

1. NAME OF THE MEDICINAL PRODUCT

LysaKare 25 g/25 g solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 1 000 mL bag contains 25 g of L-arginine hydrochloride and 25 g of L-lysine hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless solution, free from visible particles

pH: 5.1 to 6.1

Osmolality: 420 to 480 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

Adults

The recommended treatment regimen in adults consists of infusion of a full bag of LysaKare concomitantly with lutetium (^{177}Lu) oxodotreotide infusion, even when patients require PRRT dose reduction.

Antiemetics

Pre-treatment with an antiemetic 30 minutes prior to the start of LysaKare infusion is recommended to reduce the incidence of nausea and vomiting. 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

Elderly

There are limited data on the use of LysaKare in patients aged 65 years 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 4.4).

Hepatic impairment

The use of arginine and lysine has not been specifically studied in patients with severe hepatic impairment (see section 4.4).

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 hyperkalaemia in these patients. The pharmacokinetic profile and safety of lutetium (^{177}Lu) oxodotreotide in patients with baseline severe renal impairment (creatinine clearance <30 mL/min by Cockcroft-Gault formula) or end-stage renal disease have not been studied. Treatment with lutetium (^{177}Lu) oxodotreotide in patients with kidney failure with creatinine clearance <30 mL/min is contraindicated. Treatment with lutetium (^{177}Lu) oxodotreotide in patients with baseline creatinine clearance <40 mL/min (using Cockcroft-Gault formula) is not recommended. No dose adjustment is recommended for renally impaired patients with baseline creatinine clearance ≥ 40 mL/min and the benefit/risk balance for these patients will therefore always need to be weighed carefully. This should include consideration of an increased risk for transient hyperkalaemia in these patients (see section 4.4).

Paediatric population

The safety and efficacy of LysaKare in children aged less than 18 years have not been established.

No data are available.

Method of administration

For intravenous use.

To achieve optimal renal protection LysaKare should be administered as a 4-hour infusion (250 mL/hour) starting 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. The dose of the amino acid solution should not be decreased even if a reduced dose of lutetium (^{177}Lu) oxodotreotide is administered.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Pre-existing clinically significant hyperkalaemia if not adequately corrected before starting the LysaKare infusion (see section 4.4).

4.4 Special warnings and precautions for use

Hyperkalaemia

A transient increase in serum potassium levels occurs in most patients receiving LysaKare, with maximum serum potassium levels reached approximately 4 to 5 hours after the start of infusion and usually returning to normal levels by 24 hours after the start of the amino acid solution infusion. Such increases are generally mild and transient. Patients with reduced creatinine clearance may be at increased risk for transient hyperkalaemia (see "Renal impairment" in section 4.4).

Serum potassium levels must be tested before each administration of LysaKare. If hyperkalaemia is determined, the patient's history of hyperkalaemia and any concomitant medicinal product should be checked. Hyperkalaemia must be corrected accordingly before the infusion is started (see sections 4.3 and 5.1).

In case of clinically significant hyperkalaemia, patients should be retested prior to LysaKare infusion to confirm that hyperkalaemia has been successfully corrected (see section 5.1). Patients should be monitored closely for signs and symptoms of hyperkalaemia, e.g. dyspnoea, 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.

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

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. Kidney function (creatinine and creatinine clearance) should be tested before each administration.

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 hyperkalaemia in these patients. The pharmacokinetic profile and safety of lutetium (^{177}Lu) oxodotreotide in patients with baseline severe renal impairment (creatinine clearance <30 mL/min by Cockcroft-Gault formula) or end-stage renal disease have not been studied. Treatment with lutetium (^{177}Lu) oxodotreotide in patients with kidney failure with creatinine clearance <30 mL/min is contraindicated. Treatment with lutetium (^{177}Lu) oxodotreotide in patients with baseline creatinine clearance <40 mL/min (using Cockcroft-Gault formula) is not recommended. No dose adjustment is recommended for renally impaired patients with baseline creatinine clearance ≥ 40 mL/min and the benefit/risk balance for these patients will therefore always need to be weighed carefully. This should include consideration of an increased risk for transient hyperkalaemia in these patients.

Hepatic impairment

The use of arginine and lysine has not been studied in patients with severe hepatic impairment. Liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin, bilirubin) should be tested before each administration.

Care should be taken with LysaKare use in patients with severe hepatic impairment and in the event of either total bilirubinaemia >3 times the upper limit of normal or a combination of albuminaemia <30 g/L and international normalised ratio (INR) >1.5 during treatment. Treatment with lutetium (^{177}Lu) oxodotreotide is not recommended in these circumstances.

Heart failure

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

Treatment with lutetium (^{177}Lu) oxodotreotide is not recommended for patients with severe heart failure defined as class III or IV in the NYHA classification. The benefit/risk balance for these patients

will therefore always need to be weighed carefully, 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.

As LysaKare is administered with lutetium (^{177}Lu) oxodotreotide, please also refer to section 4.4 of the lutetium (^{177}Lu) oxodotreotide SmPC for further warnings specific to treatment with lutetium (^{177}Lu) oxodotreotide.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

There is no relevant use of this medicinal product in women of childbearing potential (see section 4.1).

