1 Tradename

LysaKare® 25 g/25 g solution for infusion

2 Description and composition

Pharmaceutical form

Solution for infusion (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 injections.

3 Indications

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

4 Dosage regimen and administration

Since LysaKare is indicated for administration during PRRT with lutetium (177Lu) oxodotreotide, it should only be administered by a healthcare provider experienced in the use of PRRT.

Please refer to full prescribing information of lutetium (177Lu) 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 (177Lu) oxodotreotide. The dose of LysaKare should not be decreased even if the dose of lutetium (177Lu) oxodotreotide is reduced.

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. 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 of potassium in blood associated with the use of LysaKare, this 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 Warnings and precautions).

Hepatic impairment

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

Pediatric patients (below 18 years)

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

Geriatric patients (65 years or above)

No studies have been performed in patients 65 years of age or above.

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

Method of administration

For intravenous (IV) use only.

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

LysaKare and lutetium (177Lu) oxodotreotide must be administered through separate infusion lines.

5 Contraindications

None.

6 Warnings and precautions

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

Hyperkalemia

An increase of serum potassium levels may occur in patients receiving LysaKare. According to limited available data with arginine and lysine solutions, maximum serum potassium levels should be reached approximatively 4 to 5 hours after the start of the infusion and should return to normal levels by 24 hours. Serum potassium level increases were generally mild and transient.

Serum potassium levels must be tested before each treatment with 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.

In case of pre-existing clinically significant hyperkalemia, a second monitoring prior to LysaKare infusion must confirm that hyperkalemia has been successfully corrected. The patient 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 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 instructed to drink substantial quantities of water (at least 1 glass every hour) on the day of infusion to remain hydrated and facilitate excretion 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 of potassium in blood associated with the use of LysaKare, this 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 hepatic impairment with either total bilirubinemia >3 times the upper limit of normal or albuminemia <30 g/L and prothrombin ratio <70%. 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 class IV in the New York Heart Association (NYHA) classification.

Patients with severe heart failure defined as class III or class IV in the NYHA classification should only be treated with LysaKare after careful benefit-risk assessment.

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.

7 Adverse drug reactions

Summary of the safety profile

The clinical safety of LysaKare is based on publications of studies with amino acid solutions with the same composition with regards to the amino acid content, involving 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 very 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 Warnings and precautions). These adverse reactions are mostly mild to moderate.

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 product is expected since there is no information that other drugs 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 (177Lu) oxodotreotide for pregnancy, lactation and female and male contraception recommendations related to lutetium (177Lu) 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, the elimination should be promoted by frequent micturition or 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 (177Lu) 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

Due to the intravenous route of administration, LysaKare is 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 serve 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 radiation- absorbed dose to organs. The kidneys are the critical organs for toxicity for lutetium (177Lu) oxodotreotide 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 (177Lu) 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.

13 Non-clinical safety data

There are 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 PolyVinyl Chloride (PVC) 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.

Information issued: Aug2019.SIN

® = registered trademark

Product owner:

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