29 May 2019
EMA/CHMP/363968/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LysaKare

International non-proprietary name: arginine/lysine

Procedure No. EMEA/H/C/004541/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AA	amino acids
Acetyl-CoA	Acetyl Coenzyme A
AEs	adverse events
Arg	arginine
ATC	Anatomical Therapeutic Chemical Classification System
ß	beta
13C	carbon 13
CCS	Container closure system
CHMP	Committee for Medicinal Products for Human Use
CEP	Certificate of Suitability of the EP
CNS	Central nervous system
dL	deciliter
DOTA	tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTATATE	oxodotreotide
DTPA	diethylenetriaminepentaacetic acid
EBRT	External Beam Radiotherapy
Edotreotide	DOTA0-Tyr3-octreotide
EDQM	European Directorate for the Quality of Medicines
e.g.	for example
EKG/ECG	electrocardiogram
EMA	European Medicines Agency
ENETS	European Neuro Endocrine Tumours Society
Erasmus MC	Erasmus Medical Center
ESMO	European Society for Medical Oncology
EU	European Union
g	grams
GBq	gigabecquerels
GEP-NET	gastroenteropancreatic neuroendocrine tumors
GFR	glomerular filtration rate
GMP	Good Manufacturing Practice
Gy	Gray
h	hour
Hb	hemoglobin
HCl	hydrochloric acid
HPLC	High performance liquid chromatography
IAEA	International Atomic Energy Agency
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL-8	Interleukin 8
^{111}In	111Indium
IR	Infrared
IV	intravenous
K^+	potassium
kg	kilograms
L	liter
LAR	long acting release
^{177}Lu	lutetium 177
Lys	lysine
m^2	square meter
MA	marketing authorisation
MAA	marketing authorisation application
MBq	mega-becquerel
MC	Medical Centre
mCi	milliCurie
MEq	milli-equivalents
mGy	milliGray
min	minutes
mg	milligrams
mL	milliliters
mm	millimeters

mmol	millimoles
mOsm/L	milli-osmoles/liter (osmolarity)
N/A	not applicable
NaCl	sodium chloride
NANETS	North American Neuroendocrine Tumor Society
NET	Neuroendocrine Tumours
OH	hydroxide
P	Probability
PDE	Permitted Daily Exposure
pentetreotide	DTPA-octreotide
pH	potential of hydrogen
Ph. Eur.	European Pharmacopoeia
PI	pharmacokinetics
PK	Product information
PRRT	peptide receptor radionuclide therapy
PVC	Polyvinyl chloride
q	every
r	linear relationship
ROS	reactive oxygen species
RSA	radiolabeled somatostatin analog
SAL	Sterility assurance level
SmPC	Summary of Product Characteristics
SSTR2	Total Aerobic Microbial Count
TAMC	somatostatin receptor type 2
TGF-ß	transforming growth factor beta
TYMC	Total Combined Yeasts/Moulds Count
US	United States
UV	Ultraviolet
µmol	micromole
vs	versus
w	weeks
w/	with
WEU	Well-established use
WBC	white blood cell count
WHO	World Health Organization
w/o	without
^{86}Y	Yttrium 86
^{90}Y	Yttrium 90

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Advanced Accelerator Applications submitted on 1 June 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for LysaKare, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2016. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication: Reduction of renal radiation exposure during Peptide-Receptor Radionuclide Therapy (PRRT) with lutetium (177Lu) oxodotreotide in adults.

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Mark Ainsworth

The application was received by the EMA on	1 June 2018
The procedure started on	21 June 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	11 September 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	10 September 2018

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	25 September 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	18 October 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 January 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	7 March 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 March 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 March 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 May 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to LysaKare on	29 May 2019

2. Scientific discussion

2.1. Problem statement

Currently, there are no commercial amino acid formulations approved for use in the reduction of renal radiation exposure during treatment with ^{177}Lu oxodotreotide or other RSAs. A Lys-Arg solution, preferably 2.5%, is prepared by pharmacies and must be administered concomitantly with ^{177}Lu oxodotreotide for renal protection according to the ^{177}Lu oxodotreotide EU SmPC. Approval of LysaKare would allow availability of a commercially produced 2.5% Lys-Arg solution with adequately controlled quality in the target population, which is seen as a benefit regarding standardization and quality control compared with locally produced products derived from hospital pharmacies.

2.1.1. Disease or condition

The indication of LysaKare applied for is ”Reduction of renal radiation exposure during Peptide-Receptor Radionuclide Therapy (PRRT) with lutetium (177Lu) oxodotreotide in adults”.

2.1.2. Epidemiology, risk factors and prevention

Studies that included patients receiving RSA therapy in the absence of amino acid protection reported nephrotoxicity in the range of 28% to 60% (Otte 1999, Bodei 2015). Estimates for kidney dose limits were originally derived from experience with external beam radiation whose deep tissue penetration resulted in a renal limiting dose of 18-23 Gy (Svensson 2015, Wessels 2008), with radiation dose associated with a 5% risk for developing radiation nephropathy within 5 years being 23 Gy (Emami 1991).

There are several confounding factors that can increase the risk of radiation induced-nephropathy, including age, baseline kidney function, diabetes mellitus, hypertension, prior course of chemotherapy, and presence of renal morphological abnormalities.

The type of radionuclide can also affect rates of injury. This is thought to be largely dependent on whether beta emission energies are high enough to significantly extend their reach from the proximal tubule lumen to the radiosensitive glomeruli (Valkema 2005, Cremonesi 2006). For example, the maximum range of ß- particles from ^{90}Y is 12 mm, which is long enough to reach the glomeruli as opposed to the 10 µm range of Auger electrons which are too short to even leave the tubular cell. In contrast, ^{177}Lu beta emissions have a maximal penetration range of 2.1 mm, suggesting that the glomeruli may be partially spared. Incidence and severity of long term renal injury were reduced with the use of ^{177}Lu instead of ^{90}Y for RSAs.

Long term kidney toxicities based on creatinine clearance have been reported to be higher in patients treated with peptides labeled with ^{90}Y and combinations of ^{90}Y-^{177}Lu than with ^{177}Lu alone (Bodei 2008, Bodei 2015), although some studies have reported that mean change in GFR rates was similar to that seen with normal aging (-1% per year) (Sabet 2014a, Sabet 2015, Glasscock 2009). However, some other studies have noticed that the mean GFR change was not really representative of the variability in GFR change seen between individuals or related to cumulative radiation dose (Sabet 2014a, Sabet 2014b). A retrospective study by Imhoff et al. (2011) reported that a high renal absorbed radiation dose was associated with a higher risk for radiation induced renal injury.

Since the introduction of amino acids for renal protection during RSA therapy in the late 1990’s to early 2000’s, nephrotoxicity rates post-RSA treatment have been estimated to be approximately 1% to 23%, with differences in the radionuclide and amino acid solution likely contributing to variations observed (Bodei 2015, Brabander 2017).

2.1.3. Aetiology and pathogenesis

Radiolabelled peptide analogues, such as ^{177}Lu oxodotreotide, are designed to target tumoral cells/tissues expressing their respective binding substrates. However, non-receptor mediated uptake is also observed for some peptide analogues, most notably in the kidneys. The amount of radioactivity retained in the kidneys has a significant impact on the total activity that can be administered to a patient because of potential long-term nephrotoxic effects caused by relatively high radiation doses to the organ. Clinical and histological findings have been related to radiation nephropathy during RSA treatment.

Without renal protection, the kidneys are a dose-limiting organ during PRRT with radiolabelled peptides susceptible to renal resorption such as RSAs (Bodei 2015). Radiation induced pathophysiology is related to organ and cellular radiation dose and the ability of cells to repair induced damage. Depending on the dose, irradiation may also induce a chronic state of oxidative stress by the generation of reactive oxygen species (ROS). These ROS inactivate mitochondrial enzymes and damage the DNA which may lead to cell apoptosis. Angiotensin II is an important mediator in the progression of renal disease. It primarily up-regulates the levels of several cytokines, e.g. interleukin-8 (IL-8), promoting monocyte/macrophage and neutrophil migration, and transforming growth factor (TGF)-β, stimulating the proliferation of fibroblasts (Perico 2005).

2.1.4. Clinical presentation, diagnosis and prognosis

Glomerulosclerosis and tubulointerstitial fibrosis cause decreased glomerular filtration rate (GFR) and loss of protein in the urine and lead to progressive kidney damage (Perico 2005). This becomes apparent as increased serum creatinine and decreased creatinine clearance.

2.1.5. Management

A Lys-Arg solution, preferably 2.5%, must be administered concomitantly with ^{177}Lu oxodotreotide for renal protection. The amino acids solution will help to decrease reabsorption of lutetium (177Lu) oxodotreotide through the proximal tubules, resulting in a significant reduction in the kidney radiation dose. When the recommended concomitant amino acids infusion is delivered over a 4 hour time span, a mean reduction in kidney radiation exposure of about 47% has been reported (Lutathera EU SmPC).

Renal absorbed dose is considered to be an important endpoint related to the renal protective effects of lysine and arginine (Hammond 1993, Kwekkeboom 2001, Rolleman 2003, Bodei 2003, Jamar 2003, Kashyap 2013). RSA maximum allowable dose is based on estimates of exposure to the most sensitive organ serving as the dose limiting organ. In the case of PRRT with RSAs, the kidney is the dose limiting organ in the absence of amino acid co-infusion. The ultimate consequence of reducing radiation exposure during therapy with ^{177}Lu oxodotreotide and other RSAs is that higher doses of RSAs can be used, potentially improving tumour response to the PRRT (Jamar 2003, Kong 2014).

About the product

The active substances L-lysine HCl and L-arginine HCl are positively charged amino acids produced and tested according to the standards of the European Pharmacopeia (Ph. Eur.) as supported by a Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP) issued by EDQM. L-lysine HCl and L-arginine HCl comply respectively with Ph. Eur. 0930 and Ph. Eur. 0805.

The LysaKare 25 g / 25 g solution for infusion is supplied as a sterile, ready-to-use solution for infusion which will be administered intravenously in concomitance with lutetium (^{177}Lu) oxodotreotide in adults. The finished product claims to be able to reduce the proximal tubular reabsorption of low molecular weight proteins and peptides. Radiation dose to kidneys is of clinical significance during treatment with

radiolabeled somatostatin analogues (RSAs) because of the high tubular uptake of the peptide after glomerular filtration and retention of the radionuclides in the proximal tubular cells.

The container closure system consists of a single use infusion plastic bag of 1000 mL. A single bag contains 25 g of L-Lysine Hydrochloride (HCl) and 25 g of L-Arginine Hydrochloride (HCl) in water for injections.

Mechanism of action

LysaKare is to be used during PRRT with a radiolabelled somatostatin analogue, lutetium (^{177}Lu) oxodotreotide. Following LysaKare administration, L-lysine HCl and L-arginine HCl undergo glomerular filtration and, via competition, interfere with renal resorption of lutetium (^{177}Lu) oxodotreotide, reducing the radiation dose delivered to the kidney.

Posology and method of administration

The recommended treatment regimen in adults consists of i.v. infusion of the above mentioned full bag of LysaKare, even when patients require lutetium (^{177}Lu) oxodotreotide dose reduction. The infusion must occur at the same time as the PRRT to achieve optimal renal protection.

Type of Application and aspects on development

In accordance with Article 10a of Directive 2001/83/EC, as amended, the application relies on well-established medicinal use supported by bibliographic literature. According to Article 10a of Directive 2001/83/EC, as amended it is possible to replace results of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substance of a medicinal product has been in well-established medicinal use within the Community for at least 10 years, with a recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply.

To determine if the application fulfils the requirements of Article 10a with regards to well-established medicinal use of Lys-Arg for renal protection during PRRT with lutetium (177Lu) oxodotreotide, the CHMP took into account the following factors:

- Time over which the substance has been used

The LysaKare formulation, based on a 2.5% Lysine HCl + 2.5% Arginine HCl (2.5% Lys-Arg) amino acid solution, is clinically used for renal radiation protection during PRRT since at least the year 2000, per the results of a survey conducted by the applicant in 29 clinical centres in six representative EU countries (ES, DE, NL, PT, AT, UK).

The publication by Kwekkeboom (2001), proving a significant reduction in renal radiation exposure by administration of a 2.5% Lys-Arg solution in LysaKare's target population, introduced this precaution to the clinical practice.

The scientific literature reports the use of a 2.5% Lys-Arg solution in LysaKare's target population since 2001 (see Table 1)

- Quantitative aspects of use of the substance

The LysaKare formulation, based on a 2.5% Lysine HCl + 2.5% Arginine HCl (2.5% Lys-Arg) amino acid solution, is extensively clinically used in order to reduce the renal radiation exposure during RSA treatment, e.g. as part of the "Rotterdam Protocol", which was also used in the Erasmus MC reports (see section 2.5.2. The above mentioned survey showed that 2.5% Lys-Arg solution has been administered in 29 clinical centres in six EU countries in the claimed indication to more than 3300 patients since 2000. Of

note, the incidence of all patients with the malignancy for which PRRT with lutetium (177Lu) oxodotreotide is indicated in the EU can be estimated at 2.17/100000 (Gatta 2011).

Key scientific societies such as the European Society for Medical Oncology (ESMO), the European Neuro Endocrine Tumours Society (ENETS), and The North American Neuroendocrine Tumor Society (NANETS) recommend univocally the use of 2.5% Lys-Arg solution for the reduction of renal absorbed radiation dose in their treatment guidelines for gastroenteropancreatic NETs (Zaknun et al., 2013; Hicks et al., 2017). The same applies to the ^{177}Lu oxodotreotide EU SmPC (Lutathera EU SmPC). This supports widespread use of the LysaKare formulation in its target population.

- The degree of scientific interest in the use of the substance (reflected in the published scientific literature)

Pubmed was searched up to 2017 for full-text publications of the use of 2.5 % Lys-Arg solutions in LysaKare's target population. The search identified 29 peer reviewed publications since 2001 (see Table 1), providing evidence for the high degree of scientific interest in this orphan indication.

Table 1. Full text published studies from centres in the EEA using 2.5% Lys-Arg solution in claimed indication

Article	Reporting site	Nb. Patients	Pathology	Amino acid solution used	Radioactive compound used
Kwekkeboom et al. (2001)	*The Netherlands*, Erasmus Medical Center, Rotterdam	5/6*	Medullary Thyroid Cancer, non-Hodgkin lymphoma, GEP-NET, aesthesioneuroblastoma, Hürthle cell thyroid carcinoma, papillary thyroid carcinoma	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide ^{111}In-pentetreotide (Octreoscan)
Rolleman et al. (2003)	*The Netherlands*, Erasmus Medical Center, Rotterdam	26*	End-stage NET	Comparative AA study: 2,030 ml (10.32 g Lys and 16.08 g Arg); 500 ml (25 g Lys); 1,000 ml (50 g Lys); 1,500 ml (75 g Lys); 1000 ml (25 g Lys + 25 g Arg) over 4 h	^{111}In-DTPA-Octreotide
Jamar et al. (2003)	*Belgium* Centre of Nuclear Medicine and Laboratory of Positron Emission Tomography, University of Louvain Medical School, Brussels and Louvain-la-Neuve	24	metastatic, non-resectable NET	Comparative AA study: 1,800 ml of 4 h 120 g mixed AA (26.4 g L-lysine + L-arginine); 4 h L-lysine (50 g); 10 h 240 g mixed AA (52.8 g L-lysine + L-arginine); 4 h Lys-Arg (25 g each)	^{90}Y-edotreotide
Valkema et al. (2005)	*The Netherlands*, Erasmus Medical Center, Rotterdam	65*	metastatic NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{90}Y-oxodotreotide ^{177}Lu-oxodotreotide
Esser et al. (2006)	*The Netherlands*, Erasmus Medical Center, Rotterdam	7*	SSTR2-positive metastasised NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide ^{177}Lu-edotreotide
Wehrmann	*Germany*	69	NET	25 g Lys + 25 g Arg	^{177}Lu-oxodotreoti

Article	Reporting site	Nb. Patients	Pathology	Amino acid solution used	Radioactive compound used
et al. (2007)	Department of Nuclear Medicine and Centre for PET/CT, Zentralklinik, Bad Berka			in 1500 ml over 4 h	de ^{177}Lu-DOTANOC
Kwekkeboom et al. (2008)	*The Netherlands*, Erasmus Medical Center, Rotterdam	504*	GEP-NET (458/504) Other	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Gabriel et al. (2010)	*Austria* Department of Nuclear Medicine Medical University, Innsbruck,	100	NET (68) radioiodine-negative thyroid cancer (N=6), non-neuroendocrine tumors (N=26)	25 g Lys + 25 g Arg in 1500 ml over 6 h	^{177}Lu-oxodotreotide ^{90}Y-edotreotide
Giovacchini et al. (2011)	*Switzerland*, University Hospital Basel, Basel	31	NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{90}Y-edotreotide
van Vliet et al. (2012)	*The Netherlands*, Erasmus Medical Center, Rotterdam	42*	well differentiated NET (GEP-NET and Bronchial NET) with bone metastases positive on SRS, and soft-tissue lesions	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Ezziddin et al. (2012)	*Germany* University Hospital, Bonn	23	unresectable metastatic GEP-NET (with liver-dominant metastatic disease)	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide + SIR-spheres (3.4+-2.1 GBq for ^{90}Y-RE)
Kreissl et al., (2012)	*Germany* Department of Radiation Oncology, University Hospital, Wuerzburg	10	unresectable meningioma	1500 mL of lysine-arginine solution (2.5% of lysine and 2.5% of arginine) over 3 h	^{177}Lu-oxodotreotide ^{177}Lu-edotreotide
Sainz-Esteban et al. (2012)	*Germany* Department of Nuclear Medicine and Centre for PET/CT, Zentralklinik, Bad Berka	44	NET	25 g Lys + 25 g Arg in 1500 ml over 4 h	Diagnostic: ^{68}Ga-oxodotreotide and ^{177}Lu-oxodotreotide
Budiawan et al. (2013)	*Germany* Department of Nuclear Medicine and Centre for PET/CT, Zentralklinik, Bad Berka	16	histopathologically proven non-radioiodine-avid refractory thyroid cancer	25 g Lys + 25 g Arg in 1500 ml over 4 h	^{90}Y-oxodotreotide ^{177}Lu-oxodotreotide
van Vliet et al. (2013)	*The Netherlands*, Erasmus Medical Center, Rotterdam	268*	NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Ezziddin et al. (2013)	*Germany* University Hospital, Bonn	27	metastatic, inoperable GEP-NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Sabet et al. (2013)a	*Germany* University Hospital, Bonn	203	unresectable metastatic NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Vinjamuri et	*UK,* Royal Liverpool	57	metastatic pNET	25 g Lys + 25 g Arg	^{90}Y-oxodotreotide

Article	Reporting site	Nb. Patients	Pathology	Amino acid solution used	Radioactive compound used
al. (2013)	University Hospital, Liverpool			in 1000 ml over 4 h	^{90}Y-edotreotide
Ezziddin et al. (2014a)	*Germany* University Hospital, Bonn	74	Well differentiated GEP-NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Ezziddin et al. (2014b)	*Germany* University Hospital, Bonn	68	Pancreatic NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Sabet et al. (2014b)	*Germany* University Hospital, Bonn	33	metastatic, inoperable GEP-NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Sabet et al. (2014a)	*Germany* University Hospital, Bonn	74	metastatic GEP-NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Svensson et al. (2015)	*Sweden,* Sahlgrenska University Hospital, Gothenburg	51	Advanced NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Sabet et al. (2015)	*Germany* University Hospital, Bonn	61*	unresectable metastatic NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
van Vliet et al. (2015)	*The Netherlands*, Erasmus Medical Center, Rotterdam	29*	Non-functioning pancreatic NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Bergsma et al. (2016a)	*The Netherlands*, Erasmus Medical Center, Rotterdam	320*	NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Bergsma et al. (2016b)	*The Netherlands*, Erasmus Medical Center, Rotterdam	323*	SSTR2-positive metastasized NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Magnander et al. (2016)	*Sweden,* Sahlgrenska University Hospital, Gothenburg	20*	Advanced NET	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
Brabander et al. (2017)	*The Netherlands*, Erasmus Medical Center, Rotterdam	1214	NETs	25 g Lys + 25 g Arg in 1000 ml over 4 h	^{177}Lu-oxodotreotide
TOTAL		2118			

*Not included in the estimate for total number of patients treated with amino acid solution due to potentially overlapping patient population

- *Coherence of scientific assessments*

The literature describing the co-administration of 2.5% Lys-Arg solution is conclusive and coherent with respect to supporting its use in the intended indication.