Contraception in males and females

No animal studies of developmental toxicity have been conducted with LysaKare. Since LysaKare is used with lutetium (^{177}Lu) oxodotreotide, males and females of reproductive potential should be advised to use effective contraception during treatment with lutetium (^{177}Lu) oxodotreotide. Please also refer to section 4.6 of the lutetium (^{177}Lu) oxodotreotide SmPC for further guidance specific to treatment with lutetium (^{177}Lu) oxodotreotide.

Pregnancy

There are no data on the use of arginine and lysine in pregnant women.

There is no relevant use of this medicinal product in pregnant women. Lysakare is used with lutetium (^{177}Lu) oxodotreotide, which is contraindicated during established or suspected pregnancy and when pregnancy has not been excluded due to the risk associated with the ionising radiation. Please also refer to section 4.6 of the lutetium (^{177}Lu) oxodotreotide SmPC for further guidance specific to treatment with lutetium (^{177}Lu) oxodotreotide.

No studies on animal reproductive function have been conducted (see section 5.3).

Breast-feeding

Arginine and lysine, being naturally occurring amino acids, are excreted in human milk, but effects on breast-fed newborns/infants are unlikely. Breast-feeding should be avoided during treatment with lutetium (^{177}Lu) oxodotreotide.

Fertility

There are no data on the effects of arginine and lysine on fertility.

4.7 Effects on ability to drive and use machines

LysaKare has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

There are limited data on the safety profile of arginine and lysine solution for infusion without concomitant administration of PRRT (see section 5.1), which also includes the use of anti-emetics as pre-medication and often the concomitant use of short-acting somatostatin analogues.

The main adverse reactions which are related mainly to the amino acid solution are nausea (approximately 25%), vomiting (approximately 10%) and hyperkalaemia. These adverse reactions are mostly mild to moderate.

Tabulated list of adverse reactions

The adverse reactions listed below have been identified in publications of studies involving 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 during PRRT with various radiolabelled somatostatin analogues.

The adverse reactions are listed according to MedDRA system organ class and by frequency. The frequencies are categorised as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$) and not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse 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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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.

Clinical efficacy and safety

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.

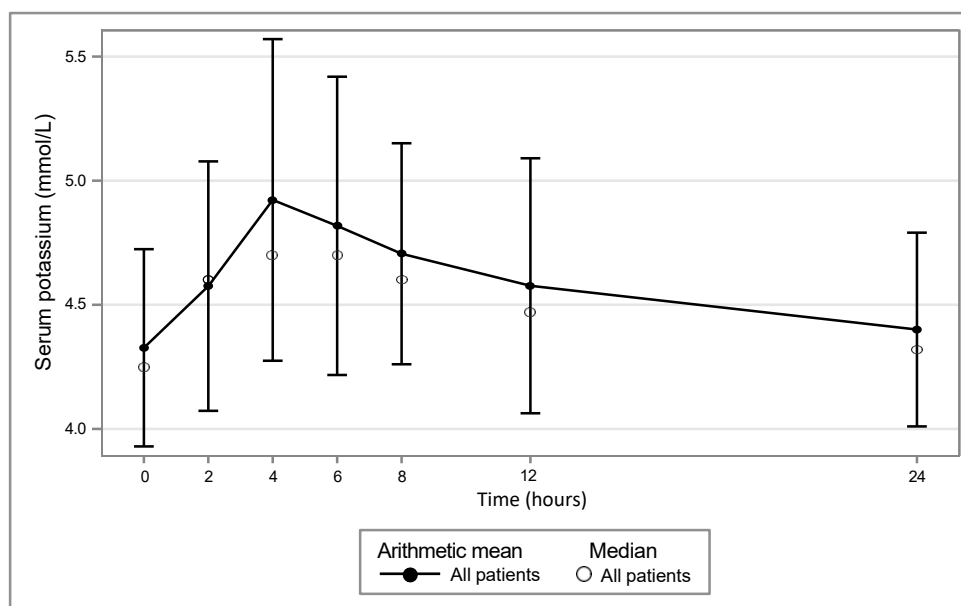
The toxicities that are observed following administration of PRRT are directly due to the radiation-absorbed dose to organs. The kidneys are the critical organs for lutetium (^{177}Lu) oxodotreotide toxicity and dose limiting if amino acids are not administered to reduce renal uptake and retention.

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 tumour 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 the occurrence of renal toxicities of 23 Gy.

A Phase IV multicentre open-label study was conducted to assess the effect of LysaKare on serum potassium concentrations and characterisation of the safety profile. A total of 41 patients with somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs), 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 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 4.3 hours (2 to 24 hours).

Figure 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.

5.2 Pharmacokinetic properties

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

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.

Paediatric population

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

5.3 Preclinical safety data

There were no non-clinical studies conducted with LysaKare.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Infusion bag made of polypropylene (PP) containing 1 000 mL of solution, wrapped in multilayer transparent films.

6.6 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1381/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 July 2019

Date of latest renewal: 25 April 2024

10. DATE OF REVISION OF THE TEXT

05/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.