LuNET-SRY solution for infusion
Lutetium [^{177}Lu]oxodotreotide 7,400 MBq/vial

1. NAME OF THE MEDICINAL PRODUCT

LuNET-SRY, 7400 MBq solution for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains ~600 MBq of lutetium-177-labeled oxodotreotide (synonym: [^{177}Lu]DOTA-TATE), as chloride salt, at the designated activity reference time (ART) (i.e., day and time of infusion).
The total amount of radioactivity per single dose vial is 7,400 MBq ± 10% (180 - 220 mCi) at the ART. To attain a constant infusion dose of 7400 MBq at the ART and considering the physical half-life of lutetium-177 (~6.7 days), the volumetric activity of the drug product at the time of release can range between 528 – 1009 MBq/mL (14.3 and 27.3 mCi/mL). This range of activity strengths at the time of quality control enables injection of a fixed dose of LuNET-SRY at the ART, which typically occurs within 20-50 h after its production.

The approximate half-life of lutetium-177 is 6.7 days. It decays to hafnium-177 by emitting a beta-minus (β^-) particle. Its most abundant (79%) β^- has a maximum energy of 498 keV. Its typically emitted gamma-rays have energies of 113 keV (6.4%) and 208 keV (11%).
LuNET SRY uses *high-specific activity* (i.e., no carrier-added (n.c.a)) lutetium-177, which is obtained from ytterbium-176 via two consecutive decay processes: ^{176}Yb (n, γ) ^{177}Yb (β^-) ^{177}Lu. The typical specific activity of the lutetium-177 obtained in this process is >3000 GBq/mg (or 850 GBq/µmol).

Excipient with known effect

Each mL of solution contains not more than 4.4 mg of sodium and 14 mg of ascorbic acid.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for intravenous infusion.
Clear, colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults.

4.2 Posology and method of administration

LuNET-SRY should be administered only by persons authorized to handle radiopharmaceuticals in designated clinical settings (see section 6.6) and after evaluation of the patient by a qualified physician.

Before starting treatment with LuNET-SRY, overexpression of somatostatin receptor in the tumor tissuemust be confirmed by medical imaging, such as positron-emission tomography (PET), wherein tumor uptake is higher than that of the normal liver parenchyma.

Posology

Adults

The recommended treatment regimen of LuNET-SRY in adults consists of 4 infusions of 7,400 MBq each. The recommended interval between each administration is 8 weeks, which could be extended up to 16 weeks in case of dose modifying toxicity (DMT).

Information on dose modifications to manage severe or intolerable adverse drug reactions is provided further under this section.

For renal protection purpose, an amino acid solution must be administered by i.v. infusion during 4 hours. The infusion of the amino acid solution should start 30 min prior to the start of LuNET-SRY infusion. To alleviate the nauseous effect of the amino acid infusion, premedication with antiemetics should be started at least 30 min prior to the start of amino acid infusion, according to the respective product information.

Amino acid solution
The amino acid solution can be prepared as a compounded product, in compliance with the hospital's sterile medicinal product preparation good practices and according to the composition specified in Table 1.

Table 1. Composition of the compounded amino acid solution

Compound	**Amount**
L-lysine HCl	25 g*
L-arginine HCl	25 g**
Sodium chloride 9 mg/mL (0.9%) solution (saline) for injection or water for injection	1 L
*Equivalent to 20.0 g lysine; ** Equivalent to 20.7 g arginine	

Some commercially available amino acid solutions containing a minimum 25 g lysine and 25 g arginine can also be used.

Treatment monitoring

Prior to each administration and between the treatments, adequate tests should be performed to assess the patient's condition and treatment toxicity and adapt the therapeutic protocol if necessary (administered dose, infusion interval and/or the total number of infusions).
The minimum laboratory tests needed before each infusion include:

- Hematology (hemoglobin (Hb), white blood cell count and platelet count).
- Kidney function (serum creatinine and creatinine clearance).
- Liver function (alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin andbilirubin).

These tests should be performed at least once within 2 to 4 weeks prior to administration, and shortly before the administration. It is also recommended to perform these tests every 4 weeks for at least 3 months after the last infusion of LuNET-SRY and every 6 months thereafter, to be able to detect possible delayed adverse reactions (see section 4.8). Dosing should be adjusted based on the test results.

Dose modification

Management of severe or intolerable adverse drug reactions may require temporary dose interruption,extending dosing interval from 8 weeks up to 16 weeks, dose reduction, or discontinuation of treatment with LuNET-SRY (see below). In case of major surgery, treatment should be withheld for 12 weeks after the date of surgery.

Proposed dose adjustments of LuNET-SRY in cases of adverse drug reactions (ADRs)

Thrombocytopenia

In case of grade 2 or higher thrombocytopenia (platelet count <75,000/mL), withhold dose until complete or partial resolution (grade 0 - 1). Subsequently, resume [^{177}Lu]DOTA-TATE at 3,700 MBq (100 mCi). If no grade 2 - 4 thrombocytopenia occurs after the reduced dose, administer LuNET-SRY at 7,400 MBq (200 mCi) in the subsequent dose.