The above mentioned recommendation by key scientific societies is based on scientific assessments coherent with the mentioned literature.

A Lys-Arg solution, preferably 2.5%, must be administered concomitantly with ^{177}Lu oxodotreotide for renal protection according to the ^{177}Lu oxodotreotide SmPC (Lutathera EU SmPC).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for infusion containing 25 g of L-arginine hydrochloride (equivalent to 20.7 g arginine) and 25 g of L-lysine hydrochloride (equivalent to 20 g lysine) as active substances.

Other ingredient is: water for injections

The product is available in an infusion bag made of polyvinyl chloride (PVC), wrapped in a polyethylene polyamine/aluminium foil as described in section 6.5 of the SmPC.

2.2.2. Active Substance

2.2.2.1. L-Lysine Hydrochloride

General information

The chemical name of lysine is (S)-2,6-diaminohexanoic acid monohydrochloride corresponding to the molecular formula $C_6H_{15}ClN_2O_2$. It has a relative molecular mass of 182.65 g/mol and the following structure:

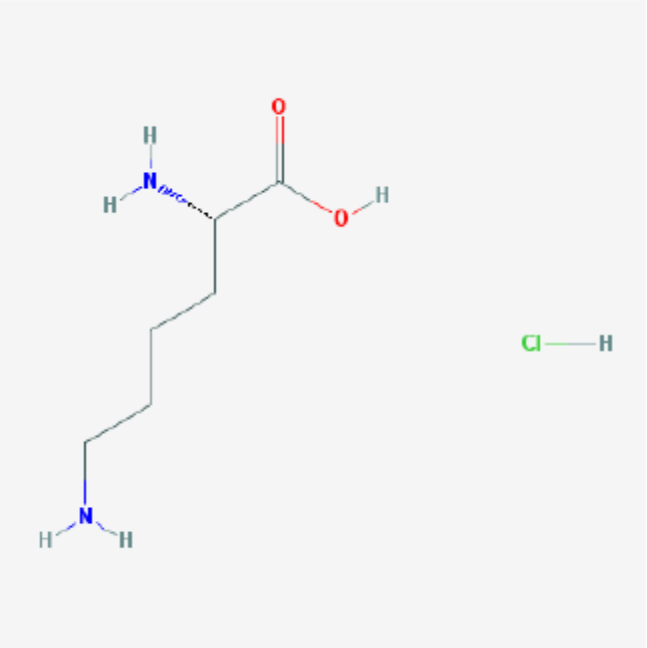


Figure 1. L-Lysine Hydrochloride

The relevant information of the chemical structure of active substance has been assessed by the EDQM before issuing the Certificate of Suitability (CEP).

The active substance is a white or almost white, crystalline powder or colourless crystals freely soluble in water, slightly soluble in ethanol.

Lysine exhibits stereoisomerism due to the presence of 1 chiral centre. The stereoisomer used is the L form.

As there is a monograph of the active substance in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The active substance is manufactured by two manufacturing sites.

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability for both manufacturers.

The information on the container closure systems (CCS) for lysine is stated on the CEP for one manufacturer and is provided separately by the other manufacturer. The second manufacturer uses a bag made of polyethylene in fibre drum or cardboard box, it is confirmed that the requirements laid down in Commission Regulation 10/2011 on plastic materials and articles intended to come into contact with food are fulfilled.

Specification

The specification of L-Lysine HCl applied by the active substance manufacturers is compliant with Ph. Eur. 0930. The active substance is a not a sterile substance but is to be used in a sterile medicinal product. Water is used as solvent during the last steps of the synthesis; therefore the testing to confirm that the active substance is free from bacterial endotoxins is performed in compliance with Ph. Eur.

The active substance specification shown includes tests for appearance (visual), solubility (visual), specific optical rotation (identification A), identification B (IR, Raman spectrometry), identification C (thin layer chromatography), identification D (visual inspection), identification E (reaction of chlorides), ninhydrin-positive substances (amino acid analysis), sulfate (SO4) (Ph. Eur.), ammonium (NH4) (amino acid analysis), iron (Fe) (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (Ph. Eur.), bacterial endotoxins (Ph. Eur), and microbial control (Ph. Eur).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for bacterial endotoxins and microbial control. All additional methods have been adequately validated and described according to ICH Q2.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

For one manufacturer, the retest period is stated on the CEP as 24 months.

For the second manufacturer, stability data from 3 commercial scale batches of active substance stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance of the power, appearance of solution, specific rotation, ammonium, related substances, loss on drying, assay, pH, and microbial contamination. The analytical methods used were stability indicating.

All the specifications are met throughout the tested stability period both under the accelerated and long term conditions.

The stability results indicate that the active substance manufactured by this supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months without any special storage conditions in the proposed container.

2.2.2.2. L-Arginine Hydrochloride

General information

The chemical name of the active substance is (2S)-2-amino-5-(diaminomethylideneamino)pentanoic hydrochloride acid, corresponding to the molecular formula $C_6H_{14}N_2O_2$ •HCl. It has a relative molecular mass of 210.662 g/mol and the following structure:

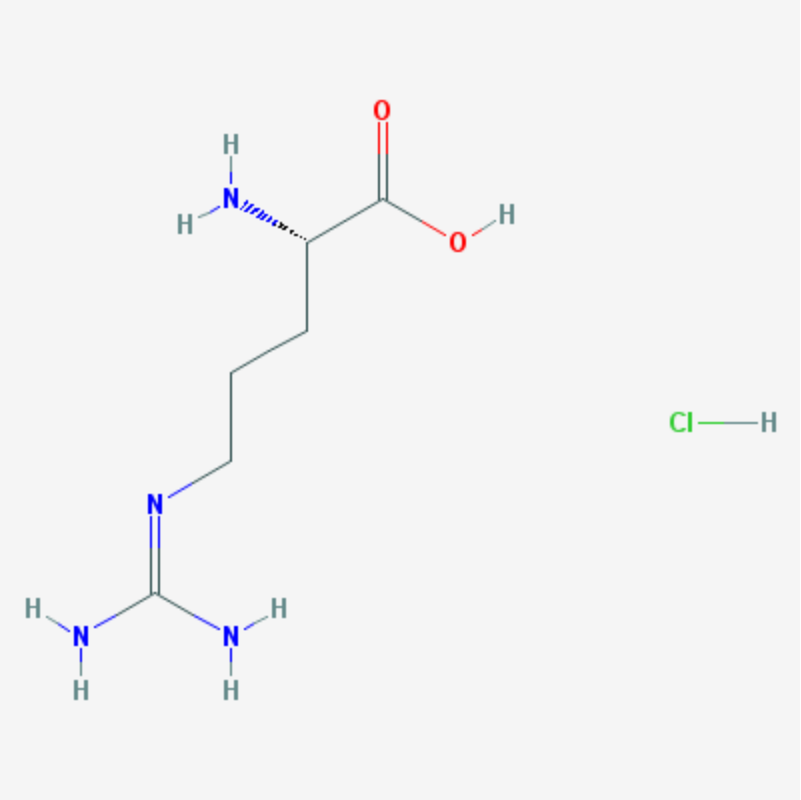


Figure 2. Active substance structure

The relevant information of the chemical structure of active substance has been assessed by the EDQM before issuing the Certificate of Suitability (CEP).

L-arginine hydrochloride is a white crystal freely soluble in water.

Arginine exhibits stereoisomerism due to the presence of one chiral centre. The stereoisomer used is the L form.

As there is a monograph of L-arginine hydrochloride in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

L-arginine hydrochloride is manufactured by one manufacturing site.

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability (CEP).

The information on the container closure systems (CCS) is provided on the CEP.

Specification

The specification of L-arginine HCl applied by the active substance manufacturer is compliant with Ph. Eur. 0805. The active substance is a not a sterile substance but is to be used in a sterile medicinal product.

Water is used as solvent during the last steps of the synthesis; therefore the testing to confirm that the active substance is free from bacterial endotoxins is performed in compliance with Ph. Eur.

The active substance specification includes tests for: appearance (visual), solubility (visual), specific optical rotation(identification A, Ph. Eur.), identification B (IR, Raman), Identification C (Thin layer chromatography), identification D (visual inspection), identification E (Reaction (a) of chlorides), ninhydrin-positive substances (amino acid analysis), sulfate (SO4) (Ph. Eur.), ammonium (NH4) (amino acid analysis), Iron (Fe) (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (Ph. Eur.), bacterial endotoxins (Ph. Eur), and microbial control (TYMC, TAMC)(Ph. Eur.).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for bacterial endotoxins and microbial control. All additional methods have been adequately validated and described according to ICH Q2.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability
The retest period is stated on the CEP as 48 months if stored in a polyethylene bag inside a siliconized polyethylene terephthalate bag in a fibre drum.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development
The finished product is a sterile solution for infusion. A single 1 litre infusion bag contains 25 g of L-lysine hydrochloride (HCl) and 25 g of L-arginine hydrochloride (HCl) in water for injections.

The active substances, L-lysine HCl and L-arginine HCl are positively charged amino acids produced and tested according to the standards of the European Pharmacopeia (Ph. Eur.) as supported by a Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP) issued by EDQM. L-lysine HCl and L-arginine HCl comply with Ph. Eur. 0930 and Ph. Eur. 0805, respectively.

The compatibility of the active substances with each other and with the excipient used in the formulation of the finished product has been demonstrated by a stability study. The results obtained during the stability assessment (up to 24 months shelf life) have shown that the variation of the two active substances assay value is in the range of ± 5 %. Both identification and assay tests at the storage temperature of 5 ± 3°C did not point out any significant variation in retention time, molecular weight and amount of the active substance.

The excipient (water for injection) is well known pharmaceutical ingredient and its quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

LysaKare 25 g / 25 g solution for infusion is able to reduce the proximal tubular reabsorption of low molecular weight proteins and peptides. Exposure of radiation to the kidneys is of clinical significance during treatment with radiolabelled somatostatin analogues (RSAs) because of the high tubular uptake of the peptide after glomerular filtration and the retention of the radionuclides in the proximal tubular cells. It is reported that positively charged amino acids, such as L-lysine and/or L-arginine, are co-infused to competitively inhibit the proximal tubular reabsorption of the radiopeptide, to counteract and reduce the high kidney retention of radiopeptides.

Based on the documented clinical experience, the 2.5% Lys-Arg formulation appeared to be the most suitable one in terms of renal protection, efficacy and tolerability.

Based on the above evidence, the European Medicine Agency (EMA) agreed to include a lysine-arginine solution as renal protectant with Lutathera. In the absence of a commercial solution specifically tailored for this purpose, the agency recommended to use commercial amino acid solutions for parenteral nutrition with lysine and arginine contents in the range of 18-24 g.

LysaKare 25 g / 25 g solution for infusion conforms to all required physico-chemical and microbiological characteristics for the parenteral products as described in ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemicals Substances.

The following physical properties have been considered relevant to the performance of the finished product: appearance, pH and osmolality.

During the development of the finished product, sodium chloride solution was replaced by water for injections to bring osmolarity closer to physiological values compared to other amino acid mixtures reported in the literature. The osmolality of the finished product has been tested on four batches and the recorded values were well within the accepted values. Using water for injections, the pH is about 5.6 which is well in acceptable range of pH for intravenous infusions and similar to the pH of other complex amino acid mixtures that have been used for the reduction of renal radiation exposure during Peptide-Receptor Radionuclide Therapy (PRRT) with RSAs.

During the development of the finished product manufacturing process, critical process parameters were identified, evaluated and optimized. The process has been then adapted to industrial constraints related to ready-to-use preparations, such as the size of the infusion bag and the batch size. The commercial manufacturing process follows conventional drug compounding and filling methods commonly used in the pharmaceutical industry.

The finished product manufacturer has chosen a moist heat terminal sterilization method for the finished product, as recommended by Ph. Eur. 5.1.1 for aqueous solutions. The standard conditions for the moist heat sterilisation (15 minutes at 121°C) couldn't be followed, due to the large volume of solution packed in the container used (1 litre). Therefore, the finished product manufacturer adopted another combination of time and temperature (40 minutes at 118°C) using moist heat terminal sterilization with and F0>8 minutes assuring a SAL (sterility assurance level) of 10^{-6}. This approach is in line with the recommendation of Ph. Eur. 5.1.1. The proposed combination of time and temperature for the terminal sterilisation cycle has been validated accordingly and it has been satisfactorily demonstrated that the process chosen delivers an adequate and reproducible level of lethality when operating routinely within the established tolerances.

The primary packaging is an infusion bag made of polyvinyl chloride (PVC) wrapped in a polyethylene polyamine/aluminium foil. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Chemical analysis, mechanical/physical tests have been conducted in accordance with Ph.Eur. 3.2.2.1 and Ph.Eur. 3.2.3 (extractables, leachables, and container closure) which demonstrate that the chosen primary packaging is adequate for its intended use.

Manufacture of the product and process controls

The manufacturing process consists of 6 main steps: weighing of raw materials and recovering of adequate volume of water for injection, compounding of the bulk solution, filtration, filling of pre-printed infusion bags, sterilisation by autoclave, and drying and packaging in overwrap. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended

quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification
The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification L-lysine (HPLC), identification L-arginine (HPLC), pH, extractable volume (Ph. Eur.), osmolality (Ph. Eur.), assay L-lysine (HPLC), assay L-arginine (HPLC), related substances (HPLC-UV), sterility test (Ph. Eur.), bacterial endotoxins (Ph. Eur.), number of sub-visible particles (Ph. Eur.) and Phtalates (HPLC-UV).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

According to the guideline for elemental impurities (International Council on Harmonisation (ICH), Q3D), the potential elemental impurities in the finished product were assessed. It was confirmed that the contamination risk from the equipment and the packaging used for manufacturing of the finished product is low. The ratio of potential uptake for each elemental impurities against Permitted Daily Exposure (PDE) described in the guideline for elemental impurities (ICH, Q3D) was calculated and the results indicated that the potential uptake for each element was less than 30% of the PDE.

Batch analysis results are provided for 4 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing

Stability of the product
Stability data from 3 commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing without outer layer of PET (polyethylene terephthalate). The attributes of the container closure system of the commercial product are otherwise similar to those used in the registration product stability protocol. It has been demonstrated that the stability attributes of the lidding foils, with and without the outer PET layer, are equivalent.

Samples were tested in line with the shelf-life specifications. The analytical procedures used were stability indicating.

The physical-chemical tested parameters for all evaluated batches of the finished product were within the quality shelf-life specification for over the tested period with no deterioration recorded when the product was stored under long term conditions. The finished product also showed good stability when stored at accelerate conditions as demonstrated by the results recorded for all tested parameters within the tested period with no deterioration in physico-chemical characteristics and no significant change or out of specification results.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Photostability testing results indicated that light had no influence on the quality of the product. No special storage precautions for light are required.

Based on available stability data, the proposed shelf-life of 24 months store bellow 25°C as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical information in this application is derived entirely from pharmacodynamic, pharmacokinetic, and toxicology data in the scientific literature.

2.3.2. Pharmacology

Pharmacodynamic studies

No non-clinical literature examining the renal protective effects of the combination of Lysine and Arginine was presented.

Safety pharmacology programme

With regard to cardiovascular safety, Boldt et al. (2009) reported an ex vivo study with lysine, demonstrating a transient positive inotropic effect at concentration of 10 mM. Two studies have been identified concerning the effects of L-arginine on the cardiovascular system in healthy dogs. One study determined the effects of the intravenous administration of L-arginine on hemodynamics including cardiac output and renal blood flow. Results of this study showed that arginine produces an elevation of renal blood flow without having a significant effect on mean arterial blood pressure, heart rate and cardiac output at the tested doses. The second study evaluated the hemodynamic splanchnic and renal changes after intravenous administration of arginine-hydrochloride. Systemic arterial blood flow and heart rate was not influenced but a local blood flow increasing effect on the arteries next to the pancreas couldn’t be completely ruled out.

No additional literature is provided assessing respiratory or CNS related effects of L-lysine or L-arginine.

Pharmacodynamic drug interactions

No data submitted.

2.3.3. Pharmacokinetics

No data submitted.

