**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 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 (≥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 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 the national reporting system listed in Appendix V.

## 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.

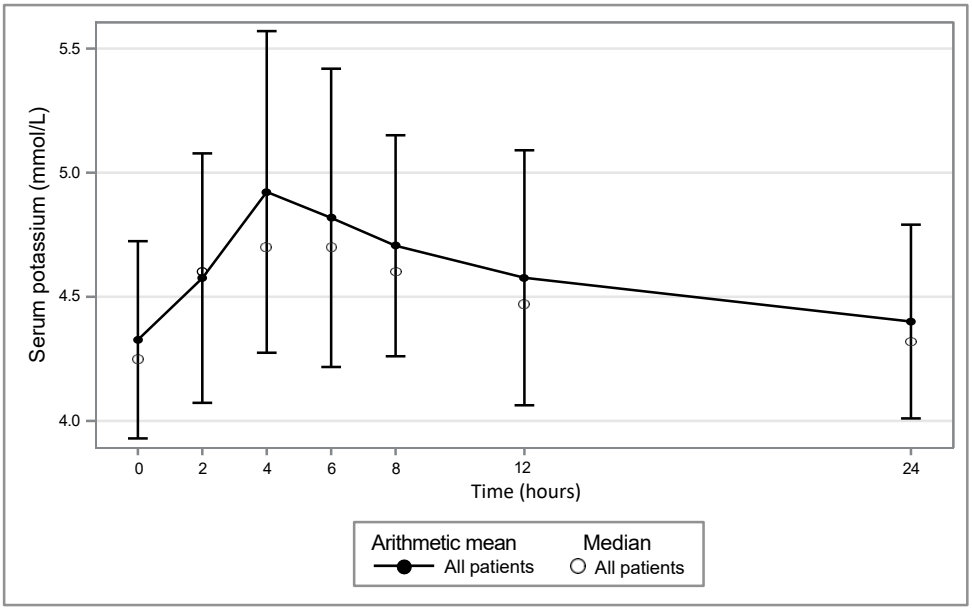
The toxicities that are observed following administration of PRRT are directly due to the radiation-absorbed dose to organs. The kidneys are the critical organs for lutetium ($^{177}$Lu) oxodotreotide toxicity and dose limiting if amino acids are not administered to reduce renal uptake and retention.

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

Advanced Accelerator Applications
8-10 Rue Henri Sainte-Claire Deville
92500 Rueil-Malmaison
France

## 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

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

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

Laboratoire Bioluz
Zone Industrielle de Jalday
64500 Saint Jean de Luz
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Multilayer transparent films**

## 1. NAME OF THE MEDICINAL PRODUCT

LysaKare 25 g/25 g solution for infusion
L-arginine hydrochloride/L-lysine hydrochloride

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

Excipient: water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 000 mL

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.
Do not remove from overwrap until ready for use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Do not reconnect partially used bags.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Advanced Accelerator Applications
8-10 Rue Henri Sainte-Claire Deville
92500 Rueil-Malmaison
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1381/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**Polypropylene (PP) infusion bag**

## 1. NAME OF THE MEDICINAL PRODUCT

LysaKare 25 g/25 g solution for infusion
L-arginine hydrochloride/L-lysine hydrochloride

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

Excipient: water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 000 mL

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.
Do not remove from overwrap until ready for use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Do not reconnect partially used bags.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Advanced Accelerator Applications
8-10 Rue Henri Sainte-Claire Deville
92500 Rueil-Malmaison
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1381/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**LysaKare 25 g/25 g solution for infusion**
L-arginine hydrochloride/L-lysine hydrochloride

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


1. What LysaKare is and what it is used for
2. What you need to know before you are given LysaKare
3. How LysaKare is given
4. Possible side effects
5. How to store LysaKare
6. Contents of the pack and other information


## 1. What LysaKare is and what it is used for

**What LysaKare is**
LysaKare contains the active substances arginine and lysine, two different amino acids. It belongs to a group of medicines which are used to reduce the side effects of anti-cancer medicine.

**What LysaKare is used for**
LysaKare is used in adult patients to protect the kidneys from unnecessary radiation during treatment with Lutathera (lutetium ($^{177}$Lu) oxodotreotide), a radioactive medicine used to treat certain tumours.

## 2. What you need to know before you are given LysaKare

Follow all of your doctor's instructions carefully. As you will receive another treatment, Lutathera, with LysaKare, **read the Lutathera leaflet carefully as well as this leaflet.**
If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

**You should not be given LysaKare**
- if you are allergic to arginine, lysine or any of the other ingredients of this medicine (listed in section 6).
- if you have high blood levels of potassium (hyperkalaemia).

**Warnings and precautions**
If any of these apply to you, tell your doctor before you are given LysaKare:
- if you have swollen feet and ankles, too much urine or not enough urine, itching or trouble catching your breath (signs and symptoms of chronic kidney disease).
- if you have itching, yellow skin or if the whites of your eyes turn yellow, if you have nausea or vomiting, fatigue, loss of appetite, pain in the upper right side of your stomach area (abdomen), dark or brown urine, or if you bleed or bruise more easily than normal (signs and symptoms of liver disease).
- if you have breathlessness, difficulty breathing when lying down and swelling of the feet or legs (signs and symptoms of heart failure).

Tell your doctor immediately if you get any of these symptoms during treatment with LysaKare:
- if you feel tired, lose your appetite, notice changes in your heartbeat, and/or have trouble thinking clearly (signs and symptoms of metabolic acidosis).
- if you have breathlessness, weakness, numbness, chest pain, palpitations and/or abnormal heart rhythm (signs and symptoms of high blood potassium level (hyperkalaemia)).