Treatment with LuNET-SRY should be permanently discontinued:

- In grade 2 thrombocytopenia or higher requiring a treatment delay of 16 weeks or longer.
- In recurrent grade 2-4 thrombocytopenia.

Anemia and neutropenia

In case of grade 2 or higher anemia (hemoglobin (Hb) <10 g/dL) or neutropenia (absolute neutrophil count (ANC) per mL <1500), withhold dose until complete or partial resolution (grade 0 - 1). Subsequently, resume [^{177}Lu]DOTA-TATE at 3,700 MBq (100 mCi). If no grade 3 - 4 anemia or neutropeina occurs after the reduced dose, administer LuNET-SRY at 7,400 MBq (200 mCi) in the subsequent dose.

LuNET-SRY should be permanently discontinued:

- In grade 3 - 4 anemia or neutropenia requiring a treatment delay of 16 weeks or longer.
- In recurrent grade 3 - 4 anemia or neutropenia.

Nephrotoxicity

In case of mild renal impairment (creatinine clearance (CrCL) <40 mL/min) or ≥40% increase in serum creatinine or ≥40% decrease in CrCL compared to baseline, withhold LuNET-SRY dose until complete resolution or return to baseline values. Subsequently, resume [^{177}Lu]DOTA-TATE at 3,700 MBq (100 mCi). If no renal toxicity occurs after the reduced dose, administer LuNET-SRY at 7,400 MBq (200 mCi) in the subsequent dose.

LuNET-SRY should be permanently discontinued:

- In case of nephrotoxicity requiring a treatment delay of 16 weeks or longer.
- In recurrent nephrotoxicity.

Hepatotoxicity

In case of grade 3 - 4 hyperbilirubinemia (total serum bilirubin >3.0× the upper limit of normal (ULN)), or hypoalbuminemia (serum albumin <30 g/L with a prothrombin ratio < 70%), withhold LuNET-SRY dose until complete resolution or return to baseline values. Subsequently, resume [^{177}Lu]DOTA-TATE at 3,700 MBq (100 mCi). If no hepatotoxicity occurs after the reduced dose, administer LuNET-SRY at 7,400 MBq (200 mCi) in the subsequent dose.

LuNET-SRY should be permanently discontinued:

- In case of hepatotoxicity requiring a treatment delay of 16 weeks or longer.
- In recurrent hepatotoxicity.

Any other ADR possibly related to LuNET-SRY

In case of grade 3 - 4 ADR, withhold dose until complete or partial resolution (grade 0 - 2). Subsequently, resume [^{177}Lu]DOTA-TATE at 3,700 MBq (100 mCi). If no grade 3 -4 toxicity occurs after the reduced dose, administer LuNET-SRY at 7,400 MBq (200 mCi) in the subsequent dose.

LuNET-SRY should be permanently discontinued:

- In case of grade 3 or higher ADR requiring a treatment delay of 16 weeks or longer.
- In recurrent grade 3 - 4 ADR.

Special populations

Elderly

No dosage adjustment is required in patients of 65 years-old or above. However, since increased risk of hematotoxicity has been associated with [^{177}Lu]DOTA-TATE treatment, close monitoring of this population is warranted.

Renal impairment

Since renal clearance is the major route of elimination of LuNET-SRY, the administered activity should be carefully considered in patients with impaired renal function, to avoid increased total body radiation exposure. The pharmacokinetic profile and safety of [^{177}Lu]DOTA-TATE in patients with severe renal impairment or end-stage renal disease have not been studied. LuNET-SRY treatment is contraindicated in severe kidney failure (CrCL <30 mL/min), and is not recommended in patients with CrCL <50 mL/min at baseline. No dose adjustment is recommended for renally impaired patients with CrCL ≥50 mL/min; however, renal function should be frequently monitored as these patients may be at a greater risk of nephrotoxicity.

Hepatic impairment

No studies have been reported on patients with hepatic impairment, therefore such patients should only be treated withLuNET-SRY after careful benefit-risk assessment. There might be increased risk for hepatotoxicity in patients with a high hepatic disease-burden. As a general recommendation, no dose adjustment is required for patients with mild or moderate hepatic impairment. For additional details about the treatment of patient with mild to moderate hepatic impairment, see sections 4.2 and 4.4.

Pediatric population

LuNET-SRY is not authorized for use in pediatric patients. The safety and efficacy of LuNET-SRY in pediatric patients have not been established yet.

Method of administration

Precautions to be taken before manipulating or administering the product

LuNET-SRY is a radioactive medicinal product and should be kept away from pregnant women. Its handling by pregnant healthcare professionals is forbidden.
Special precautions for handling of the medicinal product and its associated disposables are described in the following section, and should be done in accordance with the institutional radiation protection guidelines.

LuNET-SRY is a ready-to-use radioactive medicinal product for single use. It must be administered by slow intravenous infusion over approximately 30 min, concomitantly with the administration of a contralateral intravenous infusion of an amino acid solution. It is forbidden to inject this medicinal product as bolus. Premedication with antiemetics should be started at least 30 min prior to the start of amino acid infusion, according to the respective product information.
The recommended infusion method for administering LuNET-SRY is the gravity method described below. Throughout the entire process, the recommended radiation safety precaution measures should be undertaken (see section 6.6).