2.3.4. Toxicology

Single dose toxicity

The nonclinical information presented on the toxicological evaluation of lysine and arginine to support the marketing application is literature based and derived from publicly available scientific sources. Acute toxicity data were presented for mice, rats and dogs with after parenteral administration. As was the case for pharmacology data, more toxicology data on lysine than arginine are presented. One study in mice was cited without toxicology relevance (MTD for L-lysine 2500 µg/g i.p.). Another study reported an LD50 in rats of about 3-4 g/kg for L-lysine and L-arginine (administered as acute i.p. doses) corresponding to human equivalent doses of 480-645 mg/kg based on body surface area conversion. Dyspnoe, hypothermia and extreme prostration at this dose are reported. One effect identified in dogs was dose-dependent hyperkalemia after i.v. administration of L-lysine or L-arginine.

Repeat dose toxicity

No data submitted.

Genotoxicity

No data submitted.

Carcinogenicity

No data submitted.

Reproduction Toxicity

No data submitted.

Toxicokinetic data

No data submitted.

Local Tolerance

No data submitted.

Other toxicity studies

No data submitted.

2.3.5. Ecotoxicity/environmental risk assessment

The active substances are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, L-arginine hydrochloride and L-lysine hydrochloride are not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The presented non-clinical data package is based on bibliographic information for lysine and arginine available from the public domain. No new non-clinical studies have been performed for this application since the application is based on well-established use according to Article 10a of Directive 2001/83/EC. This is is acceptable from a non-clinical point of view due to the long-term clinical experience with both amino acids.

Pharmacodynamic

The applicant provided literature showing the protective influence of the positively charged amino acids lysine and arginine. Although no literature exists to date where both amino acids have been tested together for renal protection during PRRT in a non-clinical setting, the protective effect of co-administration has been demonstrated in clinical practice over many years. The megalin/cubulin receptor complex is responsible for the renal resorption of radiolabelled peptides and competitive inhibiton of this transporter is believed to be the primary target mediating the renal-protective effects of L-lysine and L-arginine (Melis 2005, Vegt 2011, Behr 1995). Somatostatin receptors may also play a role in mediating these effects but are not believed to be the major contributor.

Safety pharmacology

To address the safety pharmacology of the actives the applicant has submitted a summary of studies investigating the effects of exogenous lysine or L-arginine administration on cardiovascular function in non-clinical species. The combined effect of L-Lysine and L-arginine on ex-vivo cardiac tissue contractility has also been investigated. The data presented do not indicate a cardiovascular safety risk, given the lack of cardiac effects attributed to the co-infused amino acid solution in the clinic.

No evidence of effects of L-lysine or L-arginine on the respiratory system or the CNS has been reported in published animal studies. The lack of dedicated non-clinical investigations of respiratory and CNS effects is acceptable, given the extensive clinical experience and the lack of a clinical concern.

Pharmacokinetic

Non-clinical pharmacokinetic information is unavailable. This is acceptable, given the available clinical pharmacokinetic information.

Toxicology

Acute toxicity data of AA solutions has been described in dogs, rats and mice. The main toxicological findings are attributed to lysine and describe dyspnoe, hypothermia and extreme prostration. These findings are thought not to be of clinical relevance given the high dose of the amino acid administered in this study relative to the proposed clinical dose (corresponding to human equivalent doses of 480-645 mg/kg based on body surface area conversion). Other identified toxicological findings from the submitted studies relate to hyperkalaemia, elevated blood ammonia levels and increased urine bicarbonate content. Given the heterogeneity in the quality of the studies and differing administration methods the relevance of these findings to humans is unknown. Based on nonclinical pharmacology and toxicology data, the effects of L-arginine and L-lysine combination are not thought to be additive.

There are no literature data provided on repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity, local tolerance or other toxicity studies. This is considered acceptable given the nature of the actives and proposed indication and posology of LysaKare, and this lack of information is reflected in the SmPC.

Finally, since both amino acids are naturally occurring biomolecules, there is no need for ERA studies as they are considered not to be associated with any additional risk for the environment.

2.3.7. Conclusion on the non-clinical aspects

The product is approvable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

Table 2. Tabular overview of clinical studies

Studies evaluating PK

. **Summary of Studies Evaluating Pharmacokinetics of L-lysine and L-arginine**

PK parameter	Study	Study type/Dose	Key findings
Absorption	Not applicable	Not applicable	Due to intravenous route of administration, product is 100% bioavailable.
Distribution and Excretion			
L-arginine	Bode-Böger 1998	PK Healthy Volunteer, 8 males IV infusion (30 min): 30 g or 6 g of L-arg HCl in 150 mL 0.9% saline	The exposure (AUC) showed proportional increase with increasing doses. Dose-dependent elimination half-life and clearance ($t_{½}$ = 42±2 min and 60±9 min at 30 and 6 g; clearance = 544±24 ml/min and 894±164 mL/min at 30 and 6 g) indicated non-linear pharmacokinetics in the dose range tested. Volume of distribution was estimated to be 33±2 L/kg at 30 g and 68±9 L/kg at 6 g.
	Tangphao 1999	PK Healthy Volunteer, 6 males, 4 females IV infusion (30 min): 30 g of L-arg HCl in 300 mL	Biphasic elimination pattern. Concentration-dependent renal clearance: urinary excretion occurs within the first 90 min, during which the renal threshold for resorption was likely exceeded. Maximal renal clearance = 1.2 mL/min/kg. After the initial urinary loss, L-arginine declined

			slowly by non-renal clearance (5 mL/min/kg). Concentration return almost at baseline after 8 hours.
L-lysine	Irving 1986	PK Healthy Volunteer, 5 females Intravenous bolus L-[^{13}C]lysine (5 mg/kg in 3 mL) plus oral L-[^{15}N]lysine (5 mg/kg in 200 mL)	Plasma profile could be described by three-exponential decay function. L-lysine was widely distributed with plasma concentrations returning to baseline levels by 6 hours after infusion. The total volume of distribution was 1523 mL/kg, indicating important uptake into tissues Terminal half-life of i.v. administered lysine was estimated to be around 18 min.
Metabolism	Not applicable	Not applicable	Amino acids are building blocks in protein catabolism, and serve as precursors for several other products including nitric oxide, urea, creatinine, and Acetyl-CoA Note, knowledge of metabolism based on literature reviews and general textbooks (Morris 2007, Böger 2001. and Brosnan 2004, Fontana 2017).

Studies evaluating PD

Summary of PD Effects of L-Lysine and L-Arginine Relevant to PRRT Renal Protection

PD parameter	Study	Study type/Dose	Key findings
Pharmacodynamic effects on renal resorption of peptides	Studied by Mogensen 1977 Reviewed in Brosnan 2004, Silbernagl 1988	Not applicable	High doses of either L-lysine or L-arginine alone promote renal excretion of endogenous proteins. L-lysine effects > L-arginine. Attributed to prevention of renal resorption rather than increasing GFR (Mogensen 1977). Arginine: Human kidneys are estimated to filter and reabsorb ~3.1 g per day based on average arginine plasma concentrations of 90 µmol/L and GFR of 190 L/day. (Brosnan 2004). Transport of cationic amino acids from the tubular fluid across the apical membrane is by $b^{0,+}$ transporter, transport across the basolateral membrane is by the system y^+L (Brosnan 2004). Chronic renal failure is accompanied by a drastic increase in amino acid excretion (Silbernagl 1988). Multiple clinical studies of use of various amino acid solutions for renal protection during PRRT (see Section 2.5.4.3 and 2.7.3).

Studies evaluating Efficacy

Table 3. Clinical Studies Submitted to Support LysaKare Efficacy Evaluation

Reference	Study type/Comparator	RSA	Amino Acid Solution(s) Tested
Proof of Concept Studies for Amino-Acids in Renal Protection			
Hammond 1993	Prospective Proof of Concept/Untreated	^{111}In-pentreotide	Synthamin 14
Otte 1999	Prospective Proof of Concept/Untreated	^{111}In-edotreotide and ^{90}Y-edotreotide	Hartmann-Hepa 8% solution
Moll 2001	Retrospective, Pathology of RSA induced renal injury in absence of amino acids/no control	^{90}Y-edotreotide	None
Bodei 2015	Retrospective, single center cohort study/Untreated	^{90}Y-edotreotide, ^{177}Lu- DOTATATE ^{90}Y-edotreotide + ^{177}Lu-DOTATATE	Unspecified
Main Clinical Studies of Efficacy/Safety of 2.5% Lysine/Arginine Using the Rotterdam Infusion Protocol			
Kwekkeboom 2001	Prospective Efficacy/Untreated	^{177}Lu-DOTATATE	2.5% Lys-Arg in 0.225% NaCl
Rolleman 2003	Prospective Dose Response, Efficacy, Safety/Saline & Active	^{111}In-pentetreotide	2.5% Lys-Arg, Aminosteril N-Hepa 8%, lysine only (25, 50, and 75g), Saline (0.5, 1 and 2L)
**Kwekkeboom 2008, Bergsma 2016a, Bergsma 2016b, Brabander 2017	Retrospective Efficacy, Safety	^{177}Lu-DOTATATE	2.5% Lys-Arg in 0.225% NaCl
Strosberg 2017a	Prospective Phase III Netter-1 study	^{177}Lu-DOTATATE	Aminosyn II and Vamin 18 (mixed AA formulations)
Publications from spontaneous clinical studies supporting use of 2.5% Lys-Arg Using the Rotterdam Infusion Protocol			
**Hubble 2010, Kashyap 2013	Retrospective Efficacy, Safety	^{177}Lu-DOTATATE	2.5% Lys-Arg in 0.9% NaCl
**Gupta 2012, Gupta 2013	Prospective Cohort Efficacy, Safety	^{177}Lu-DOTATATE	2.5% Lys-Arg in unspecified buffer

**Ezziddin 2013, Sabet 2013, Ezziddin 2014a, Ezziddin 2014b, Sabet 2014a, Sabet 2014b, Sabet 2015	Retrospective Efficacy, Safety	^{177}Lu-DOTATATE	2.5% Lys-Arg in 0.9% NaCl
Svensson 2015	Retrospective Efficacy, Safety	^{177}Lu-DOTATATE	2.5% Lys-Arg in 0.9% NaCl
Other studies (AA Composition, and Infusion protocols)			
Bodei 2003	Prospective Comparison Dose Response, Efficacy, Safety/Active	^{90}Y-edotreotide	2% Lysine only, Lys/Arg combination (2% lys 4% arg, 2 different infusion protocols) all in 0.9% NaCl
Jamar 2003, Barone 2004	Prospective Comparison Formulation, Infusion Protocol Efficacy, Safety/Untreated and Active	^{86}Y-edotreotide	Modified Proteinsteril Hepa 8%, 1.7% Lysine + 1.6% arginine, 3.5% Lysine only, untreated, effects of 4 and 10-hour infusions also considered. All formulations q 1.8 L with lactate Ringers buffer.
Rolleman 2003	Prospective Formulation, Infusion/Active and Saline	^{111}In-pentetreotide	2.5% Lys-Arg in 0.225% NaCl, Aminosteril N-Hepa 8%, lysine only (25, 50, and 75g), Saline (0.5, 1 and 2L)
Barone 2005	Retrospective, Observational Efficacy /None	^{90}Y-edotreotide	Modified Proteinsteril Hepa + lactated Ringer's
†Valkema 2005	Retrospective, Observational Efficacy/None	^{90}Y-edotreotide ^{177}Lu-DOTATATE	4h infusion with 2L modified Proteinsteril Hepa 8% for ^{90}Y-edotreotide 4 h infusion with 2.5% Lys-Arg in 1L 0.9% NaCl, 250 ml/h for 4 h (starting 30 min prior to PRRT)
Cwikla 2010	Prospective Efficacy, Safety/None	^{90}Y- DOTATATE	Vamin 18 (mixed AA formulation)
Bodei 2011	Prospective Efficacy, Safety/None	^{177}Lu-DOTATATE	2.5% lysine only in 1L 0.9% NaCl solution with extended infusion protocol (Day 1, 2, and 3) Day 1= day of PRRT
Giovacchini 2011	Prospective Safety	^{177}Lu-DOTATATE	2.5% Lys-Arg in 1L 0.9% NaCl (infusion begun 1 h prior to PRRT and lasting total of 4 h)
Imhof 2011	Prospective Efficacy, Safety/None	^{90}Y-edotreotide	2% Lys-Arg in 0.9% NaCl (3.5 h infusion)
Kashyap 2013	Retrospective Infusion Protocol Efficacy, Safety/Active	^{177}Lu-DOTATATE	2.5% Lys-Arg in 1L 0.9% NaCl (2.5 vs 4 h infusion protocols)
Sansovini 2013	Prospective Cohort Efficacy, Safety/None	^{177}Lu-DOTATATE	70 MEq lysine only day 1 (1L starting 30 min prior to PRRT), 0.5 L 60 MEq lysine only 1h infusion day 2
Lapa 2014a, Lapa 2014b	Retrospective & Prospective Safety/crossover study	^{177}Lu-DOTATATE, ^{177}Lu- edotreotide	37.5g each L lysine HCL and L-arginine HCl in 1500 mL 0.9% NaCl, 25g each L-lysine HCl and L-arginine HCl in 2000 mL 0.9% NaCl

**Publications that potentially include overlapping patient populations are grouped together on the same line

†Valkema 2005 likely also includes some overlap with Jamar 2003 and Kwekkeboom 2008 papers.

Studies evaluating Safety

Summary of Exposure to 2.5% Lys-Arg Using "Rotterdam Protocol" Contributing to LysaKare Safety Evaluation

Publication	# of patients	Number of doses per person
Rolleman 2003	9	At least one patient received up to 7 doses
†Kwekkeboom 2008, Bergsma 2016b, Brabander 2017	610	Some proportion of patients received less than intended dose
Hubble 2010	27	Median 3 doses/person
Gupta 2012	47	2-6 doses per patient
*Ezziddin 2013, Sabet 2013, Ezziddin 2014b, Sabet 2014b, Sabet 2015,	203	Targeted 3-4 doses per patient
Svensson 2015	51	Median 3 doses (1-5 range) Dosing limited by disease progression in 3 patients and persistent haematological toxicity in 4 patients
Totals	**947**	Majority of patients receive 3 to 4 doses (6-14 week intervals), range 1-7 doses

†Series of reports associated with a large 1,214 patient Phase I/II clinical study at Erasmus Medical Center in which all patients received 2.5% Lys-Arg for renal protection. Safety evaluation was conducted on 610 patients.

*Reports from same medical center with potentially overlapping patient populations

Summary of Exposure to Other Amino Acid Formulations Providing Supportive Data to LysaKare Safety Assessment

Publication	# of patients	Number of doses per person	Amino Acid Formulation
Otte 1999	29	2 pts had received AA for all PRRT cycles 13 pts had received AA during some but not all PRRT cycles	Hartmann-Hepa 8% solution
Bodei 2015*	807	mean 4.75 (range 1-10) per person	Unspecified AA solution
Bodei 2003	40	1 dose per pt crossover comparison study	2% Lysine only, Lys/Arg combination (2% lys 4% arg, 2 different infusion protocols)
Jamar 2003 (and companion paper Barone 2004)	18	1-2	Modified Proteinsteril Hepa 8%, 1.7% Lysine + 1.6% arginine, 3.5% Lysine only, untreated, effects of 4 and 10 hour infusions also considered.
Rolleman 2003	25	1	2.5% Lys-Arg, Aminosteril N-Hepa 8%, lysine only (25, 50, and 75g), Saline (0.5, 1 and 2L)
Cwikla 2010	60	17 pts received 2 doses 2 pts received 1 dose 38 pts received 3 doses 11 pts received 4 doses	Vamin 18 (mixed AA formulation)
Bodei 2011	51	Low dose radiation group median 6 doses High dose radiation group median 4 doses	2.5% lysine only solution with extended infusion protocol (Day 1, 2, and 3) Day 1= day of PRRT
Giovacchini 2011	31	19 doses were with furosemide	2.5% Lys-Arg with modified infusion protocol
Imhoff 2011	1109	Median 2 doses, range 1-10	2% Lys-Arg NaCl (3.5 h infusion)
Sansovini 2013	52	Target 5 doses per patient	70 MEq lysine only day 1 (1L starting 30 min prior to PRRT), 0.5 L 60 MEq lysine only 1h infusion day 2
Lapa 2014a, Lapa 2014b	76	1 dose each amino acid	75 g aa (37.5 g each L-lysine HCl, L-arginine HCl) in 1500 mL 0.9% NaCl, 4h infusion starting 0.5h

			prior to RSA 50 g aa (25g each L-lysine HCl, L-arginine HCl) in 2000 ml 0.9% NaCl, 4h infusion starting 0.5 h prior to RSA
Strosberg 2017a and 2017b	111	Target 4 doses of Vamin 18 or AminoSyn II 10% per patient	Aminosyn II and Vamin 18
Totals	**>24009**	Majority of patients received at least 2 doses, range 1-10	

2.4.2. Pharmacokinetics

Absorption

The route of administration of LysaKare is IV. Thus, assessment of absorption is not applicable.

Distribution

No studies describing the distribution of L-arginine and L-lysine when given in combination have been provided. One study (Bode-Böger, 1998) has data on the distribution of L-arginine (varying from 33 L/kg in the 30 g i.v. dose to 68 L/kg in the 6 g i.v. dose), and one study (Irving, 1986) has data on the distribution of L-lysine (initial V_d 195 mL/kg, total V_d 1523 mL/kg). The high total volume of distribution of 1.5 L/kg for L-Lysin was also explained by uptake into the tissue where intracellular lysine levels exceed those in plasma.

Elimination

L-Lysine and L-Arginine are naturally occurring molecules. Due to their small size, they are subject to glomerular filtration and subsequent resorption in the kidney. Urinary excretion of amino acids is normally very small, that is below 1% of the filtered load. The proximal tubule and thin ascending limb of Henle's loop serve as the sites for resorption. Amino acid resorption in the kidneys involves transepithelial transport, requiring transporters (b0,+ and y+L) on the apical and basolateral membranes of the tubular cells.