Follow your doctor's advice on how much to drink on the day of your treatment so you stay well hydrated.

If you are aged 65 years or above, you may be more likely to have kidney problems, and your doctor will determine on the basis of the blood test results whether you can receive LysaKare treatment.

Monitoring before and during your treatment with LysaKare
Your doctor will ask you to have an initial blood test to check whether you are eligible for this treatment and then regular blood tests during treatment to detect any side effects as early as possible. If necessary, the electrical activity of your heart will also be checked with a test called an electrocardiogram (ECG). Based on the results, your doctor may decide to stop the treatment.

The doctor will check your blood potassium level and correct it before starting the infusion if it is too high. The doctor will also check your kidney and liver function before starting the infusion. For other tests which need to be performed before your treatment, please read the Lutathera leaflet.

**Children and adolescents**
This medicine should not be given to children and adolescents under 18 years old because it is not known whether it is safe and effective in this age group.

**Other medicines and LysaKare**
Tell your doctor if you are taking, have recently taken, or might take any other medicines.

**Pregnancy, breast-feeding, and fertility**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine since Lutathera must not be used in pregnant women because radiation is dangerous for the unborn baby and breast-feeding must be avoided during treatment with Lutathera.

**Driving and using machines**
It is considered unlikely that LysaKare will affect your ability to drive or to use machines.

## 3. How LysaKare is given

The recommended dose of LysaKare solution is 1 L (1 000 mL). You should receive the full LysaKare dose, regardless of any Lutathera dose adjustments.

LysaKare is given as an infusion (drip) into a vein. The infusion of LysaKare will start 30 minutes before you are given Lutathera, and will last over a 4-hour period.

Patients who receive amino acid infusions commonly experience nausea and vomiting. You will therefore be given medicines to prevent nausea and vomiting 30 minutes before the LysaKare infusion.

**If you receive more LysaKare than you should**
LysaKare will be given in a controlled clinical setting and is provided as a single dose bag. It is therefore unlikely that you will receive more of the infusion than you should as your doctor will monitor you during the treatment. However, in the event of an overdose, you will receive the appropriate treatment.

If you have any further questions on the use of this medicine, ask your doctor.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects could be serious**
**Very common** (may affect more than 1 in 10 people):
- vomiting
- nausea

**Not known** (frequency cannot be estimated from the available data):
- high potassium levels (seen in blood tests)
- abdominal (belly) pain
- dizziness

**Other possible side effects**
**Not known** (frequency cannot be estimated from the available data):
- headache
- flushing

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store LysaKare

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.
Store below 25°C.
You will not have to store this medicine. The correct storage, use and disposal of this medicine are under the responsibility of the specialist in appropriate premises. You will receive LysaKare in a controlled clinical setting.

The following information is intended for the healthcare specialist charged with your care.
Do not use this medicine:
- if you notice that the solution is cloudy or has deposits.
- if the overwrap has been previously opened or damaged.
- if the infusion bag is damaged or leaking.

## 6. Contents of the pack and other information

**What LysaKare contains**
- The active substances are arginine and lysine.
  Each infusion bag contains 25 g of L-arginine hydrochloride and 25 g of L-lysine hydrochloride.
- The other ingredient is water for injections.

**What LysaKare looks like and contents of the pack**
LysaKare 25 g/25 g solution for infusion is a clear and colourless solution free from visible particles, and is supplied in a single-use flexible plastic bag.
Each infusion bag contains 1 L of LysaKare solution.

**Marketing authorisation holder**
Advanced Accelerator Applications
8-10 Rue Henri Sainte-Claire Deville
92500 Rueil-Malmaison
France

**Manufacturer**
Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

Laboratoire Bioluz
Zone Industrielle de Jalday
64500 Saint Jean de Luz
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

**България**
Novartis Bulgaria EOOD
Тел: +359 2 489 98 28

**Česká republika**
Novartis s.r.o.
Tel: +420 225 775 111

**Danmark**
Novartis Sverige AB
Tlf.: +46 8 732 32 00

**Deutschland**
Novartis Pharma GmbH
Tel: +49 911 2730

**Eesti**
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

**Ελλάδα**
ΒΙΟΚΟΣΜΟΣ ΑΕΒΕ
Τηλ: +30 22920 63900
ή
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

**Lietuva**
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

**Luxembourg/Luxemburg**
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

**Magyarország**
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

**Malta**
Novartis Pharma Services Inc.
Tel: +356 2122 2872

**Nederland**
Novartis Pharma B.V.
Tel: +31 88 04 52 111

**Norge**
Novartis Sverige AB
Tlf: +46 8 732 32 00

**Österreich**
Novartis Pharma GmbH
Tel: +43 1 86 6570

**España**
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

**France**
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

**Hrvatska**
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

**Ireland**
Novartis Ireland Limited
Tel: +353 1 260 12 55

**Ísland**
Novartis Sverige AB
Sími: +46 8 732 32 00

**Italia**
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

**Κύπρος**
ΒΙΟΚΟΣΜΟΣ ΑΕΒΕ
Τηλ: +30 22920 63900
ή
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

**Latvija**
SIA Novartis Baltics
Tel: +371 67 887 070

**Polska**
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

**Portugal**
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

**România**
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

**Slovenija**
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

**Slovenská republika**
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

**Suomi/Finland**
Novartis Sverige AB
Puh/Tel: +46 8 732 32 00

**Sverige**
Novartis Sverige AB
Tel: +46 8 732 32 00

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.