LuNET-SRY should be infused directly from its original container. The vial must not be opened nor the solution be transferred to another container, and only disposable materials should be used for handling it.
The medicinal product should be infused through an intravenous catheter placed in the vein exclusively for LuNET-SRY infusion.

Transport and storage of the vial

LuNET-SRY solution is supplied in a pre-sealed sterile 20 mL clear borosilicate glass bottle, stored inside two radioprotective containers:

1. An inner container made of poly(methyl methacrylate) (PMMA), which attenuates the emitted betta minus particles, and
2. An outer lead container, which attenuates the emitted gamma photons and x-rays. Prior to transport, the lead container is placed within a polyoxymethylene (POM) case stored within a shielded box.

Room and equipment preparation:

Administration room:

The floor and furniture should be covered with sufficient absorbent paper to avoid contamination. Dedicated waste bags indicated with a radioactive sign should be used for discarding all the disposables.

Care supplies and equipment:

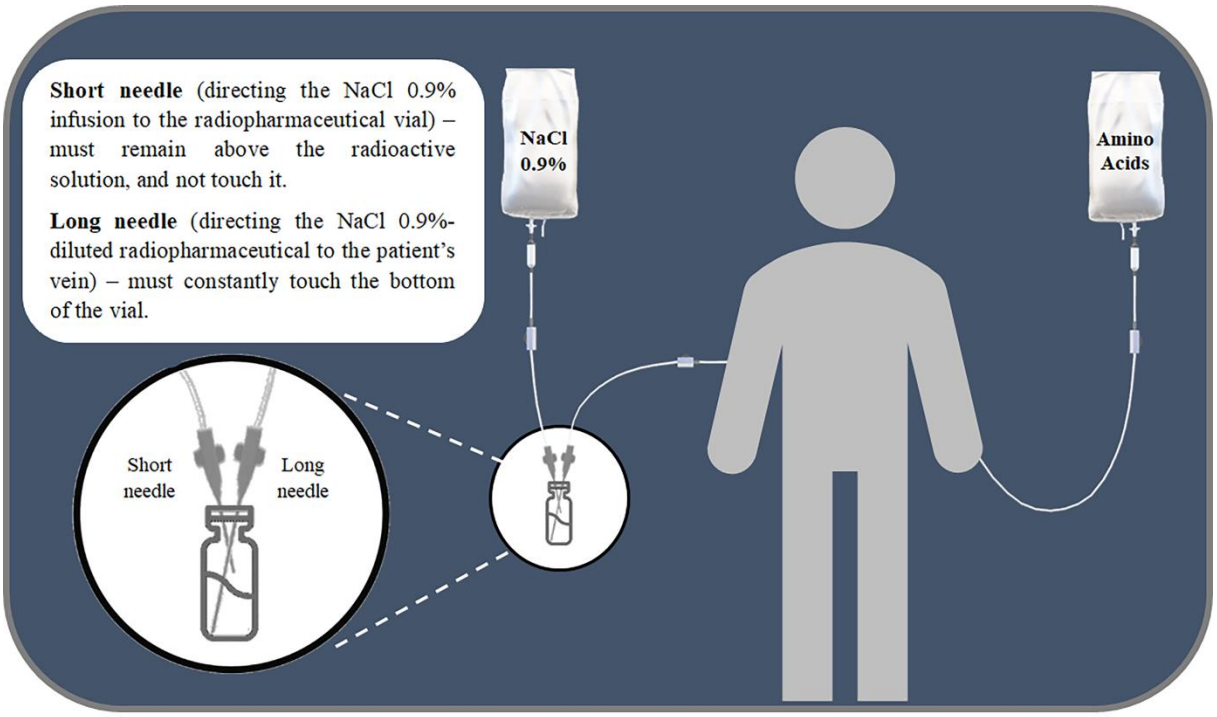
Two infusion poles (for LuNET-SRY and for the amino acid infusion)
Two gravity intravenous infusion sets with a clamp for regulating the flow
One Long needle (recommended 90 – 100 mm, 18 gauge)
One Short needle (recommended 25 mm, 20 gauge)
Two peripheral intravenous plastic catheters
One sterile tubing line with a clamp to regulate or stop the flow
A pair of long forceps for handling the vial of the radiopharmaceutical
A calibrated radioactivity measurement system and a dosimeter for monitoring radioactivity

Administration procedure (gravity method)

Throughout the infusion, the flow of saline solution for injection into the LuNET SRY vial increases the pressure inside the vial, facilitating the flow of the entirety of the drug product into the catheter inserted in the patient's peripheral vein.
Careful monitoring of vital signs during the infusion is recommended.