- *L-arginine*: Excretion was dose dependent. Tmax was 22-30 min depending on amount infused during continuous iv infusion. Half-life was dose-dependent (42 ± 2 min, 60 ± 9 min, and 76 ± 9 min for 30 g i.v., 6 g i.v., and 6 g p.o., respectively). AUC (0, ∞) values showed a proportional increase with increasing doses of L-arginine. Urinary excretion occurred only within the first 90 min, during which the renal threshold for reabsorption was presumably exceeded. After this initial urinary loss, plasma L-arginine declined slowly by non-renal clearance (about 5 mL/min/kg). Maximal renal clearance of i.v. L-arginine during the first 90 min post-dose in 2 volunteers was 1.16 and 1.18 mL/min/kg. Average non-renal clearance was 360 mL/min. Table 3. summarises the pharmacokinetic data of the study by Tangphao.
- *L-lysine*: The terminal half-life of i.v. administered lysine was estimated to be around 177 min.

Specific pharmacokinetic studies of the combination of L-lysine and L-arginine are not available.

Table 3. Summary of pharmacokinetic data in 10 normal volunteers. For the intravenous study, 30 g L-Arginine hydrochloride was infused over 30 min. For the oral study, 10 g L-Arginine solution was swallowed in less than 2 min.

Subject	AUC_{EX} i.v. ($\mu g\ ml^{-1}\ min$)	AUC_{EX} oral ($\mu g\ ml^{-1}\ min$)	F	Non-renal clearance ($ml\ min^{-1}$)	Non-renal clearance ($ml\ min^{-1}\ kg^{-1}$)
1	94 745	5442	0.14	264	4.55
2	72 151	7530	0.26	346	4.28
3	60 980	11 968	0.50	416	4.63
4	71 718	5455	0.19	349	4.84
5	39 798	4575	0.29	628	7.85
6	63 160	4439	0.18	396	5.82
7	79 130	3744	0.12	320	5.16
8	105 235	6219	0.15	238	3.17
9	107 366	2257	0.05	235	4.20
10	61 963	6611	0.27	403	5.68
Average	75 624	5824	0.21	360	5.02
±s.e.mean	±6779	±832	±0.04	±37	±0.40

Source: Tangphao (1999)

Dose proportionality and time dependencies

Dose proportionality

For L-arginine there is not dose proportionality, and V_d, Cl and t½ declines with higher doses. The provided literature does not discuss possible dose proportionality of L-lysine.

Time dependency

LysaKare is not expected to show time dependency. No evidence regarding time dependency is provided in the referenced literature.

No data after multiple doses have been provided.

Special populations

Impaired renal function: Given that L-lysine and L-arginine PK (and clinical activity) are dependent in part on normal renal perfusion and resorption, perturbations in renal function may affect therapeutic effects. Chronic renal failure has been associated with an increase in amino acid urinary excretion as it can be associated with a greater filtered load saturating renal resorption processes (review by Silbernagl 1988).

Impaired hepatic function: LysaKare does not undergo hepatic metabolism and thus impaired hepatic function is not expected to influence the PK of LysaKare.

Gender: Gender is not known to influence the PK of LysaKare.

Race: Race is not known to influence the PK of LysaKare.

Weight: Weight is not known to influence the PK of LysaKare.

Elderly: LysaKare is not known to exhibit different PK in elderly patients.

Children: LysaKare is not known to exhibit different PK in paediatric patients.

Pharmacokinetic interaction studies

No reports for clinical studies evaluating extrinsic factors relating to lysine and arginine PK are available.

Pharmacokinetics using human biomaterials

No data submitted.

2.4.3. Pharmacodynamics

Mechanism of action

The effect on the megalin/cubulin transport complex is associated with the cationic properties of Arg and Lys and has been exploited for use in reducing the renal radiation exposure during PRRT therapy with ^{177}Lu-DOTATATE and other RSAs.

Primary and Secondary pharmacology

Primary pharmacology

Mogensen and Solling (1977) found that substances with a positively charged group located terminally in the molecule (ornithine, lysine, arginine, and the almost not metabolized epsilon-amino-caproic acid and cyclocaprone) proved to instantaneously inhibit renal tubular protein resorption. Lysine was found to be most effective in promoting urinary excretion of albumin, Ig light chains, and Beta-2-microglobulin, while arginine had a lesser effect.

Results from multiple clinical studies show that in patients receiving PRRT with RSAs, amino acids interfere with renal resorption of the radiolabeled peptides. In these studies, formulations of L-lysine alone or combinations of L-lysine and L-arginine have performed similarly or better than complex amino acid mixtures. These observations indicate that amino acids, and more specifically L-lysine, and L-arginine act by a similar mechanism of action to prevent renal resorption of RSAs in patients as they do with endogenous protein resorption in healthy subjects. Several studies have been conducted to evaluate the contributions of each amino acid to clinical effects of reduced renal radiation absorbed dose. Results from these studies have shown that a 2.5% L-Lysine HCl, 2.5% L-Arginine HCl combination provides an better risk benefit balance to patients compared to complex amino acid mixtures, lysine only formulations, and other combinations of lysine and arginine.

Secondary pharmacology

L-arginine has also been associated with nitric oxide synthesis, vasodilation leading to decreased blood pressure and compensatory increase in heart rate (Bode-Böger 1994, Bode-Böger 1998) – see Figure 3.

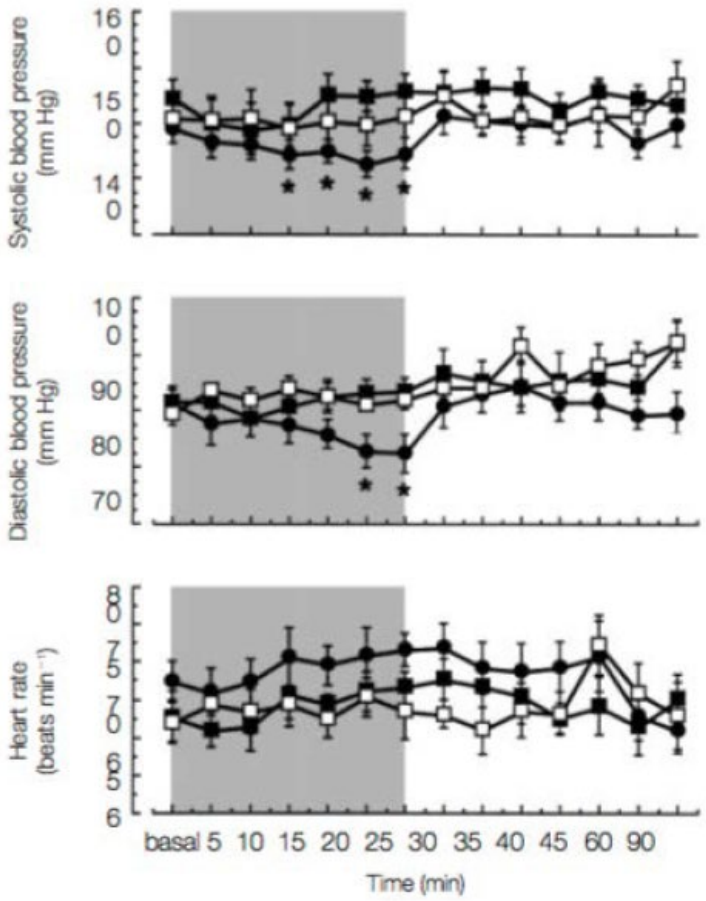


Figure 8. Blood Pressure Effects of Intravenous L-argininine (Bode-Boger 1998)

intravenous L-arginine (30 mg closed circle, 6 mg closed square, and placebo open square) on systolic and diastolic blood pressure in healthy human subjects. Values represent mean ± SEM of n=8 subjects. The shaded area represents the duration of the infusion. *P< 0.05 vs baseline.

Figure 3. Blood Pressure Effects of Intravenous L-arginine (Bode-Boger 1998)

Pharmacodynamic interactions with other medicinal products or substances

L-arginine has been shown to decrease blood pressure. A pharmacodynamic interaction with anti-hypertensive drugs and other vasodilatating drugs has not been investigated.

Genetic differences in PD response

LysaKare is not known to exhibit a different PD response due to genetic differences.

Relationship between plasma concentration and effect

No discussion or studies describing a relationship between plasma concentration and effect have been provided and no studies investigating the relationship between dose and the degree of inhibition of renal resorption of ^{177}Lu-DOTATATE have been provided. However in the study by Mogensen (1977), different amino acids are administered in different doses, and are found to induce renal excretion of a range of different peptides.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The applicant has not provided any pharmacokinetic data on the administration of LysaKare or any other combination of L-arginine and L-lysine. All the pharmacokinetic parameters come from studies administrating either L-arginine or L-lysine. Moreover, the study investigating the PK of L-lysine used a far smaller dose of L-lysine than the dose proposed to be administered with LysaKare. For L-arginine, the dose used in the studies investigating the PK is also (slightly) different from the dose proposed to be administered with LysaKare, and is infused over 30 min, and not as with LysaKare over 4 hours. Thus, pharmacokinetics of Lysakare is based on extrapolation of results obtained with the individual components (L-arginine and L-lysine) in amounts not identical to the ones used in Lykare. Considering the nature of the components and the short duration of treatment, this is considered acceptable.

For L-arginine the pharmacokinetic parameters are expected to be approximately as follows: A Vd of 33L/kg body weight, a half-life of 42 min and a clearance of 544 mL/min. There is no dose proportionality, and high doses lead to saturation of renal resorption with urinary excretion as a consequence, however it is not known whether the infusion of LysaKare will lead to urinary excretion.

For L-lysine the half life is short, approximately 177 min and Vd seems to be smaller than for L-arginine (around 1523 mL/kg body weight). It is not known whether dose proportionality exists. No accumulation would be expected as the amino acid solution will be administered parallel to Lutathera, which has a recommended interval between each administration of 8 weeks.

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.

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.

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.

No studies describing the pharmacokinetics in target- or special populations have been provided. The studies provided to support the pharmacokinetics of LysaKare provide only a scarce understanding of the pharmacokinetics of LysaKare. LysaKare is contraindicated if GFR < 30 mL/min, but no discussion of the impact of impaired renal function with a GFR > 30 mL/min has been provided. This is acceptable, given the LysaKare and Lutathera use restriction in this population in their PIs. PK in low or high body weight and PK in the elderly is not known, but expected to be similar to PK in healthy subjects.

As also discussed, taking into account the large inter-administration intervals of 8 weeks associated with the Lutathera dosing regimen, there is no opportunity for L-Lysine and L-Arginine to accumulate.

No interaction studies have been performed. This is acceptable, as 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 (SmPC, section 4.5).

Interactions

No studies on interactions have been provided. Since LysaKare consists of naturally occurring amino acids with known excretion pathways, it is not expected to interact with other medicines. It is however noted in the EPAR for Lutathera, as described under the section excretion, that a combination of L-lysine and L-arginine changes the elimination of Lutathera. This effect is known and is the basis for development of LysaKare.

It has to be taken into account that this is a well-established use application for an amino acid solution which has been used in similar composition in combination with Peptide-Receptor Radionuclide Therapy

for over a decade to treat patients with rare diseases like somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours. Data on clinical efficacy and safety discussed further below are overall regarded to be sufficient to assess benefit-risk, even though the aforementioned limitations in pharmacokinetic profiling exist.

Pharmacodynamics

As discussed by the applicant, the intravenous route of delivery ensures that the amino acids are 100% systemically available where they will become subject to glomerular filtration and can then interfere with transporter systems in the proximal tubule membrane and prevent substrate binding and subsequent resorption of the radiolabelled peptides.

Co-infusion of LysaKare with Lutathera ensures that L-Lysine and L-Arginine are present during the period when renal radiation exposure is highest and plasma levels will drop down to normal within few hours after infusion is stopped.

With regard to PD, the provided information gives an adequate insight on the proposed mechanism of action. L-Lysine and L-Arginine are naturally occurring molecules. Due to their small size, they are subject to glomerular filtration and subsequent resorption in the kidney. High doses of these amino acids have been shown to interfere with resorption of endogenous peptides. It is this property that is being exploited for their use for reducing the renally absorbed radiation dose during Lutathera therapy.

From a safety pharmacology point of view, after infusion of LysaKare, a secondary pharmacological effect of the infusion could e.g. be vasodilation, possibly leading to decreased blood pressure and compensatory increase in heart rate, possibly leading to blood pressure lowering effects in heart failure and possibly to pharmacodynamic interactions of LysaKare with antihypertensive medicinal products. However, as treatment duration is very short and as autoregulatory mechanisms including the baroreceptor reflex will limit any effect, the lack of formal investigation is considered acceptable.

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. Treatment with lutetium (177Lu) oxodotreotide is not recommended for patients with renal function between 30 and 50 mL/min therefore, the benefit risk for these patients will always need to be weighed carefully, which should include consideration of an increased risk for transient hyperkalemia in these patients (SmPC, section 4.4).

The use of arginine and lysine has not been studied in patients with severe hepatic impairment. Care should be taken with LysaKare use in patients with severe hepatic impairment and in case of either total bilirubinemia >3 times the upper limit of normal or albuminemia <30 g/L and prothrombin ratio <70% during treatment. Treatment with lutetium (177Lu) oxodotreotide is not recommended in these circumstances (SmPC, section 4.4).

2.4.5. Conclusions on clinical pharmacology

Taking into account that this is a well-established use application for an amino acid solution which has been used in similar composition in combination with Peptide-Receptor Radionuclide therapy for over a decade to treat patients with rare diseases like somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours and in light of the indication proposed, namely to reduce renal radiation

exposure during Peptide-Receptor Radionuclide Therapy (PRRT), overall, the PK and PD properties are acceptably described by the referenced literature.

Regarding PD, the mechanism of action is considered sufficiently described.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Rolleman 2003

Study design: A prospective, comparison, single center, crossover study.

Study Participants: Patients with end-stage NET, receiving RSA treatment.

Treatments: Patients received RSA (^{111}In-DTPA-octreotid, not the ^{177}-DOTATATE, which is the RSA intended for use in combination with LysaKare) treatment with and without other amino-acid co-infusion than the Lysakare formulation. To study the effect of volume administration alone, patients received 500, 1000, or 2000 mL of 0.45% saline, 2.5% glucose solution administered as a 4-hour infusion started 30 minutes prior to RSA treatment.

Objective: to compare the effects of various amino-acid formulations and the effects of volume infusion alone on radiation uptake in the kidneys in patients receiving RSA treatment.

Outcomes/endpoints: Radiation uptake in kidney, tumour and spleen were measured for up to 72 hours post-RSA administration. Side effects were also recorded.

Sample size: 26 patients.

Results: Saline had no effects on radiation uptake in kidneys, tumours, or spleen at any volume tested, showing that there was no infusion effect on radiation uptake. The amino acid solutions were all effective in reducing renal radiation uptake scores as described in Table 4 below. The most significant decrease in renal uptake was seen in the first 24 hours post-RSA treatment, the effects remained significant through 72 hours post-RSA administration.

Table 4. Amino Acids and Observations of Vomiting during PRRT or Scintography in Rolleman 2003

	Dose and radionuclide administered	# of patients	Vomiting in	
			Patients	Treatments
Control	7-10 GBq [^{111}In-DTPA^{0}]-octreotide	8		3/52 (6%)
AA	7-10 GBq [^{111}In-DTPA^{0}]-octreotide	8	4/8 (50%)	
Lys25 or Lys50	7-10 GBq [^{111}In-DTPA^{0}]-octreotide	8		3/22 (9%)
2.5% Lys-Arg	220 MBq [^{111}In-DTPA^{0}]-octreotide	11	1/9*	

*Event not considered dose related. Patient also had subfebrile temperature, malaise and nausea before the first treatment. During this treatment she vomited twice, 'probably due to tumor necrosis.' No problems observed during five subsequent infusions.

Kwekkeboom 2001

Study design: Single center, cross over study. AA- treatment was not randomized, and only given with the second RSA treatment.

Study participants: Patients with medullary thyroid cancer, non-Hodgkin lymphoma, gastroenteropancreatic neuroendocrine tumours (GEP-NET), aesthesioneuroblastoma, Hürthle cell thyroid carcinoma, and papillary thyroid carcinoma.

Treatments: ^{177}Lu- DOTATATE was administered twice separated by a 6-9 week interval. The amino acid co-infusion was given only with the second treatment, allowing comparison of dosimetry in the kidney with and without amino acid co-infusion in the same patient. The amino acid solution was made of 2.5% L-lysine HCl and 2.5% L-arginine HCl in 1L of 0.225% NaCl (2.5% Lys-Arg; not identical to Lysakare). The infusion was given over 4 hours at a rate of 250 ml/h, beginning 30 minutes prior to RSA treatment ("Rotterdam Protocol").

Objective: Comparison of dosimetry in the kidney with and without amino acid co-infusion in the same patient receiving RSA treatment (^{177}Lu- DOTATATE).

Outcomes/endpoints: Radiation uptake in kidney, Liver, spleen and Bone marrow.

Sample size: 5 patients

Results:

From Table 5 (below) it appears that the absorbed radiation doses in the kidneys were significantly reduced when the Lys-Arg solution was co-administered mean 47% (range 34-59%). No formal statistics has been presented. Renal dosimetry-data for Lys-Arg co-administration is missing for patient no. 2 (Table 5), and age and sex has not been specified for any of the patients.

No adverse events were reported.

Table 5. Patient Organ Doses in cGy (rad)/3700 MBq (100 mCi) (Kwekkeboom 2001)

Patient	Kidneys		Liver	Spleen	Bone marrow
	No co-infusion	With Arg-Lys sol.			
1	825	403	90	803	26
2	533	-	76	1.010	29
3	692	282	112	770	27
4	359	252	44	662	27
5	648	366	75	740	20
Mean	611	326	79	797	26

2.5.2. Main study(ies)

The main studies providing the supportive data for this application according to Article 10a of the Directive 2001/83/EC as amended ("well-established use application") are the Erasmus MC reports and the Phase III Netter-1 study.

The experience at Erasmus MC on PRRT with 177Lu-DOTATATE is published in multiple articles, including Kwekkeboom 2008, Bergsma 2016b and Brabander 2017. The renal protection protocol with Lysine 2.5% - Arginine 2.5% solution (same lysine and arginine content as LysaKare, 1 L, 4-hour infusion, starting 30

minutes before 177Lu-DOTATATE administration) has been applied in more than 1200 NET patients treated with 177Lu- DOTATATE, with a median follow-up period of more than 70 months.

Another main study submitted is the Netter-1 multicenter Phase III trial in which two commercial amino acid formulations for parenteral nutrition were used: Aminosyn II and Vamin 18. These solution contain a complex amino acid mixture, but with a content of lysine and arginine similar to the one of LysaKare. The study was reported in Strosberg 2017a.

