without PRRT. The primary endpoint was to evaluate serum potassium levels after LysaKare administration at 2, 4, 6, 8, 12 and 24 hours. In 25 patients who were evaluable for primary analysis, the mean (SD) serum potassium level pre-dose was 4.33 (0.39) mmol/L and peaked at 4.92 (0.65) mmol/L at 4 hours post-dose with a mean absolute change (SD) of 0.60 (0.67) mmol/L, then gradually returned to around pre-dose level 24 hours post-dose with a mean serum potassium level of 4.40 (0.39) mmol/L and a mean serum potassium absolute change of 0.07 (0.39) mmol/L (Figure:12-1). The mean (SD) of maximum serum potassium change was 0.82 (0.617) mmol/L, (range: -0.6 to 2.6 mmol/L). The median (range) time to maximum change in serum potassium was 4.3h (2 to 24 h).

Figure 12-1 Mean (SD) concentration-time profiles for serum potassium levels



There were no serious adverse events leading to treatment interruption or discontinuation reported during this study. Overall, the safety profile of LysaKare remains consistent with the current safety profile as presented based on literature and clinical practice.

13 Non-clinical safety data

There were no non-clinical studies conducted with LysaKare.

14 Pharmaceutical information

Incompatibilities

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

Special precautions for storage

Store below 25˚C.

The product is packaged in a Polypropylene (PP) bag.

Special precautions for disposal

This medicinal product is for single use only.

Do not remove unit from overwrap until ready to use.

Do not use if overwrap has been previously opened or damaged. The overwrap is a moisture barrier.

Do not reconnect partially used bags.

LysaKare must not be diluted.

Do not use solutions which are cloudy or have deposits. This may indicate that the product is unstable or that the solution has become contaminated.

Once the container has been opened, the contents should be used immediately.

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

Manufacturer:

See folding box.

® = registered trademark

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