1. Two intravenous plastic catheters should be inserted into the patient's peripheral veins, one in each arm unless contraindicated. These catheters are eventually connected to two infusion sets: one for LuNET-SRY administration and one for infusing the amino acid solution.
2. Antiemetic premedication should be administered at least 30 min prior to the start of aminoacid solution infusion (see section 4.2).
3. The amino acid solution should be administered over 4 hours, beginning 30 min prior to LuNET-SRY infusion, and proceeding for an additional 3 hours after the cessation of LuNET-SRY infusion.
4. Before connecting the LuNET-SRY vial with the infusion system, measure its radioactive content using a calibrated radioactivity measurement system.
5. *LuNET-SRY vial tubing connection (Figure 1)*:
   - 5.1 The tubing line for administering the radiopharmaceutical should be pre-filled with sodium chloride 9 mg/mL (saline) solution for injection and then connected with the venous catheter previously inserted to the patient's arm.
   - 5.2 The infusion set should be connected to a bag of saline solution for injection and pre-filled by opening the clamp.
   - 5.3 The septum of the LuNET-SRY vial should be poked with the short needle. Care should be taken to position the needle *without touching the radioactive solution*. This step equilibrates the pressure between the vial content and the ambient pressure, and reduces the risk of leakage. Subsequently, the short needle should be connected to the pre-filled saline infusion set (described in step 5.2).
   - 5.4 The long needle should be connected to the pre-filled tubing line (described in step 5.1) and then inserted into the LuNET-SRY vial, so that it reaches the bottom of the vial, allowing complete transfer of the radiopharmaceutical solution.
6. It is advised to administer LuNET-SRY infusion over 30 ± 10 min, starting 30 min after the initiation of the amino acid infusion. The pressure within the LuNET-SRY vial should be maintained constant during the infusion. For recommendations in case of extravasation, refer to section 4.4.

Figure 1. LuNET-SRY and amino acid solution tubing connection scheme



7. LuNET-SRY administration should be initiated by opening first the tubing line connected to the patient's peripheral vein, followed by opening the infusion set connected to the bag of saline solution for injection. Refrain from moving the position of the patient's arm.
8. The flow of LuNET-SRY solution from the vial to the patient's vein should be monitored during the entire infusion. Soon after starting the infusion, the radioactivity emission over the patient's thorax should be measured using a dosimeter to confirm the presence of LuNET-SRY in the bloodstream.Subsequent 5-6 additional follow-up checks of radioactivity emission should be performed at the level of the patient's thorax and at the level of the vial during LuNET-SRY infusion. Throughout this time, the radioactivity emitted from the patient's thorax should steadily increase, with a concomitant decrease in the emitted activity from the LuNET-SRYvial.
9. To ensure administration of the entire drug product, the LuNET-SRY solution inside the vial should be kept under constant pressure. The level of solution in the vial should remain constant during the entire infusion time. Visual control of the solution level should be repeated during the infusion by direct visual inspection, using a pair of dedicated tongs to handle the vial.
10. The infusion should be stopped once the radioactivity emitted from the vial becomes stable for several min. The volume of saline solution for injection necessary to complete the infusion may vary between treatments.
11. The total administered activity equals the measured activity in the vial before infusion minus the remaining activity in the vial after the infusion. Measurements should be performed using the same calibrated system.

Table 2 summarizes the treatment-related procedures during a single administration of LuNET-SRY using the gravity method:

Table 2. Summary of antiemetic, amino acid and LuNET-SRY administration

Administered agent	Relative start time (min)	Duration
Antiemetic	At least 30 min prior to the amino acid solution	As per prescribing information
Amino acid solution	0	4 hours
LuNET-SRY infusion	30	30 ± 10 min

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6).
- Kidney failure with creatinine clearance <30 mL/min.

4.4 Special warnings and precautions for use

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.
Given the mechanism of action and the tolerance profile of LuNET-SRY, it is not recommended to start treatment with LuNET-SRY in patients with somatostatin receptor-negative or mixed visceral lesions according to somatostatin receptor imaging.

Myelosuppression

Because of the potential for undesirable effects, blood counts must be monitored at baseline and during treatment and until resolution of any eventual toxicity (see section 4.2). Patients with impaired hematological function and patients who have received prior chemotherapy or external beam radiotherapy (involving more than 25% of the bone marrow) may be at higher risk of hematological toxicity during LuNET-SRY treatment. Treatment initiation is not recommended in patients with severely impaired hematological function at baseline (e.g. Hb <4.9 mmol/L or 8 g/dL, platelets <75 g/L or 75 × 10^3/mm^3, or leukocytes <2 g/L or 2000/mm^3) (except lymphopenia).

Myelodysplastic syndrome and acute leukaemia

Late-onset myelodysplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with [^{177}Lu]DOTA-TATE (see section 4.8), occurring approximately 29 months (9–45) for MDS and 55 months (32-125) for AL after the first [^{177}Lu]DOTA-TATE infusion. The etiology of these therapy-related secondary myeloid neoplasms (t-MNs) is unclear. Factors such as age >70 years, impaired renal function, baseline cytopenias, prior number of therapies, prior exposure to chemotherapeutic agents (specifically alkylating agents), and prior radiotherapy are suggested as potential risks and/or predictive factors for MDS/AL.