Erasmus MC reports

Kwekkeboom 2008

Study Design: a retrospective single-arm study.

Study Participants: Patients with GEP-NET.

Treatments: ^{177}Lu-DOTA0Tyr3-octreotate and 2.5% Lys-Arg for renal protection according to the "Rotterdam Protocol." Granisetron was administered as an anti-emetic against nausea experienced during amino acid infusion. Cumulative doses up to 29.6 MBq were administered, in fractionated doses administered 6 to 10 weeks apart.

Objective: a retrospective analysis of patients receiving ^{177}Lu-DOTA0Tyr3-octreotate between January 2000 to August 2006 at the Erasmus Medical Center, Netherlands.

Outcomes/endpoints: Adverse reactions incl. renal toxicity.

Sample size: 504 patients. Data from a total of 1772 administrations was available.

Results: Acute adverse effects seen within 24 hours after PRRT administration were nausea after 25% of administrations, vomiting after 10% of administrations and abdominal discomfort or pain after 10% of administrations. Six patients were hospitalized within 2 days of dosing because of hormone-related crises.

Subacute RSA-related hematological toxicity (WHO Grade 3 or 4) were seen 3-4 weeks after 3.6% of administrations, affecting 9.5% of patients. Temporary hair loss was seen in 62% of patients. Serious delayed toxicities were seen in 9 patients (2 renal insufficiency, 3 hepatic toxicity/failure, and 4 myelodysplastic syndrome). The renal insufficiencies were attributed to pre-existing factors (existing renal function deterioration and increasing tricuspid valve insufficiency) rather than treatment. Delayed renal insufficiencies was observed in 2 cases (0.4 %), both grade 4, and were both thought to be related to pre-existing factors rather than RSA treatment.

Brabander 2017

Study Design: A retrospective study.

Study Participants: Patients with somatostatin receptor positive tumours, who received ^{177}Lu-DOTATATE between January 2000 to January 2015. The study focused on 610 patients residing in The Netherlands, who had received at least 3.7 GBq radiation dose.

Treatments: ^{177}Lu- DOTATATE (1.85-7.4 GBq/dose) and 2.5% Lys-Arg for renal protection.

Objective: To provide follow-up information on 610 patients in the Erasmus MC phase I/II study.

Endpoint/outcome: Renal toxicity/creatinine clearance.

Sample size: 610 patients

Results: A median of 64 months follow-up data was available (range 58-70 months).

Creatinine grade 3 /4 toxicities occurred in 2/581 patients (0.3%). Serum creatinine levels normalized in all patients by 3 months after treatment completion. Renal failure was reported in 6 patients (1%) during follow-up. The most probable cause of the renal failure was postrenal in one patient (hydronephrosis) and prerenal in the other patients (hypotension after gastrointestinal bleeding in one patient and in 4 patients, dehydration caused by severe vomiting and diarrhea).

The use of 2.5% Lys-Arg solution proved to be effective in reducing the renal radiation exposure, the mean kidney absorbed radiation dose being below the toxicity threshold. However, these data has not been presented in the application. Renal failure was observed in 6/582 (~ 1 %), but was considered unrelated to RSA and AA treatment.

Bergsma 2016b

Study Design: A retrospective study, follow-up for 3 years post RSA.

Study participants: Dutch patients with somatostatin positive tumours and no prior treatment with PRRT.

Treatments: ^{177}-DOTATATE (1.85-7.4 GBq/dose, up to 4 doses 6-16 week interval).

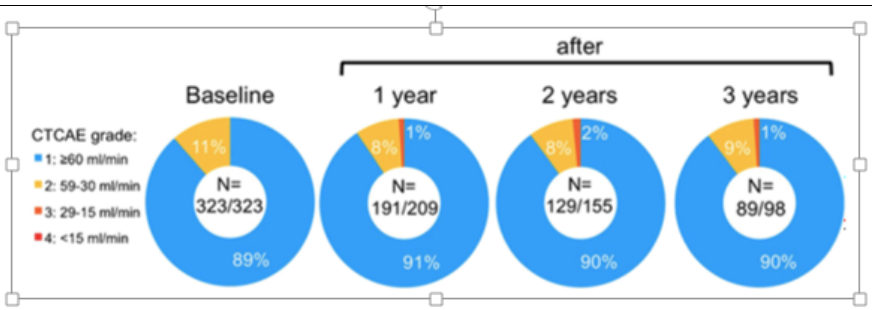
Objective: Bergsma et al (2016b) publication is a companion paper to the Bergsma et al (2016a) publication and focused on the nephrotoxicity.

Outcomes/endpoints: Renal toxicity/creatinine clearance. Renal dosimetry.

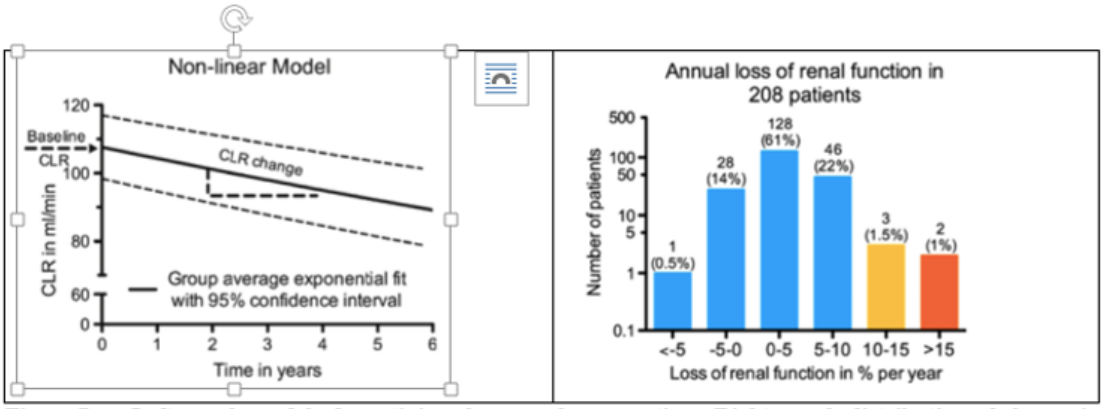
Sample Size: 323 patients. Follow-up data for 1, 2, and 3 years after the last therapy were available for 209, 155 and 98 patients, respectively.

Results: Renal dosimetry: the renal absorbed radiation dose was calculated in 228 patients and was determined to be 20.1 $\pm$ 4.9 Gy. One figure in Figure 4 (below) summarizes creatinine clearance toxicity based on CTCAE grade at 1, 2 and 3 years post treatment. Grade 1 renal toxicity (creatinine increase >26.5 µmol/L) was observed in 14 (4%) of patients. Three patients (1%) developed Grade 2 renal toxicity (creatinine increase >1.5 to 3X baseline or upper limit of normal). These were not considered related to therapy. Grade 3 kidney toxicity was observed in 5/323 patients. All 5 patients had a baseline clearance < 60 ml/min, making them more prone to more severe renal function impairment. One patient was lost to follow-up due to renal failure. No risk factors for renal toxicity could be identified. No CTCAE grade 4 events were observed.

The other figure in Figure 4 (below) summarizes the annual decrease in renal function based on creatinine clearance. The estimated average annual decrease in clearance (± SD) was 3.4 ± 0.4% and the estimated average baseline clearance was 108 ± 5 mL/min. In 203/208 patients, the annual decrease in renal function was < 10%. Five patients had an annual decrease in clearance of ≥ 10%, and 2 had an annual decrease of ≥ 15%. In 29/208 patients (14%) an improvement in renal function was observed. No patient showed an annual decrease in renal function of ≥ 20%.



Distribution of creatinine clearance by CTCAE grade in 323 patients followed up to 3 years after start of RSA (Bergsma 2016b)



Left panel: model of creatinine clearance loss over time; Right panel: distribution of change in creatinine clearance per year (Bergsma 2016b)

Colored bars represent annual loss of renal function <10% (blue), 10-15% (yellow) and >15% (orange).

Figure 4. Creatinine clearance figures

Netter-1 (reported in Strosberg 2017a)

Study Design: a prospective, randomized, open label, Phase III clinical study (Netter-1).

Study Participants: Patients with advanced, progressive, somatostatin-receptor-positive midgut neuroendocrine tumours. The patients were enrolled from across 41 centers in the United States and Europe, between September 2012 through mid-January 2016.

Treatments: Patients assigned to the ^{177}Lu- DOTATATE were scheduled to receive 4 treatments of 7.4 GBq (200 mCi) Lutathera and co-infusion with 2 L of a commercial amino acid mix starting 30 minutes prior to PRRT and administered for at least 4 hours. The two amino acid solutions allowed were Aminosyn II 10% [21.0 g of L-lysine and 20.4 g L-arginine in 2 L] and Vamin 18 [18 g L-lysine and 22.6 g L-arginine]. The octreotide long-acting release (LAR) control group received 60 mg every 4 weeks.

Objective: To compare the tumour response of Lutathera (^{177}Lu-DOTATATE) to long acting octreotide.

Endpoint/outcome: Patients were evaluated for treatment response and safety, the outcome has not been further specified.

Sample size: 229 patients

Results: A total of 229 patients (116 males, 113 females) were enrolled. Median patient age was 63-64 years in each group. Of the 229 enrolled, 221 received at least one dose, 77% of patients in the Lutathera arm completed all 4 planned doses. Patients were followed for up to 60 months (median 14 months).

No evidence of renal toxic effects as detected by changes in creatinine clearance was seen during the observed timeframe (median follow-up 14 months) (Figure 5, below).

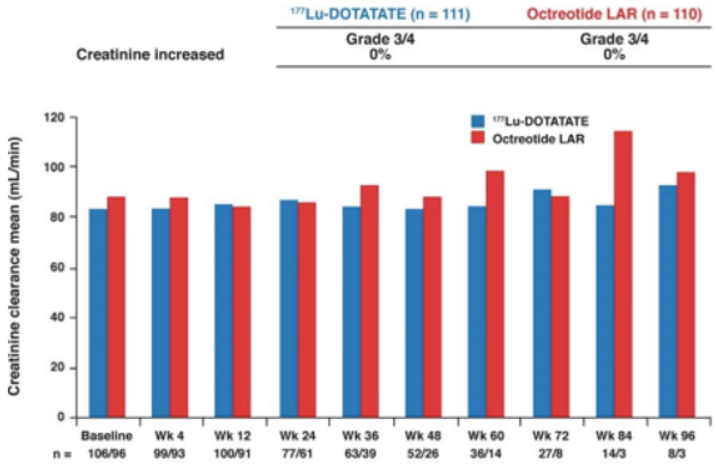


Figure 8. Summary of temporal changes in creatinine clearance seen with Lutathera and Octreotide LAR dosing (Strosberg 2017a)

Figure 5. Creatinine clearance in Strosberg 2017a

Analysis performed across trials (pooled analyses and meta-analysis)

None.

Clinical studies in special populations

Age

The effectiveness of amino-acids for renal protection during RSA treatment was shown in patients ranging from 11 to 91 years of age. The effectiveness of the 2.5% Lys-Arg formulation in particular and using the proposed dosing regimen was demonstrated in patients 17 to 89 years old (see subsection in Table 2. Studies evaluating Efficacy).

Gender

Males and females were well represented in clinical studies for amino-acids and 2.5% Lys-Arg, with approximately 40% to 60% representation in most studies (see Table 2. Studies evaluating Efficacy).

Tumor Type

Patients with various NETs in multiple stages were represented across study populations. Tumor load was also considered (see Table 2. Studies evaluating Efficacy).

Supportive study(ies)

Fifteen additional publications reporting clinical use of 2.5% Lys-Arg for renal protection during treatment with ^{177}Lu-DOTATATE or other RSAs were also submitted in support of this application (see Table 2). They provide data to support claims of well-established use of the 2.5% Lys-Arg solution for renal protection and/or additional information on safety and efficacy of the product.

2.5.3. Discussion on clinical efficacy

It has been adequately substantiated that concomitant amino acid infusions can reduce the renally absorbed radiation dose and that this can translate into clinically significant kidney protection, whereby the most relevant study for this well-established use application is the Erasmus MC reports and, to a lesser extent, the Phase III Netter-1 study in which commercially available amino acid solutions were used for renal protection. Both studies are of good quality to substantiate efficacy.

These two studies are also the pivotal studies for the benefit risk assessment in the present MAA for Lutathera.

The experience at Erasmus MC on PRRT with ^{177}Lu-DOTATATE is published in multiple articles. The renal protection protocol with Lysine 2.5% - Arginine 2.5% solution (same lysine and arginine content as LysaKare, 1 L, 4-hour infusion, starting 30 minutes before ^{177}Lu-DOTATATE administration) has been applied in more than 1200 NET patients treated with ^{177}Lu- DOTATATE, with a median follow-up period of more than 70 months.

Clinical data gained in clinical trials with other amino acid solutions with similar lysine and arginine content, such as complex commercial amino acid solution for parenteral nutrition, which have been used in PRRT with ^{177}Lu-DOTATATE or other RSAs, have also been considered and they are generally supportive for LysaKare safety and efficacy. It was clarified that the small differences in osmolality and pH of LysaKare the AA solutions used in the main studies supporting this application and will not affect its efficacy.

As noted in the PK assessment, it is not possible to understand the pharmacokinetics of LysaKare in detail. However, it appears that different compositions of AA-solutions have a generally similar effect on renal reabsorption.

The applicant reveals that ”the rationale of the 2.5% Lys-Arg formulation was primarily derived from the results of Rolleman et al. (2003), which demonstrated that 1 L of the formulation (25 g each amino acid) had similar efficacy (as determined by renal absorbed dose) but better tolerability (nausea and vomiting) compared to a 75g lysine only formulation.” However, the RSA used in the study presented was 111In-DTPA-octreotid and not the 177-DOTATATE, which is the RSA intended for use in combination with LysaKare.

No explicit dose response studies have been performed for LysaKare. The applicant cited and discussed clinical studies in which different formulations of amino acid solutions have been used in different treatment protocols, which is overall regarded acceptable for this WEU application even though dose-response study/studies with parallel groups with fixed titration to different maintenance doses per body weight of the i.v. solution LysaKare would have been preferable.

The scientific rationale for the frequent use of the “Rotterdam Protocol” in the PRRT setting nowadays seems to a great extent to be based on the scientific knowledge which was gained in the clinical studies provided and discussed by the applicant. The dose and posology proposed for LysaKare is in turn based on the extensive use of the “Rotterdam Protocol”, which seems therefore reasonable.

The performed main trials did not report separate outcomes for different age groups, gender or tumour types.

Overall, the literature data as provided describes the co-administration of 2.5% Lys-Arg solution, covers a sufficient number of patients and are conclusive and coherent with respect to the intended indication. The total body of evidence that emerges upon assessment leads to The efficacy of an 2.5% Lys-Arg solution in the proposed indication has been adequately proven, e.g. in Brabander (2017), in which only 0.3 % of subjects suffered creatinine grade 3 /4 toxicities, and serum creatinine levels normalized in all patients by 3 months after treatment completion.

In only one study (Kwekkeboom 2001), the effect of amino acid infusion vs. no infusion was evaluated on renal radiation-uptake in the kidneys in patients receiving 177Lu- DOTATATE. The doses to the kidneys were reduced by a mean of 47% (range 34-59%) when the 2.5% Lys-Arg solution was co-infused. However, the reliability of the study is may be seen critical since the number of trial participants was small (n=5), although all of them had the AA-solution administered at the second 177Lu- DOTATATE treatment. Age distribution was unknown, and no formal statistics on the observed differences has been presented.

Based on the published clinical studies discussed it was also shown that the reduction of the renally absorbed radiation dose can increase the theoretical maximum allowed dose for PRRT, which could be reasonably expected to increase the efficacy of the PRRT.

2.5.4. Conclusions on the clinical efficacy

The efficacy of 2.5% Lys-Arg solution for the reduction of renal radiation exposure during Peptide-Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-oxodotreotide has been adequately documented. The cited publications indicate that radiation doses to the kidneys can be significantly reduced when amino acid solutions are co-infused (reduction of renal radiation uptake). They further illustrate that the reduction of renal uptake enables higher radiation doses which is a direct benefit for patients.

The exact LysaKare formulation has not been tested in combination with ^{177}Lu-DOTATATE in any of the presented studies. However, different compositions of AA-solutions have a generally similar effect on renal reabsorption of RSAs, which supports efficacy of the LysaKare formulation in the indication applied for.

2.6. Clinical safety

Patient exposure

Safety information for 2.5% Lys-Arg and other amino acid formulations from a total of 28 publications reporting data on reduction of renal absorbed radiation dose during RSA treatment are included in this summary supporting LysaKare.

There has been extensive experience with 2.5% Lys-Arg and other amino acid formulations for the reduction of renal radiation exposure during RSA as summarized in the table below:

Table 6. Summary of Exposure with Safety Data for 2.5% Lys-Arg Using the "Rotterdam Protocol"

Publication	# of patients	Total # of doses	Number of doses per person
Rolleman 2003	9	16	At least one patient received up to 7 doses
†Kwekkeboom 2008, Bergsma 2016a, Brabander 2017	610	1772+	Some proportion of patients received less than intended dose
Hubble 2010	27	69	Median 3 doses/person
Gupta 2012	47	>94	2-6 doses per patient
***Ezziddin 2013, Sabet 2013, Ezziddin 2014b, Sabet 2014b, Sabet 2015,**	203	632	Targeted 3-4 doses per patient
Svensson 2015	51	Not indicated	Median 3 doses (1-5 range) Dosing limited by disease progression in 3 patients and persistent haematological toxicity in 4 patients
Totals	**947**	**>2583**	Majority of patients receive 3 to 4 doses (6-14 week intervals), range 1-7 doses

†Series of reports associated with a large 1,214 patient Phase I/II clinical study at Erasmus Medical Center in which all patients received 2.5% Lys-Arg for the reduction of renal radiation exposure; safety analysis was conducted on 610 patients

**Reports from same medical center with potentially overlapping patient populations*

Briefly, the safety information for 2.5% Lys-Arg is based on 12 literature reports of studies involving over 900 patients receiving more than 2500 doses of 2.5% Lys-Arg during RSA with various radiolabelled somatostatin analogues (RSAs) and up to 3 years of follow-up data. The majority of patients received 3-4 doses of 2.5% Lys-Arg administered 6-14 weeks apart (administered concomitantly with RSA). This is likely an underestimate of the overall population exposed to 2.5% Lys-Arg as the Kwekkeboom 2008 and related publications only report on a subgroup of patients treated in the 1,214 patient Phase I/II Erasmus Medical Center study in which all patients received 2.5% Lys-Arg.

Additional supportive data is drawn from literature reports of other amino acid formulations, experience with which includes treatment of 2409 patients receiving a total of approximately 6959 amino acid co-infusions with various RSAs. Follow-up data out to 13 years is available. The majority of these patients received 2 doses of amino acids, with range being 1-10 doses. Dosing intervals generally mimic those commonly used for RSA treatment (6-14 week intervals).

The patient populations included in the provided studies were diverse comprising patients with varying stages of disease of different origins, ages, previous/concomitant treatments, including other radioactive therapies or types of chemotherapy, and co-morbidities. Further, the inclusion / exclusion criteria varied between the studies, as some only required a diagnosis of NET, other studies had criteria based on creatinine clearance, s-creatinine levels, or baseline GFR. The applicant has adequately provided the requested summary of the demographics of patients included in the studies, which used the

25-Arg/25-Lys infusion. There are no marked differences in the demographics in these studies to be taken into account in the evaluation of the safety profiles of the respective studies.

Adverse events

Based on the above criteria, the following events were determined to be relevant to amino acid solutions containing the same amino acid content and using the same infusion protocol as that proposed for LysaKare:

Very common Events (≥ 10% of subjects): Nausea, Vomiting

Individual reports: Hyperkalemia, Headache, Dizziness, Flushing, Abdominal pain

The events are reversible, and have been reported at rates up to 70% (nausea in the presence of anti-emetics).

Studies with amino acid formulations and infusion protocols other than 2.5% Lys-Arg were also considered, as they are considered anyway to provide supportive data to LysaKare safety assessment. Data from three controlled studies show differential safety profiles for the different parameters tested. These studies indicate that limiting infusion volume and overall amino acid load reduce the incidence and/or severity of nausea, vomiting, and hyperkalaemia. Other adverse events reported in these studies were deemed not related to amino acid infusion. For example, hypophosphatemia was reported in one of the studies using a formulation of mixed amino acids, but this was not supported by two other studies.

Hyperkalemia

Transient, sometimes severe (>6 mmol/L) hyperkalemia was associated with 2.5% Lys-Arg and other amino acid formulations in a number of publications. Generally, serum potassium levels returned to baseline within 24 hours. Transient hyperkalemia itself (increases < 6mmol/l) seems to be quite common, with the incidence of severe hyperkalemia affecting a lesser proportion.

Lapa et al (2014a and b) published results from a prospective, cross-over study evaluating the tolerability of two different combinations of L-Lysine HCl and L-Arginine HCl conducted in 22 patients (13 male, 9 female) aged 31-82 years. Clinical symptoms and biochemical changes were monitored through 24 h post RSA treatment.

Dose 1 consisted of a 75 g amino acid dose (37.5 g each L-Lysine HCl and L-Arginine HCl in 1500 mL 0.9% NaCl) administered as a 4 h infusion (375 ml/h) starting 0.5 to 1 hour prior to treatment with 7.5 ± 0.7 GBq of ^{177}Lu-Dotatate.

Dose 2 was administered at an unspecified interval after Dose 1 and involved a 50 g amino acid dose (25 g each L-Lysine HCl and L-Arginine HCl in 2000 mL 0.9% NaCl) administered as a 4 h infusion (500 mL/h) starting 0.5 to 1 hour prior to treatment with 7.6 ± 0.3 GBq ^{177}Lu-edotreotide.

Hyperkalaemia was reported to a similar degree following both amino acid formulations. Three of 22 patients in the 75 g group presented with palpitations, chest pain and/or general discomfort. Evaluation of ECG revealed flattened P waves and high peaked T waves. Two of these three patients also became symptomatic after the 50 g AA dose. These observations at ECG level were not associated with any change in cardiac conduction times. All remaining patients tolerated the treatment without discomfort. In all symptomatic cases, serum potassium levels were ≥6.1 mmol/l with peak values of 7.9 mmol/l and required prompt intervention by infusion of 20 IU insulin with 20% glucose in 500 mL saline.

Elevations in serum K^+ levels were common with both AA formulations. At baseline, mean K^+ levels were 4.4 ± 0.4 mmol/l (75g) and 4.3 ± 0.4 mmol/l (50g), respectively. At 4 h, 20/22 subjects (91%) in both groups had serum potassium levels ≥ 5.0 mmol/l with a mean of 5.8 ± 0.7 mmol/l (75g) and 5.7 ± 0.8

mmol/l (50 g), respectively. Increases in K^+ levels were comparable (25% for 75 g, $p<0.001$ and 24% for 50 g AA $p<0.001$).

In both groups, severe hyperkalaemia defined as $K^+ > 6$ mmol/l was observed in 8/22 (36%) patients. After 24h, K^+ levels almost returned to baseline (mean, 4.5 ± 0.4 mmol/l (75g AA) vs mean 4.6 ± 0.4 mmol/l (50 g AA). No significant differences between both AA protocols were found at any time point.

At 4 h post-infusion, all other parameters investigated showed only minor differences. Only glomerular filtration rates ($p = 0.011$ and creatinine levels at 24 h ($p = 0.016$) varied significantly between the 50 g AA and 75 g AA doses at 24 h post-infusion.

In a response the applicant clarified that in more than 3500 patients treated with Lutathera to date (including 1214 patients in Erasmus MC, 112 patients in NETTER-1, and 2511 patients in the Compassionate Use programs) equaling approximately 9000 co-administrations of AA solution and Lutathera (including administrations of LysaKare in France and the UK since September 2017), 11 cases were identified using the SMQ "Cardiac arrhythmias". Of these 11 cases, five were reported from clinical studies, four were from named patient use and the remaining two were spontaneous. None of these cases had a fatal outcome.

Nine cases included events such as "Atrial fibrillation (4), electrocardiogram QT prolonged, atrioventricular block II degree, cardiac failure, electrocardiogram repolarization abnormality, bundle branch block right". There were confounding factors in six of these cases (previous cardiac history, concomitant medications and absence of important laboratory investigation results - particularly potassium) and the remaining three cases provided little information.

The remaining two cases reported hyperkalemia. The first case was about a 55-year-old female patient, who, at the end of her third Lutathera cycle, reported weakness and was unable to walk. Laboratory results revealed a serum potassium of 7.9 mmol/L leading to hospitalization. No ECG abnormalities were reported. On the next day, the patient was discharged with serum potassium of 4.3 mmol/L. No treatment details were provided. The second case was about a 70-year-old patient who received her fourth Lutathera cycle. Baseline serum potassium was 4.7 mmol/L. Creatinine clearance was 50 mL/min. At around 2.30 pm (approximately at the end of the treatment infusion), serum potassium was 6.1 mmol/L, and at 5.30 pm it was 5.6 mmol/L. No clinical signs or symptoms were reported. The ECG was unremarkable. Treatment included one spoon full of sodium polystyrene sulfonate; One day later, serum potassium was at 4.1 mmol/L In both the above cases, the composition of the amino acids was unknown despite multiple follow up attempts by the applicant. However, on a very recent follow-up (16-Jan-2019), the amino acid infused for the patient in the second case was clarified as LysaKare. No ECG abnormalities pertaining to cardiac conduction time were seen.

Phlebitis

Phlebitis and infusion site reactions were not reported in any of the publications considered in the evaluation of literature relevant for LysaKare safety, including studies infusing large volumes of commercial amino acid solutions with pH similar to that of LysaKare (e.g. Vamin 18, AminoSyn II 10%).

Other adverse events

Other adverse events described in the literature reports were considered to be either related to the RSA (e.g., hematological toxicities, hair loss) or related to the patient's underlying disease (e.g., abdominal pain due to tumors, flushing due to tumor lysis syndrome, liver toxicities in the presence of liver metastases).

Serious adverse event/deaths/other significant events

The Supplementary Material of the phase III, key study by Strosberg (2017a) reported two SAEs to be related to the amino acid infusions by the investigator:

The serious adverse reactions (SARs) reported by the investigators in the ^{177}Lu-DOTATATE arm were:

- One patient suffered from a serious episode of hepatic encephalopathy which required hospitalization but resolved without sequelae within 1 week. This SAR was related to the amino acids administration according to the investigator.
- One patient suffered from an episode of syncope which was considered medically significant and related to amino acid infusion by the investigator. The SAR resolved spontaneously within few hours.

Laboratory findings

Laboratory data apart from the information on hyperkalaemia have not been presented with the application.

Safety in special populations

Use of amino acids for reducing the renal absorbed radiation dose during RSA therapy may be limited by either restrictions related to the amino acid co-infusion or the RSA itself.

Renal Impairment

There have been no studies addressing efficacy and safety of amino acid co-infusions in patients with renal insufficiency. In the case of Lutathera, treatment has been contraindicated in patients with severe renal impairment (<30 mL/min/1.73 m^2). Lutathera dose can be modified for patients with less severe renal impairment. Even in cases where Lutathera dose is reduced, the full infusion of LysaKare is still recommended.

Hepatic Impairment

There have been no studies addressing the safety and efficacy of 2.5% Lys-Arg in hepatic insufficiency. The prescribing information for complex amino solutions used for parenteral nutrition purposes include warnings stating that the use of amino-acid solutions in patients with hepatic impairment may result in plasma amino acid imbalances, hyperammonemia, pre-renal azotemia, stupor, and coma. The total amino acid dose associated with these parenteral formulations includes much larger amounts of amino acids and greater infusion volumes than LysaKare. In the 28 publications containing safety information supporting the use of amino acids and the 2.5% Lys-Arg formulation in PRRT the reduction of renal radiation exposure, liver toxicities were only reported for 3 patients, none of which progressed to hepatic failure. All 3 events were attributed to liver metastases rather than the amino acid treatment itself. However, a serious adverse event of hepatic encephalopathy in one patient warranted further clarification. In the response, it was clarified that this patient was hospitalized for bilirubin increase before the first dose due to a cholangitis because of a potential stent dysfunction.

As stated in the warning (4.4) section of the current SmPC for Lutathera, it is not recommended to start a treatment with Lutathera is in patients Liver impairment with either total bilirubinaemia > 3 times the upper limit of normal or albuminuria < 30 g/L and prothrombin ratio decreased < 70%. Section 4.2 of the Lutathera SmPC states "*Careful consideration of the activity to be administered to patients with hepatic*

impairment is required since an increased radiation exposure is possible in these patients. The pharmacokinetic profile of lutetium (^{177}Lu) oxodotreotide in patients with severe hepatic impairment has not been studied, therefore treatment with Lutathera in those patients is not recommended."

Thus, in this circumstance, the limitations associated with the RSA would limit use of LysaKare in patients with either total bilirubinaemia > 3 times the upper limit of normal or albuminuria < 30 g/dL and prothrombin decreased < 70%.

Cardiac Insufficiency

There have been no studies addressing the safety and efficacy of 2.5% Lys-Arg in patients with cardiac insufficiency.

Elderly

The safety and effectiveness of 2.5% Lys-Arg (or amino acids in general) for the reduction of renal radiation exposure during RSA treatment have not been established in elderly patients, although they were well represented in the clinical studies considered for the LysaKare application.

Pediatrics

The safety and efficacy of 2.5% Lys-Arg (or amino acids in general) for the reduction of renal radiation exposure during RSA treatment have not been established in patients under 18 years of age and the safety profile of paediatric populations of different ages is not known.

Other Populations at Potential Risk

LysaKare is intended to be used in association with Lutathera and therefore it is subjected to the same restrictions. No specific populations at potential risk, other than those indicated in the Lutathera EU SmPC, are identified for LysaKare use.

Immunological events

No immunological events were reported.

Safety related to drug-drug interactions and other interactions

The applicant stated that there are no known drug interactions of concern.

Discontinuation due to adverse events

Discontinuations have not been systematically captured in most of the provided studies for the infusion solutions due to the retrospective nature of these studies. Therefore, it seems not possible to assess the discontinuation rate related due to AES caused by the applied product. From the Lutathera trials, discontinuation due to AES was 7 patients in the NETTER-1 study, which was lower than in the Sandostatin LAR arm.

Post marketing experience

All safety data reported above is post marketing.

2.6.1. Discussion on clinical safety

Safety information for 2.5% Lys-Arg and other amino acid formulations from a total of 28 publications have been included in the applicant's summary to support the safety of LysaKare. These studies include

reports of clinical use of the 2.5% Lys-Arg formulation (Erasmus MC) administered to reduce the kidney absorbed radiation dose during RSA treatment dating back to 2001. Altogether, the applicant has gathered data on reported clinical experience in over 1200 patients receiving 2.5% Lys-Arg using the infusion regimen proposed for LysaKare (the "Rotterdam Protocol" applied in the Erasmus MC study). Available data include up to 70 months of follow-up.

Additional supportive data is drawn from other clinical studies using other amino acid formulations and slightly different infusion protocols. Moreover, the clinical experience of renal protection in PRRT with RSAs other than ^{177}Lu-DOTATATE is considered relevant to support the safe and effective use of LysaKare during PRRT with Lutathera, as the different RSAs share the same mechanism of renal uptake.

The safety profile of 2.5% Lys-Arg is not easy to characterize, as the amino acid solution is co-administered with RSAs and therefore the cause of safety events may be difficult to discern. Evaluation is further confounded with the wide clinical adoption of anti-emetic pre-treatment, due to the nausea and vomiting associated with the amino acid infusions. For the purposes of this dossier, the safety events that are considered related to lysine and arginine were those with a close temporal association with the infusion itself. The assessment is based on a qualitative evaluation of incidence and severity of events occurring during or soon after infusion. Observation of the same events in multiple studies (and at different clinical centres) provides confidence in the strength of association between the events and the treatment regimen. The approach of choosing adverse events with a narrow timely relationship to the amino acid infusion is restrictive, but responses with a thorough review of all adverse events registered in the publications revealed that adverse events most likely related to the amino acid infusion occurred during this interval.

The presented studies that have employed a solution of lysine and arginine in the same quantities as proposed in LysaKare in combination with ^{177}Lu-dotatate are single-arm, mainly retrospective studies and information on adverse events has not been systematically generated or collected. The safety information in these studies generally consists of laboratory tests, such as blood counts and assessment of liver and kidney function, which in some studies are further specified as s-creatinine and s-ALT, s-AST. Some studies have also measured GFR or assessed absorbed dose of radioactivity. Only 116 patients have been exposed to a Lys-arg solution in a randomised controlled trial (Strosberg 2017a). However, in this study, lysine and arginine were not administered in the same quantities as proposed in LysaKare.

Nausea and vomiting have been determined to occur in $\geq$ 10% of subjects and have be stated to be "very common"; hyperkalaemia, abdominal pain, flushing, headache, dizziness occur with "unknown" frequency. The frequency category of "hyperkalaemia" will be clarified in below mentioned PASS.

"Pre-existing clinically significant hyperkalaemia if not adequately corrected before starting the LysaKare infusion" has been included in section 4.3 of the SmPC as a contraindication. The applicant clarified the temporal relationship between the infusion of the amino acid solution and the hyperkalaemia (i.e. how fast the onset is and how long the duration is), the physiological mechanism behind the occurrence of hyperkalaemia, and the patient populations who may be at higher risk of developing hyperkalaemia, as follows.

An increase of serum potassium levels may occur in patients receiving arginine and lysine. Serum potassium level increases are generally mild and transient. According to limited available data maximum levels should be reached approximatively by 4 to 5 hours after start of the infusion and should return to normal levels by 24 hours. Serum potassium levels must be tested before each treatment with LysaKare. In case of hyperkalaemia, patient's history of hyperkalaemia and concomitant medication should be checked. Hyperkalaemia must be corrected accordingly before starting the infusion. In case of pre-existing clinically significant hyperkalaemia, a second monitoring prior to LysaKare infusion must confirm that hyperkalaemia has been successfully corrected. During treatment and up to 24 hours thereafter, the patient 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). After the infusion 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 (SmPC section 4.4).

A PASS investigating systematically the hyperkalaemia risk with LysaKare and confirming the safety profile documented in the literature will be conducted by the applicant.

It is agreed that, except for hyperkalaemia, most of the adverse events described in the scientific literature to be directly related to the amino acid solution are of mild nature and transient. This is especially true for vomiting and nausea, being reported at rates up to 70%. Moreover, it needs to be considered that these symptoms may also be caused by the underlying tumour disease.

Two serious adverse events have been reported in the randomised controlled trial by Strosberg (2017a); these were syncope and hepatic encephalopathy. Both events were reported to be related to the amino acid solution by the investigator, but evaluation of the details provided in the response document indicated rather a causal relation to underlying other diseases.

Similarly, the reported increases of hepatic transaminases in a small part of the patients were also mentioned in one of the retrospective studies (from the Rotterdam center) are more likely to reflect the hepatic metastasis from the treated NET tumours than a drug related hepatotoxicity of LysaKare. It should be kept in mind that the patients, whom these publications concern, are severely ill due to unresectable, often metastasised tumours.

In general, it needs to be considered that due to the concomitant radioactive treatment blood sampling is technical difficult in this setting.

Renal radiation absorbed dose appears to be inversely related to renal function, such that patients with renal impairment tend to have higher renal absorbed doses than patients with normal renal function. It is not known if this is reflective of decreased efficacy of amino acid co-infusion or other unknown effects. It is possible that patients with reduced renal function are more prone to develop adverse events, e.g. hyperkalemia. Therefore, a special warning and a precaution has been included in the PI of LysaKare, and similar ones are already included in Lutathera's PI.

Patients with cardiac insufficiency are known to have problems with fluid overload by intravenous fluids. Thus, large volume infusions associated with commercial parenteral amino acid formulations are not recommended. The reduced infusion volume offered by the 2.5% Lys-Arg formulation makes it the recommended approach in treatment guidelines. Both the LysaKare and the Lutathera PI include special warnings and precautions regarding patients with severe heart failure defined as class III or IV in the New York Heart Association classification: "Due to 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 class IV in the NYHA classification. Treatment with lutetium (177Lu) oxodotreotide is not recommended for patients with severe heart failure defined as class III or class IV in the NYHA classification therefore, the benefit risk for these patients will always need to be weighed carefully." (SmPC, section 4.4)

Older age has been associated with declines in renal function of ~1% per year predisposing this population to potentially higher renal radiation doses. However, in the studies considering risk factors for renal toxicities, age was not strong enough to influence clinical outcome on its own. Older patients may also possess other risk factors, which further increase the risk for elevated renal absorbed radiation dose. Thus, elderly patients receiving RSA and LysaKare should be carefully monitored.