Renal toxicity

Because [^{177}Lu]DOTA-TATE is almost exclusively eliminated through the renal system, it is mandatory to concomitantly administer an amino acid solution containing the amino acids L-lysine and L-arginine. The amino acid solution will help to decrease reabsorption of [^{177}Lu]DOTA-TATE through the proximal tubules, resulting in a significant reduction in the kidney radiation dose (see section 4.2). When the recommended concomitant amino acid solution infusion is delivered over a 4-hour time span, a mean reduction in kidney radiation exposure of about 47% has been reported.
It is not recommended to decrease the amount of amino acid solution in case of LuNET-SRY dose adjustment.

Patients should be encouraged to empty their bladder as frequently as possible during the administration of amino acid solution and in the hours after administration.
Renal function as determined by serum creatinine and calculated creatinine clearance must be assessed at baseline, during and for at least the first year after treatment (see section 4.2).
Patients with renal impairment at baseline, or with renal or urinary tract morphological abnormalities, may be at greater risk of toxicity. Treatment with LuNET-SRY in patients with creatinine clearance <40 mL/min (using Cockcroft-Gault) at baseline is not recommended. More frequent monitoring of renal function is recommended in renally impaired patients with creatinine clearance ≥40 mL/min (see section 4.2).
For patients with creatinine clearance <50 mL/min, an increased risk for transient hyperkalemia due to the amino acid solution should also be taken into consideration (see Warning and precaution regarding the co-administered renal protective amino acid solution).

Hepatic toxicity

Since many patients referred for LuNET-SRY therapy have hepatic metastasis, it may be common to observe patients with altered baseline liver function. Patients with hepatic metastasis or pre-existing advanced hepatic impairment may be at increased risk of hepatotoxicity due to radiation exposure. Therefore, it is recommended to monitor ALT, AST, bilirubin and serum albumin during treatment (see section 4.2).
Patients with baseline liver impairment with either total bilirubin >3 times the upper limit of normal or albuminemia <30 g/L and INR >1.5, should only be treated with LuNET-SRY after careful benefit-risk assessment (see section 4.2).

Hypersensitivity

Cases of hypersensitivity reactions (including isolated angioedema events) have been reported in the post-marketing setting in patients treated with [^{177}Lu]DOTA-TATE (see section 4.8). In the event of serious hypersensitivity reactions, treatment with LuNET-SRY should be discontinued immediately. Appropriate medicinal products and equipment to manage such reactions should be available for immediate use.

Nausea and vomiting

To avoid treatment-related nausea and vomiting, an intravenous bolus of an antiemetic medicinal product should be injected at least 30 minutes prior to the start of amino acid solution infusion to reach the full antiemetic efficacy (see section 4.2).

Concomitant use of somatostatin analogues

Somatostatin and its analogues competitively bind to somatostatin receptors and may interfere with the efficacy of LuNET-SRY (see section 4.5).

Neuroendocrine hormonal crises

Crises due to excessive release of hormones or bioactive substances may occur following treatment with LuNET-SRY, therefore observation of patients by overnight hospitalization should be considered in some cases (e.g. patients with poor pharmacological control of symptoms). In case of hormonal crises, recommended treatments are: intravenous high-dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhea and/or vomiting.

Tumor lysis syndrome

Tumor lysis syndrome has been reported following therapy with medicines containing lutetium-177. Patients with a history of renal insufficiency and high tumor burden may be at greater risk and should be treated with increased caution. Renal function and electrolyte balance should be assessed at baseline and during treatment.

Radioprotection rules

LuNET-SRY should always be infused through an intravenous catheter placed exclusively for its infusion. The correct positioning of the catheter should be checked before and during infusion.

Patients under treatment with LuNET-SRY should be kept away from others during administration and until the

radiation emission limits stipulated by the applicable laws are reached, usually within the 4-5 hours following medicinal product administration. The nuclear medicine physician should determine when the patient can leave the controlled area of the hospital, i.e. when the radiation exposure to third parties does not exceed regulatory thresholds.

Patients should be encouraged to urinate as much as possible after LuNET-SRY administration. They should be instructed to drink substantial quantities of water (1 glass every hour) on the day of infusion and the day after to facilitate elimination. They should also be encouraged to defecate every day and to use a laxative if needed. Urine and feces should be disposed of according to the national regulations.

Provided the patient's skin is not contaminated, such as from the leakage of the infusion system or because of urinary incontinence, radioactivity contamination is not expected on the skin and in the vomited mass. However, it is recommended that when conducting standard care or examinations with medical devices or other instruments which come into contact with the skin (e.g. electrocardiogram (ECG)), basic protection measures should be observed such as wearing gloves, installing the material/electrode before the start of radiopharmaceutical infusion, changing the material/electrode after measurement, and eventually monitoring the radioactivity of equipment after use.

Before the patient is released, the nuclear medicine physician should explain the necessary radioprotection rules for interacting with other members of the same household and the general public, and the general precautions the patient must follow during daily activities after treatment (as given in the next paragraph and the package leaflet) to minimize radiation exposure to others.

Close contact (less than 1 meter) with other people should be limited for 7 days following each administration of LuNET-SRY. For children and/or pregnant women, close contact (less than 1 meter) should be limited to less than 15 minutes per day for 7 days. Patients should sleep in a separate bedroom from other people for 7 days following each administration of LuNET-SRY. Patients should sleep in a separate bedroom from children and/or pregnant women for 15 days.

<u>Recommended measures in case of extravasation</u>

Disposable waterproof gloves should be worn. The infusion of the medicinal product must be immediately ceased and the administration device (catheter, etc.) removed. The nuclear medicine physician and the radiopharmacist should be informed.
All the administration device materials should be kept in order to measure the residual radioactivity and the activity actually administered and the absorbed dose should be determined. The extravasation area should be delimited with an indelible pen and a picture should be taken if possible. It is also recommended to record the time of extravasation and the estimated volume extravasated.
To continue LuNET-SRY infusion, it is mandatory to use a new catheter, possibly placing it in a contralateral venous access.

No additional medicinal product can be administered to the same side where the extravasation occurred.
In order to accelerate medicinal product dispersion and to prevent its stagnation in tissue, it is recommended to increase blood flow by elevating the affected arm. Depending on the case, aspiration of extravasation fluid, flush injection of sodium chloride 9 mg/mL (0.9%) solution for injection, or application of warm compresses or a heating pad to the infusion site to accelerate vasodilation should be considered.

Symptoms, especially inflammation and/or pain, should be treated. Depending on the situation, the nuclear medicine physician should inform the patient about the risks linked to extravasation injury, and give advice about potential treatment and necessary follow-up requirements. The extravasation area must be monitored until the patient is discharged from the hospital. Depending on its severity, this event should be declared as an adverse reaction.

Patients with urinary incontinence

During the first 2 days following administration of this medicinal product, special precautions should be taken with patients with urinary incontinence to avoid spread of radioactive contamination. This includes the handling of any materials possibly contaminated with urine.

Patients with brain metastases

There are no efficacy data in patients with known brain metastases, therefore individual benefit-risk must be assessed in these patients.

Secondary malignant neoplasms

Exposure to ionizing radiation is linked with cancer induction and a potential for development of hereditary defects. The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation exposure are less than from the disease itself.

Other patients with risk factors

Patients presenting with any of the conditions below are more prone to develop adverse reactions. Therefore, it is recommended to monitor such patients more frequently during the treatment. Please see section 4.2 in case of dose modifying toxicity.

- Bone metastasis;
- Previous oncological radiometabolic therapies with ^{131}I compounds or any other therapy using unshielded radioactive sources;
- History of other malignant tumors unless the patient is considered to have been in remission for at least 5 years.

Specific warnings

Sodium content
This medicinal product contains up to 2.7 mmol (55 mg) sodium per dose, equivalent to 2.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Precautions with respect to environmental hazard see section 6.6.

Specific warnings and precautions regarding the co-administered renal protective amino acid solution

Hyperkalemia
A transient increase in serum potassium levels may occur in patients receiving arginine and lysine, usually returning to normal levels within 24 hours from the start of the amino acid solution infusion. Serum potassium levels must be tested before each administration of amino acid solution. In case of hyperkalemia, the patient's history of hyperkalemia and concomitant medication should be checked. Hyperkalemia must be corrected accordingly before starting the infusion.
In case of pre-existing clinically significant hyperkalemia, a second monitoring prior to amino acid solution infusion must confirm that hyperkalemia has been successfully corrected. The patient should be monitored closely for signs and symptoms of hyperkalemia, e.g. dyspnea, weakness, numbness, chest pain and cardiac manifestations (conduction abnormalities and cardiac arrhythmias). An electrocardiogram (ECG) should be performed prior to discharging the patient.
Vital signs should be monitored during the infusion regardless of baseline serum potassium levels. Patients should be instructed to drink substantial quantities of water (at least 1 glass every hour) on the day of infusion to remain hydrated and facilitate excretion of excess serum potassium.
In case hyperkalemia symptoms develop during amino acid solution infusion, appropriate corrective measures must be taken. In case of severe symptomatic hyperkalemia, discontinuation of amino acid solution infusion should be considered, taking into consideration the risk-benefit of renal protection versus acute hyperkalemia.
Heart failure
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 (New York Heart Association) classification. Patients with severe heart failure defined as class III or class IV in the NYHA

classification should only be treated after careful benefit-risk assessment, taking into consideration the volume and osmolality of the amino acid solution.

Metabolic acidosis
Metabolic acidosis has been observed with complex amino acid solutions administered as part of total parenteral nutrition (TPN) protocols. Shifts in acid-base balance alter the balance of extracellular- intracellular potassium and the development of acidosis may be associated with rapid increases in plasma potassium.

4.5 Interaction with other medicinal products and other forms of interaction

Somatostatin and its analogues competitively bind to somatostatin receptors and may interfere with the efficacy of LuNET-SRY. Therefore, administration of long-acting somatostatin analogues should be avoided within 30 days prior to the administration of this medicinal product. If necessary, patients may be treated with short-acting somatostatin analogues up to 24 hours preceding LuNET-SRY administration.