It is acknowledged that data on co-infusion of LysaKare in special patient sub-populations is limited by the lack of direct experience (severe renal and severe hepatic impairment) and restrictions in the Lutathera product information. However, there are special warnings and precautions in the Lysakare PI for the subpopulations of patients with renal impairment, hepatic impairment, cardiac insufficiency and elderly, as well as in the Lutathera PI, which are adequate.

Lysakare exerts its effect through the interaction with megaline/cubiline system by decreasing the uptake of positively charged molecules at the tubular level. Potentially, drugs that are re-absorbed by the same system could compete. However, no information was found about possible drugs being re-absorbed by this mechanism and thus it is agreed that no specific warning on drug-drug interactions is indicated.

From the information provided is seems unlikely that the minor differences in the formulation of LysaKare would negatively influence the electrolyte balance and pH value to a higher and possibly unacceptable degree.

As discussed before and described by Pfob (and also Giovacchini 2011, Lapa 2014a and Lapa 2014b), infusion of amino acid infusions is often associated with severe metabolic acidosis and the concurrent hyperkalaemia are potentially harmful or even lethal. Pfob et al. state "even if to date no serious cardiovascular events have been reported, the level of potassium reached with amino acid infusion is potentially harmful or even lethal and cannot be ignored, even if the elevation is transient." This risk is addressed by a special warning in LysaKare's EU SmPC.

Immunological events are not expected, as L-Lysine and L-Arginine are naturally occurring amino acids. In the context of the underlying disease and the Lutathera adverse events discontinuation due to AES from Lysakare is very low.

Given that the reported hypophosphataemia lacked the robustness to be seen in multiple studies, it was deemed not to be a relevant event associated with amino acid infusions. Serum potassium seems to be the only electrolyte consistently affected by amino acid infusions as no changes in serum sodium chloride, or in other serum electrolytes were observed.

Phlebitis is a theoretical risk with amino acid infusion, but is not believed to represent a risk for LysaKare. Phlebitis at the site of injection has been attributed to hyperosmolarity of the infused amino acid solution which could be treated with local vasoprotective creams. LysaKare was formulated to have an osmolarity much closer to physiologic levels than that of parenteral amino acid mixtures that have been used for reducing the kidney absorbed radiation dose during RSA treatment in relevant studies reported in the literature.

The applicant states that modifying the LysaKare formulation compared to the 2.5% Lys-Arg formulation was to improve patient tolerance. The rationale of lowering the osmolality to a lower, more physiologic value seems plausible. However, removing NaOH for pH adjustment to bring the osmolality of LysaKare closer to the physiological one resulted in a lower pH value in comparison to the 2.5% Lys-Arg used in the Erasmus MC trial. Although the pH value of LysaKare is lower compared to that of the preparations used in the cited clinical studies, it was clarified with the applicant's response that the maximum concentration of free [H+] in the LysaKare solution is about 0.008 mmol/L, equivalent to 0.008 mEq/L. This value is well below the blood buffering capacity which is, considering only the chemical buffers of plasma in whole blood, in the range of 24 - 38 mEq/L. Thus, this initial concern has been resolved.

There are no data on the use of arginine and lysine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (SmPC, section 4.6). There is no relevant use of this medicinal product in women of childbearing potential since lutetium (177Lu) oxodotreotide is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded due to the risk associated with the ionizing radiation (SmPC, section 4.6).

Arginine and lysine, being naturally occurring amino acids, are excreted in human milk, but effects on the breastfed newborns/infants are unlikely. Breast-feeding should be avoided during treatment with lutetium (177Lu) oxodotreotide (SmPC, section 4.6).

There are no data on the effects of arginine and lysine on fertility (SmPC, section 4.6), which is acceptable, given among others the fertility precaution of lutetium (177Lu) oxodotreotide.

Taking into account that (177Lu) oxodotreotide is indicated for the treatment of GEP-NETs, which represent a rare disease, and taking into account the overall amount of experience with amino acid solutions, the safety data base is deemed sufficient for this WEU application. From the safety database all the adverse reactions reported have been included in the PI.

2.6.2. Conclusions on the clinical safety

The data presented allow characterization of the safety profile of LysaKare. A similar safety profile of the applied product compared with those Arg-Lys formulations already used in clinical practice can be reasonably assumed.

The CHMP considers the following measures necessary to address issues related to safety: An international post-authorization safety study to assess the effect of LysaKare administration on potassium blood levels concentration up to 24h compared to baseline (category III).

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hyperkalaemia
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
An international category 3 postauthorization safety study to assess the effect of LysaKare administration on potassium blood levels concentration up to 24h compared to baseline (category III)	hyperkalaemia	Planned	Protocol for submission 30/11/2019 Clinical Study Report release in Q4 2022

Risk minimisation measures

Safety concern	**Risk minimisation measures**
Hyperkalaemia	Routine risk minimisation measures: Sections in the SmPC:

Safety concern	Risk minimisation measures
	4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects Additional risk minimisation measures: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication is as follows: 'Reduction of renal radiation exposure during Peptide-Receptor Radionuclide Therapy (PRRT) with lutetium (^{177}Lu) oxodotreotide in adults'.

3.1.2. Available therapies and unmet medical need

Currently, there are no commercial amino acid formulations that have been approved for use in the reduction of renal radiation exposure during treatment with ^{177}Lu-DOTATATE or other RSAs.

The LysaKare formulation is based on a 2.5% Lysine HCl + 2.5% Arginine HCl (2.5% Lys-Arg) amino acid solution that has been clinically used for reducing the renal radiation exposure during RSA treatment

since at least 2001, e.g. as part of the "Rotterdam Protocol" also used in the Erasmus MC study. Currently the 2.5% Lys-Arg amino acid solution in line with the Rotterdam Protocol needs to be prepared as extemporaneous preparation in (hospital) pharmacies.

It is noted that international guidelines as well as the SmPC for currently centrally approved (^{177}Lu) oxodotreotide (Lutathera) request the simultaneous infusion of Lysine and Arginine in quantities corresponding to what is present in LysaKare.

3.1.3. Main clinical studies

3.2. Favourable effects

Kwekkeboom et al (2001) reported the results of a study on the effect of amino acid infusion vs. no infusion in the same patient receiving ^{177}Lu-DOTATATE (1850 MBq or 50 mCi).The amino acid solution was made of 2.5% L-Lysine HCl and 2.5% L-Arginine HCl in 1L of 0.225% NaCl (2.5% Lys-Arg). The infusion was given over 4 hours at a rate of 250 ml/h, beginning 30 minutes prior to RSA treatment ("Rotterdam Protocol").

The RSA doses to the kidneys were significantly reduced by a mean of 47% (range 34-59%) when the 2.5% Lys-Arg solution was co-infused.

Brabander et al. (2017) provided further follow-up information on 610 patients in the Erasmus MC phase I/II study who had received ^{177}Lu- DOTA^{0}Tyr^{3}-octreotate between January 2000 to January 2015. The study focused on 610 patients residing in The Netherlands ('Dutch' patients) who had received at least 3.7 GBq radiation dose. A median of 64 months follow-up data was available (range 58-70 months). 2.5% Lys-Arg was used for renal protection. In this report, the effectiveness of the antitumor effects of ^{177}Lu-DOTATATE treatment continued to be supported, with median overall survival being 63 months, median progression free survival being 29 months and the median time to progression being 36 months. Moreover, the use of 2.5% Lys-Arg solution proved to be effective in reducing the renal radiation exposure, the mean kidney absorbed radiation dose being below the toxicity threshold.

The effectiveness of amino-acids for renal protection during RSA treatment was shown in patients ranging from 11 to 91 years of age. The effectiveness of the 2.5% Lys-Arg formulation in particular and using the proposed dosing regimen was demonstrated in patients 17 to 89 years old.

Both males and females were represented in the clinical studies with approximately 40% to 60% representation in most studies. Patients with various NETs in multiple stages were represented across study populations. Tumor load was also considered.

3.3. Uncertainties and limitations about favourable effects

There are no remaining uncertainties and limitations that have an impact on the benefit-risk balance (see section 3.7.).

3.4. Unfavourable effects

The following key events were determined to be relevant to amino acid solutions containing the same amino acid content and using the same infusion protocol as that proposed for LysaKare:

Very common events (≥ 10% of subjects): Nausea, Vomiting

The events are reversible during 24 h after start of infusion and are most pronounced at the end of infusion (after 4 hours). Up to 70% of subjects reported nausea.

Not reported in all studies: Hyperkalemia

Transient, sometimes severe (>6 mmol/L) serum hyperkalemia was associated with 2.5% Lys-Arg and other amino acid formulations in a number of publications. Generally, serum potassium levels returned to baseline within 24 hours. Mild hyperkalemia (< 6mmol/l) was reported in up to 91 % of subjects, severe hyperkalemia (> 6mmol/l) in up to 36 % of subjects. Severe cases presented with palpitations, chest pain and/or general discomfort. Evaluation of ECG revealed flattened P waves and high peaked T waves. These observations at ECG level were not associated with any change in cardiac conduction times. A maximum of 7.9 mmol/l was reported.

3.5. Uncertainties and limitations about unfavourable effects

The exact incidence, severity, duration, reversibility, dose-response relationship of hyperkalaemia is unknown. Likewise, the frequencies of withdrawals and treatments given to correct the hyperkalaemia are unknown.

The included studies are, with a few exceptions, retrospective with a lack of systematically generated and collected safety data. The only phase III randomised controlled trial used amino acid infusions in a different concentration of that proposed in LysaKare. These methodological shortcomings hampered the evaluation of LysaKare's safety profile in general. Additionally, the product is used during PRRT with ^{177}Lu oxodotreotide, which is approved for the treatment of GEP-NETs, a rare disease entity. The limited number of patients makes assessment of differences in safety events in subgroups rather difficult, particularly, as this product is used in a target population suffering from a severe malignancy.

3.6. Effects Table

Table 7. Effects Table for LysaKare indicated for reduction of renal radiation exposure during Peptide-Receptor Radionuclide Therapy (PRRT) with lutetium (177Lu) oxodotreotide in adults

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Renal radiation uptake	Reduction of renal radiation uptake by 34-51% compared to non-treated controls.	Organ Doses in cGy (rad)/ 3700 MBq (100 mCi)	^{177}Lu-DOTATATE twice, 6-9 week apart. 2.5% Lys-Arg ("Rotterdam Protocol") co-administered with the second treatment	no AA solution	The study was limited by having only 5 participants, and all patients had the AA-solution administered only during the second ^{177}Lu- DOTATATE treatment. Age distribution was unknown, and no formal statistics on the observed differences has been presented.	Kwekkeboom 2001
Renal toxicity	RSA-related renal toxicity prevented	Renal toxicity graduation 0-4 and assessment of relatio	^{177}Lu-DOTATATE and 2.5% Lys-Arg for renal protection.	none	Data was collected retrospectively, and without a control group.	Kwekkeboom 2008 Brabander 2017

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
		nship				
Renal toxicity	No renal toxic effects during the observed time-frame (median follow-up 14 months)	Creatinine clearance.	Lutathera, 4 treatments 7.4 GBq (200 mCi), co-infusion of Aminosyn II 10% [21.0 g of L-lysine and 20.4 g L-arginine in 2 L] or Vamin 18 [18 g L-lysine and 22.6 g L-arginine]	Octreotide long-acting release (LAR), 60 mg every 4 weeks.	No formal statistics have been provided for temporal changes in creatinine clearance seen with Lutathera and Octreotide. No information about number of patients adminstered Aminosyn II vs. Vamin 18 has been provided.	Strosberg 2017a
Unfavourable Effects						
Hyperkalaemia	Individual reports of hyperkalaemia of up to 8.5 mmol/L, along with typical ECG changes and clinical symptoms of dizziness, weak muscles and malaise, in a minority of the submitted studies.	number of reports	AAs containing Lys and Arg	none	Only a minority of the studies report to have used ECG monitoring and blood tests during the amino acid infusions or right after the termination of the infusion. Furthermore, there are differences between the studies with respect to e.g. infusion rate.	Giovacchini, Lapa (both)
Nausea	25 %	Percentage of doses	^{177}Lu-DOTATATE and 2.5% Lys-Arg for renal protection.	none	Data was collected retrospectively, and without a control group.	Kwekkeboom 2008, Bergsma 2016b, Brabander 2017
Vomiting	10 %	Percentage of doses	^{177}Lu-DOTATATE and 2.5% Lys-Arg for renal protection.	none	Data was collected retrospectively, and without a control group.	Kwekkeboom 2008, Bergsma 2016b, Brabander 2017

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Published studies demonstrate that 2.5% Arg-Lys solutions reduce renal radiation exposure by 47% (range 34% to 59%). This effect is considered of clinical importance. Thus, reduction of radiation exposure is very likely to reduce the risk of acute and chronic radiation damage to the kidneys. Furthermore, as the kidneys are the dose limiting organ for this type of therapy, reduction of renal radiation exposure is also considered important in order to allow adequate dosing of the RSAs to increase the likelihood of a clinically relevant oncological effect of this treatment. Concomitant administration of AA solutions reduces RSA-induced acute and chronic kidney damage and facilitates adequate RSAs exposure to increase likelihood of a favourable oncological result. Both can be considered relevant beneficial effects for patients. The data allow extrapolation of efficacy data from the solutions used in the published studies to the product applied for. It can be assumed that LysaKare has the same efficacy in the intended

indication. The limitations regarding number of patients, design, completeness of data, and analysis are acceptable.

The safety data presented indicates that infusion of amino acid solutions is associated with hyperkalaemia, nausea and vomiting. As regards hyperkalaemia, this condition is potentially life-threatening if unrecognized and/or untreated and as such clinically important. On the other hand, if predicted/recognized and treated adequately, hyperkalaemia can be managed. Potassium levels in blood increase during the 4 hours of amino acid infusion and are at highest at the end of this period. Normalisation to baseline levels was observed during the next 24 hours. Specific risk factors for developing hyperkalaemia were not identified, but clearly other clinical situations promoting development of hyperkalaemia like metabolic acidosis (which has been observed with complex AA solutions) or renal impairment have to be considered as risk factors. Therefore, a respective contraindication, special precautions and warnings have been implemented in the PI in order to allow an adequate control of this identified risk. A PASS investigating systematically the hyperkalaemia risk with LysaKare and confirming the safety profile documented in the literature will be conducted by the applicant. The limitations of retrospective data collection and lack of control arm with respect to the risks of nausea and vomiting are acceptable.

Given that the product is intended for the use in patients with a rare condition, a full evaluation of the efficacy and safety across different populations, e.g. age, gender, concomitant diseases was not possible due to the limited population available. There are special warnings and precautions in the Lysakare PI for the subpopulations of patients with renal impairment, hepatic impairment, cardiac insufficiency and elderly, which are expected to sufficiently control the potential risks in these patients.

3.7.2. Balance of benefits and risks

The well-established use of Arg-Lys solutions for the reduction of renal radiation exposure during Peptide-Receptor Radionuclide Therapy (PRRT) with lutetium (177Lu) oxodotreotide has been adequately documented. The cited publications indicate that doses to the kidneys can be significantly reduced when a 2.5% Arg-Lys solution are co-infused (reduction of renal radiation uptake). Concomitant administration of 2.5% Arg-Lys solutions reduces RSA-induced acute and chronic kidney damage and facilitates adequate RSA exposure to increase likelihood of a favourable oncological result. Both can be considered relevant beneficial effects for patients.

The main risk of LysaKare is severe hyperkalaemia. The respective contraindication, special warning and precaution are expected to control it adequately.

3.8. Conclusions

The overall B/R of LysaKare is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of LysaKare is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

5. Literature references

Aminosyn II 10% (2004). US package insert. Hospira Inc., Lake Forest, Illinois.

Barone R, Pauwels S, de Camps J, Krenning EP, Kvols LK, Smith MC, Bouterfa H, Devuyst O, Jamar F. (2004). Metabolic effects of amino acid solutions infused for renal protection during therapy with radiolabeled somatostatin analogues. Nephrol Dial Transplant, 19 2275-2281.

Barone R, Borson-Chazot F, Valkema R, Walrand S, Chauvin F, Gogou L, Kvols LK, Krenning EP, Jamar F, Pauwels S. (2005). Patient-specific dosimetry in predicting renal toxicity with 90Y-DOTATOC: relevance of kidney volume and dose rate in finding a dose-effect relationship. J Nucl Med, 46(Suppl 1): 99S-106S.

Behr TM, Sharkey RM, Juweid ME, Blumenthal RD, Dunn RM, Griffiths GL, Bair H-J, Wolf FG, Becker WS, Goldenberg DM (1995). Reduction of the renal uptake of radiolabeled monoclonal antibody fragments by cationic amino acids and their derivatives. Cancer Res, 55: 3825-3834.

Bergsma H, Konijnenberg MW, Kam BLR, Teunissen JJM, Kooij PP, de Herder WW, Franssen GJH, van Eijck CHJ, Krenning EP, Kwekkeboom DJ (2016a). Subacute haematotoxicity after PRRT with 177Lu-DOTA-octreotate: prognostic factors, incidence and course. Eur J Nucl Med Mol Imaging, 43: 453-463.

Bergsma H, Konijnenberg MW, van der Zwan WA, Kam BLR, Teunissen JJM, Kooij PP, Mauff KAL, Krenning EP, Kwekkeboom DJ (2016b). Nephrotoxocity after PRRT with 177Lu-DOTA-octreotate. Eur J Nucl Med Mol Imaging, 43: 1802-1811.

Bode-Böger SM, Böger RH, Creutzig A, Tsikas D, Gutzki FM, Alexander K, Frölich JC (1994). L-arginine infusion decreases peripheral arterial resistance and inhibits platelet aggregation in healthy subjects. Clinical Science, 87: 303-310.