There is some evidence that corticosteroids can induce down-regulation of SST2 receptors. Therefore, as a matter of cautiousness, repeated administration of high-doses of glucocorticoids should be avoided during LuNET-SRY treatment. Patients with a history of chronic use of glucocorticoids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known if there is of interaction between glucocorticoids used intermittently for the prevention of nausea and vomiting during LuNET-SRY administration. Therefore, glucocorticoids should be avoided as preventive anti-emetic treatment. In the case where the treatments previously provided for nausea and vomiting are insufficient, a single dose of corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of LuNET-SRY infusion.
The absence of inhibition or significant induction of the human CYP450 enzymes, and the absence of specific interaction with P-glycoprotein (efflux transporter) or OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and BCRP transporters in pre-clinical studies, suggest that [^{177}Lu]DOTA-TATE has a low probability of causing significant other drug-drug interactions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in any doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionizing radiation (if there are any) should be offered to the patient. Before the use of LuNET-SRY, pregnancy should be excluded using an adequate/validated test.

Contraception in males and females

LuNET-SRY can cause fetal harm when administered to a pregnant woman. During treatment with LuNET-SRY and for a minimum of 6 months after the end of the treatment, appropriate measures must be taken to avoid pregnancy; this applies to both male and female patients.

Pregnancy

No studies on animal reproductive function have been conducted with [^{177}Lu]oxodotreotide. Radionuclide procedures carried out on pregnant women also involve a radiation dose to the fetus. The use of LuNET-SRY is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded due to the risk associated with the ionizing radiation (see section 4.3). Pregnant women should be advised of the risk to a fetus.

Breast-feeding

It is unknown whether [^{177}Lu]DOTA-TATE is excreted in breast milk. A risk to the breast-fed child associated with ionizing radiation cannot be excluded. Breast-feeding should be avoided during treatment with this medicinal product. If treatment with LuNET-SRY during breast-feeding is necessary, the child must be weaned.

Fertility

No animal studies have been performed to determine the effects of [^{177}Lu]DOTA-TATE on male and female fertility. Ionizing radiation of [^{177}Lu]DOTA-TATE may potentially have temporary toxic effects on female and male gonads. Genetic consultation is recommended if the patient wishes to have children after treatment. Cryopreservation of sperm or eggs can be discussed as an option for patients before treatment.

4.7 Effects on ability to drive and use machines

LuNET-SRY has no or negligible influence on the ability to drive and use machines. Nevertheless, the general condition of the patient and the possible adverse reactions to treatment must be taken into account before driving or using machines.

4.8 Undesirable Effects

Summary of the safety profile

Adverse reactions reported following treatment with LuNET-SRY in a single medical center in Israel were mostly associated with mild and transient bone-marrow/hematologic toxicities, manifesting as reductions in blood counts affecting all lineages. Two additional cases of mild renal toxicity (as indicated by reduction in the estimated glomerular filtration rate (eGFR)) have also been reported. No information was available on the frequency of nausea, vomiting, fatigue or decreased appetite following treatment with LuNET-SRY.

The overall safety profile of [^{177}Lu]DOTA-TATE is based on pooled data from patients from clinical studies (NETTER-1 phase III and Erasmus phase I/II Dutch patients) and from compassionate use programs.

The most common adverse reactions in patients receiving [^{177}Lu]DOTA-TATE treatment were nausea and vomiting, which occurred at the beginning of the infusion in 58.9% and 45.5% of patients, respectively. The causality of nausea/vomiting is confounded by the emetic effect of the concomitant amino acid solution infusion administered for renal protection.

Due to the bone marrow toxicity of [^{177}Lu]DOTA-TATE, the most expected adverse reactions were related to hematological toxicity: thrombocytopenia (25%), lymphopenia (22.3%), anemia (13.4%) and pancytopenia (10.2%).

Other very common adverse reactions reported include fatigue (27.7%) and decreased appetite (13.4%).

At the time of the NETTER-1 final analysis, after a median follow-up duration of 76 months in each study arm, the safety profile remained consistent with that previously reported.

Tabulated list of adverse reactions

The adverse reactions are listed in Table 3 according to the frequency and the MedDRA System Organ Class (SOC). The frequencies are categorized as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 3. Frequency of adverse reactions reported from clinical studies and post-marketing surveillance