Bode-Böger SM, Boger RH, Galland A, Tsikas D, Frölich JC (1998). L-arginine-induced vasodilation in healthy humans: pharmacokinetic–pharmacodynamic relationship. Br J Clin Pharmacol, 46: 489–497

Bodei L, Cremonesi M, Zoboli S, Grana C, Bartolomei M, Rocca P, Caracciolo M, Mäcke HR, Chinol M, Paganelli G (2003). Receptor-mediated radionuclide therapy with 90Y-DOTATOC in association with amino acid infusion: a phase I study. Eur J Nucl Med, 30: 207-216.

Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, Baio SM, Sansovini M, Paganelli G (2008). Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging, 35: 1847-1856.

Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, Bartolomei M, Lombardo D, Ferrari ME, Sansovini M, Chinol M, Paganelli G (2011). Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging, 38: 2125-2135.

Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, Lepensky C, Kwekkeboom DJ, Baum RP, Krenning EP, Modlin IM (2015). Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging, 42: 5-19.

Bodei L, Cremoseni M, Ferrari M, Krenning E, Sierra ML, Erion JL, Santoro P, Chicco D, Mariani MF (2018). Renal protection during Lutathera treatment using lysine and arginine solutions. Abstract for EANM in press.

Böger RH, Bode- Böger SM (2001). The clinical pharmacology of L-arginine. Annu Rev Pharmacol Toxicol, 41: 79-99.

Boldt A, Gergs U, Frenker J, Simm A, Silber RE, Klöckner U, Neumann J (2009). Inotropic effects of

L-lysine in the mammalian heart. Naunyn-Schmied Arch Pharmacol, 380: 293-301.

Brabander, T, van der Zwan, WA, Teunissen, JJM, Kam, BLR, Feelders, RA, de Herder, WW, van Eijck, CHJ, Franssen, GJH, Krenning, EP and Kwekkeboom, DJ (2017). "Long-Term Efficacy, Survival, and Safety of [177Lu-DOTA0,Tyr3]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors." Clin Cancer Res 23(16): 4617-4624.

Brosnan ME, Brosnan JT (2004). Renal arginine metabolism. J Nutr, 134 (10 Suppl): 2791S – 2895S.

Clinisol 15% (2014). US package insert. Baxter Healthcare Corporation, Deerfield, IL.

Cremonesi M, Ferrari M, Paganelli G, Rossi A, Chinol M, Bartolomei M, Prisco G, Tosi G (2006). Radiation protection in radionuclide therapies with 90Y-conjugates: risks and safety. Eur J Nucl Med Mol Imaging, 33(11): 1321-7.

Cwikla JB, Sankowski A, Seklecka N, Buscombe JR, Nasierowska-Guttmejer A, Jeziorski KG, Mikolajczak R, Pawlak D, Stepien K, Walecki J (2010). Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. Ann Oncol, 21(4): 787-94.

Emami B, Lyman J, Brown A, Cola L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M (1991). Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21(1):109-122

Esser JP, Krenning EP, Teunissen JJ, Kooij PP, van Gameren AL, Bakker WH*, et al.* (2006). Comparison of [(177)Lu-DOTA(0),Tyr(3)]octreotate and [(177)Lu-DOTA(0),Tyr(3)]octreotide: which peptide is preferable for PRRT? Eur J Nucl Med Mol Imaging 33**:** 1346-1351.

Ezziddin S, Meyer C, Kahancova S, Haslerud T, Willinek W, Wilhelm K, et al. (2012). 90Y Radioembolization after radiation exposure from peptide receptor radionuclide therapy. J Nucl Med 53: 1663-1669.

Ezziddin S, Reichmann K, Yong-Hing C, Damm M, Risse J, Ahmadzadehfar H, Logvinski T, Guhlke S, Biersack HJ, Sabet A (2013). Early prediction of tumour response to PRRT. The sequential change of tumour-absorbed doses during treatment with 177Lu-octreotate. Nuklearmedizin, 52: 170-177.

Ezziddin S, Attassi M, Yong-Hing CJ, Ahmadzadehfar H, Willinek W, Grünwald F, Guhlke S, Biersack HJ, Sabet A (2014a). Predictors of long-term outcome in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with 177Lu-octreotate. J Nucl Med, 55: 183-190.

Ezziddin S, Khalaf F, Vanezi M, Haslerud T, Mayer K, Al Zreiqat A, Willinek W, Biersack HJ, Sabet A (2014b). Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging, 41: 925-933.

Fontana J, Mad'a P, Ivák P, Lavríková P, Nováková L, Pavelka M, Sajadiková M, Smída J, Blanková B, Petr V, Balínová B, Dyba J, Kroupa J, Mezera V, Kyselica M, Polách J, Pavlí nková , Dusíková K (2017 Aug 3). 12 Metabolism of Amino Acids chapter in Functions of Cells and Human Body online textbook. http://fblt.cz/en/skripta/ii-premena-latek-a-energie-v-bunce/12-metabolismus-aminokyselin/.

Gabriel M, Andergassen U, Putzer D, Kroiss A, Waitz D, Von Guggenberg E*, et al.* (2010). Individualized peptide-related-radionuclide-therapy concept using different radiolabelled somatostatin analogs in advanced cancer patients. Q J Nucl Med Mol Imaging 54**:** 92-99

Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, Otter R, Licitra L, Mallone S, Tavilla A, Trama A, Capocaccia R, (2011). Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer 47(17):2493-2511

Giovacchini G, Nicolas G, Freidank H, Mindt TL, Forrer F (2011). Effect of amino acid infusion on potassium serum levels in neuroendocrine tumour patients treated with targeted radiopeptide therapy. Eur J Nucl Med Mol Imaging, 38: 1675-1682.

Glasscock RJ, Winearls C (2009). Ageing and the glomerular filtration rate: truths and consequences. Trans Am Clin Climatol Assoc, 120: 419-428.

Gupta SK, Singla S, Thakral P, Bal C (2013). Dosimetric analyses of kidneys, liver, spleen, pituitary gland, and neuroendocrine tumors of patients treated with 177Lu-DOTATATE. Clin Nucl Med, 38: 188-194.

Gupta SK, Singla S, Bal C (2012). Renal and hematological toxicity in patients of neuroendocrine tumors after peptide receptorradionuclide therapy with 177Lu-DOTATATE. Cancer Biother Radiopharm, 27(9): 593-599.

Hammond PJ, Wade AF, Gwilliam ME, Peters AM, Myers MJ, Gilbey SG, Bloom SR, Calam J (1993). Amino acid infusion blocks renal tubular uptake of an indium-labelled somatostatin analogue. Br. J. Cancer, 67: 1437-1439.

Hicks RJ, Kwekkeboom DJ, Krenning E, Bodei L, Grozinsky-Glasberg S, Arnold R, Borbath I, Cwikla J, Toumpanakis C, Kaltsas G, Davies P, Hörsch D, Tiensuu Janson E, Ramage J, Antibes Consensus Conference participants (2017). ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. Neuroendocrinology; 105(3):295-309

Hubble D, Kong G, Michael M, Johnson V, Ramdave S, Hicks RJ (2010). 177Lu-octreotate, alone or with radiosensitising chemotherapy, is safe in neuroendocrine tumour patients previously treated with high-activity 111In-octreotide. Eur J Nucl Med Mol Imaging, 37: 1869-1875.

Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, Mäcke HR, Rochlitz C, Müeller-Brand J, Walter MA (2011). Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol, 29: 2416-2423.

Irving CS, Thomas MR, Malphus EW, Marks L, Wong WW, Boutton TW, Klein PD (1986). Lysine and protein metabolism in young women: subdivision based on the novel use of multiple stable isotopic labels. J Clin. Invest, 77: 1321-1331.

Jamar F, Barone R, Mathieu I, Walrand S, Labar D, Carlier P, de Camps J, Schran H, Chen T, Smith MC, Bouterfa H, Valkema R, Krenning EP, Kvols LK, Pauwels S (2003). 86Y-DOTA0-D-Phe1-Tyr3-octreotide (SMT487)-a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. Eur J Nucl Med Mol Imaging, 30: 510-518.

Kashyap R, Jackson P, Hofman MS, Eu P, Beauregard JM, Zannino D, Hicks RJ (2013). Rapid blood clearance and lack of long-term renal toxicity of 177Lu-DOTATATE enables shortening of renoprotective amino acid infusion. Eur J Nucl Med Mol Imaging, 40(12): 1853-60.

Kong G, Thompson M, Collins M, Herschatal A, Hofman MS, Johnston V, Eu P, Michael M, Hicks RJ (2014). Assessment of predictors of response and long-term survival of patients with neuroendocrine tumour treated with peptide receptor chemoradionuclide therapy (PRCRT). Eur J Nucl Med Mol Imaging, 41: 1831-1844.

Konijnenberg M, Melis M, Valkema R, Krenning E, de Jong M (2007). Radiation dose distribution in human kidneys by octreotides in peptide receptor radionuclide therapy. J Nucl Med, 48: 134-142.

Kreissl MC, Hänscheid H, Lohr M, Verburg FA, Schiller M, Lassmann M*, et al.* (2012). Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of

advanced symptomatic meningioma. Radiat Oncol 7**:** 99.

Kwekkeboom DJ, Bakker WH, Kooij PP, Konijnenberg MW, Srinivasan A, Erion JL, Schmidt MA, Bugaj JL, de Jong M, Krenning EP (2001). [177Lu-DOTA0,Tyr3]octreotate: comparison with [111In-DTPA0]octreotide in patients. Eur J Nucl Med, 28: 1319-1325.

Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, Feelders RA, van Aken MO, Krenning EP (2008). Treatment with the radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3] octreotate: toxicity, efficacy, and survival. J Clin Oncol, 26: 2124-2130.

Lapa C, Werner R, Bluemel C, Lückerath K, Schirbel A, Strate A, Buck AK, Herrmann K (2014a). Influence of the amount of co-infused amino acids on post-therapeutic potassium levels in peptide receptor radionuclide therapy. EJNMMI Research, 4:46

Lapa C, Werner R, Bluemel C, Lückerath K, Muegge DO, Strate A, Haenscheid A, Allen-Auerbach MS, Bundschuh RA, Buck AK, Herrman K (2014b). Prediction of clinically relevant hyperkalemia in patients treated with peptide receptor radionuclide therapy. EJNMMI Research, 4:74

Larsson M, Bernhardt P, Svensson JB, Wängberg B, Ahlman H, Forssell-Aronsson E (2012). Estimation of absorbed dose to the kidneys in patients after treatment with 177Lu-octreotate: comparison between methods based on planar scintigraphy. EJNMMI Research, 2:49.

Ljunberg M, Gleisner KS (2015). Hybrid imaging for patient-specific dosimetry in radionuclide therapy. Diagnostics (Basel), 5(3): 296-317.

Lutathera EU SmPC. Retrieved from https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf

Magnander T, Svensson J, Bath M, Gjertsson P, & Bernhardt P (2016). Improved Planar Kidney Activity Concentration Estimate by the Posterior View Method in 177lu-Dotatate Treatments. Radiat Prot Dosimetry 169**:** 259-266

Melis M, Krenning EP, Bernard BF, Barone R, Visser TJ, de Jong M (2005). Localisation and mechanism of renal retention of radiolabeled somatostatin analogues. Eur J Nucl Med Mol Imaging 32: 1136-1143.

Mogensen CE, SØlling K (1977). Studies on renal tubular protein reabsorption: partial and near complete inhibition by certain amino acids. Scand J Clin Lab Invest, 37: 477-486.

Moll S, Nickeleit V, Mueller-Brand J, Brunner FP, Maecke HR, Mihatsch MJ (2001). A New Cause of Renal Thrombotic Microangiopathy: Yttrium 90-DOTATOC Internal Radiotherapy. American Journal of Kidney Diseases, 37, No 4: 847-851

Morris SM (2007). Arginine metabolism: boundaries of our knowledge. J Nutr, 137: 1602S-1609S.

Otte A, Herrmann R, Heppeler A, Behe M, Jermann E, Powell P, Maecke HR, Muller J (1999). Yttrium-90 DOTATOC: first clinical results. Eur J Nucl Med, 26: 1439-1447.

Perico N, Codreanu I, Schieppati A, Remuzzi G (2005). Pathophysiology of disease progression in proteinuric nephropathies. Kidney Int, 67 (S94): S79-S82.

Pfob CH, Eiber M, Lupa P, Maurer F, Maurer T, Tauber R, D'Alessandria C, Feurecker B, Scheidhauer K, Ott A, Heemann U, Schwaiger M and Schmaderer C (2018). Hyperkalemia in patients treated with endoradiotherapy combined with amino acid infusion is associated with severe metabolic acidosis. EJNMMI Research 8: 17.

Rolleman EJ, Valkema R, de Jong M, Kooij PP, Krenning EP (2003). Safe and effective inhibition of renal uptake of radiolabeled octreotide by a combination of lysine and arginine. Eur J Nucl Med, 30:9-15.

Sabet A, Ezziddin K, Pape UF, Reichman K, Haslerud T, Ahmadzadehfar H, Biersack HJ, Nagarajah J, Ezziddin S (2014a). Accurate assessment of long-term nephrotoxicity after peptide receptor radionuclide therapy with 177Lu-octreotate. Eur J Nucl Med Mol Imaging, 41: 505-510.

Sabet A, Haslerud T, Pape UF, Sabet A, Ahmadzadehfar H, Grünwald F, Guhlke S, Biersack HJ, Ezziddin (2014b). Outcome and toxicity of salvage therapy with 177Lu-octreotate in patients with metastatic gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging, 41: 205-210.

Sabet A, Dautzenberg K, Haslerud T, Aouf A, Sabet A, Simon B, Mayer K, Biersack HJ, Ezziddin S (2015). Specific efficacy of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced neuroendocrine tumours of the small intestine. Eur J Nucl Med Mol Imaging, 42: 1238-1246.

Sainz-Esteban A, Prasad V, Schuchardt C, Zachert C, Carril JM, & Baum RP (2012). Comparison of sequential planar 177Lu-DOTA-TATE dosimetry scans with 68Ga-DOTA-TATE PET/CT images in patients with metastasized neuroendocrine tumours undergoing peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging 39**:** 501-511.

Sansovini M, Severi S, Ambosetti A, Monti M, Nanni O, Sarnelli A, Bodei L, Garaboldi L, Bartolomei M, Paganelli G (2013). Treatment with the radiolabeled somatostatin analog 177Lu-DOTATATE for advanced pancreatic neuroendocrine tumors. Neuroendocrinology, 97(4): 347-354.

Silbernagl S (1988). The renal handling of amino acids and oligopeptides. Physiol rev, 68(3): 911-1007.

Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, Mittra E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O'Dorisio TM, Baum RP, Kulkarni HR, Caplin M, Legtahi R, Hobday T, Delpassand E, Van Cutsem E, Benson A, Srirajaskanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregni E, Öberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruszniewski P, Kwekkeboom D, Krenning E (2017a). Phase 3 Trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med, 376: 125-35.

Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, Mittra E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O'Dorisio TM, Baum RP, Kulkarni HR, Caplin M, Legtahi R, Hobday T, Delpassand E, Van Cutsem E, Benson A, Srirajaskanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregni E, Öberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruszniewski P, Kwekkeboom D, Krenning E (2017b). Supplementary Appendix. N Engl J Med, http://www.nejm.org/action/showSupplements?doi=10.1056%2FNEJMoa1607427&viewType=Popup&viewClass=Suppl. Last accessed Sept 17, 2017.

Svensson J, Berg G, Wängberg B, Larsson M, Forssell-Aronsson E, Bernhardt P (2015). Renal function affects absorbed dose to the kidneys and haematological toxicity during 177Lu-DOTATATE treatment. Eur J Nucl Med Mol Imaging, 42(6): 947-955.

Tangphao O, Grossmann M, Chalon S, Hoffman BB, Blaschke TF (1999). Pharmacokinetics of intravenous and oral L-arginine in normal volunteers. Br J Clin Pharmacol, 47(3): 261-266.

Valkema R, Pauwels SA, Kvols LK, Kwekkeboom DJ, Jamar F, de Jong M, Barone R, Walrand S, Kooij PPM, Bakker WH, Lasher J, Krenning EP (2005). Long-term follow-up of renal function after peptide receptor radiation therapy with 90Y-DOTA0,Tyr3-octreotide and 177Lu-DOTA0,Tyr3-octreotate. J Nucl Med, 46: 83S-91S.

Vamin 18 Summary of Product Characteristics (2016). Fresenius Kabi Limited, Runcorn, Cheshire.

Van Vliet EI, Hermans JJ, de Ridder MA, Teunissen JJ, Kam BL, de Krijger RR, et al. (2012). Tumor response assessment to treatment with [177Lu-DOTA0,Tyr3]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors: differential response of bone versus soft-tissue lesions. J Nucl Med 53: 1359-1366.

Van Vliet EI, Krenning EP, Teunissen JJ, Bergsma H, Kam BL, & Kwekkeboom DJ (2013). Comparison of response evaluation in patients with gastroenteropancreatic and thoracic neuroendocrine tumors after treatment with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med 54: 1689-1696.

Van Vliet EI, van Eijck CH, de Krijger RR, Nieveen van Dijkum EJ, Teunissen JJ, Kam BL, et al. (2015). Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [177Lu-DOTA0,Tyr3]Octreotate. J Nucl Med 56: 1647-1653.

Vegt E, Melis M, Eek A, de Visser M, Brom M, Oyen WJG, Gotthardt M, de Jong M, Boerman OC (2011). Renal uptake of different radiolabeled peptides is mediated by megalin: SPECT and biodistribution studies in megalin-deficient mice. Eur J Nucl Med Mol Imaging, 38: 623-632.

Wehrmann C, Senftleben S, Zachert C, Muller D, & Baum RP (2007). Results of individual patient dosimetry in peptide receptor radionuclide therapy with 177Lu DOTA-TATE and 177Lu DOTA-NOC. Cancer Biotherapy & Radiopharmaceuticals 22**:** 406-416

Wessels BW, Konijnenberg MW, Dale RG, Breitz HB, Cremonesi M, Meredith RF, Green AJ, Bouchet LG, Brill AB, Bolch WE, Sgouros G, Thomas SR (2008). MIRD pamphlet No. 20: the effect of model assumptions on kidney dosimetry and response—implications for radionuclide therapy. J Nucl Med, 49(11): 1884-99.

Zaknun JJ, Bodei L, Mueller-Brand J, Pavel ME, Baum RP, Hörsch D, O'Dorisio MS, O'Dorisiol TM, Howe JR, Cremonesi M, Kwekkeboom DJ (2013). The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging, 800-816.