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Not known
Infections and infestations			Conjunctivitis Respiratory tract infection Cystitis Pneumonia Herpes zoster Ophthalmic herpes zoster Influenza Staphylococcal infections Streptococcal bacteremia	
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Refractory cytopenia with multilineage dysplasia (myelodysplastic syndrome)	Acute myeloid leukaemia Acute leukaemia Chronic myelomonocytic leukaemia	
Blood and lymphaticsystem disorders	Thrombocytopenia[2] Lymphopenia[3] Anemia[4] Pancytopenia	Leukopenia[5] Neutropenia[6]	Refractory cytopenia with unilineage dysplasia Nephrogenic anemia Bone marrow failure Thrombocytopenic purpura	
Immune system disorders			Hypersensitivity	Angioedema
Endocrine disorders		Secondary hypothyroidism	Hypothyroidism Diabetes mellitus Carcinoid crisis Hyperparathyroidism	
Metabolism and nutrition disorders	Decreased appetite	Hyperglycemia Dehydration Hypomagnesaemia Hyponatremia	Hypoglycemia Hypernatremia Hypophosphatemia Tumor lysis syndrome Hypercalcemia Hypocalcaemia Hypoalbuminemia Metabolic acidosis	
Psychiatric disorders		Sleep disorders	Anxiety Hallucination Disorientation	
Nervous system disorders		Dizziness Dysgeusia Headache[10] Lethargy Syncope	Formication Hepatic encephalopathy Paraesthesia Parosmia Somnolence Spinal cord compression	
Eye disorders			Eye disorders	
Ear and labyrinthdisorders			Vertigo	
Cardiac disorders		Electrocardiogram QT prolonged	Atrial fibrillation Palpitations Myocardial infarction Angina pectoris Cardiogenic shock	
Vascular disorders		Hypertension[7] Flushing Hot flush Hypotension	Vasodilatation Peripheral coldness Pallor Orthostatic hypotension Phlebitis	
Respiratory, thoracic and mediastinal disorders		Dyspnea	Oropharyngeal pain Pleural effusion Sputum increased Choking sensation	

Gastrointestinal disorders	Nausea Vomiting	Abdominal distension Diarrhea Abdominal pain Constipation Abdominal pain upper Dyspepsia Gastritis	Dry mouth Flatulence Ascites Gastrointestinal pain Stomatitis Haematochezia Abdominal discomfort Intestinal obstruction Colitis Pancreatitis acute Rectal hemorrhage Melena Abdominal pain lower Hematemesis Hemorrhagic ascites Ileus	
Hepatobiliary disorders		Hyperbilirubinaemia[9]	Pancreatic enzymes decreased Hepatocellular injury Cholestasis Hepatic congestion Hepatic failure	
Skin and subcutaneous tissue disorders		Alopecia	Rash Dry skin Swelling face Hyperhidrosis Pruritus generalized	
Musculoskeletal and connective tissue disorders		Musculoskeletal pain[8] Muscle spasms		
Renal and urinary disorders		Acute kidney injury Hematuria Renal failure Proteinuria	Leukocyturia Urinary incontinence Glomerular filtration rate decreased Renal disorder Acute pre-renal failure Renal impairment	
General disorders and administration site conditions	Fatigue[1]	Injection site reaction[11] Edema peripheral Administration site pain Chills Influenza like illness	Injection site mass Chest discomfort Chest pain Pyrexia Malaise Pain Death Feeling abnormal	
Investigations		Blood creatinine increased GGT* increased ALT** increased AST*** increased Blood ALP**** increased	Blood potassium decreased Blood urea increased Glycosylated hemoglobin increased Hematocrit decreased Protein urine Weight decreased Blood creatine phosphokinase increased Blood lactate dehydrogenase increased Blood catecholamines C-reactive protein increased	
Injury, poisoning and procedural complications			Clavicle fracture	
Surgical and medical procedures		Transfusion	Abdominal cavity drainage Dialysis Gastrointestinal tube insertion Stent placement Abscess drainage Bone marrow harvest Polypectomy	
Social circumstances			Physical disability	

[1] Includes asthenia and fatigue
[2] Includes thrombocytopenia and platelet count decreased
[3] Includes lymphopenia and lymphocyte count decreased
[4] Includes anemia and hemoglobin decreased
[5] Includes leukopenia and white blood cell count decreased
[6] Includes neutropenia and neutrophil count decreased
[7] Includes hypertension and hypertensive crisis
[8] Includes arthralgia, pain in extremity, back pain, bone pain, flank pain, musculoskeletal chest pain and neck pain
[9] Includes blood bilirubin increased and hyperbilirubinemia
[10] Includes headache and migraine
[11] Includes injection site reaction, injection site hypersensibility, injection site induration, injection site swelling

*Gamma-glutamyltransferase
**Alanine aminotransferase
***Aspartate aminotransferase

****Alkaline phosphatase

Description of selected adverse reactions

Bone marrow toxicity
Bone marrow toxicity (myelo-/haematotoxicity) manifested with reversible/transient reductions in blood counts affecting all lineages (cytopenias in all combinations, i.e. pancytopenia, bicytopenias, isolated monocytopenias – anemia, neutropenia, lymphocytopenia, and thrombocytopenia). In spite of an observed significant selective B-cell depletion, no increase in the rate of infectious complications occurs after peptide receptor radionuclide therapy (PRRT). Cases of irreversible hematological pathologies, i.e. premalignant and malignant blood neoplasms (i.e. myelodysplastic syndrome and acute myeloid leukemia, respectively) have been reported following [^{177}Lu]DOTA-TATE treatment.

Nephrotoxicity

Lutetium-177-labeled oxodotreotide is excreted by the kidneys.
The long-term trend of progressive glomerular filtration function deterioration demonstrated in the clinical studies confirms that [^{177}Lu]DOTA-TATE-related nephropathy is a chronic kidney disease that develops progressively over months or years after exposure. An individual benefit-risk assessment is recommended prior to treatment with LuNET-SRY in patients with mild or moderate renal impairment. For additional details see section 4.2 and section 4.4. The use of LuNET-SRY is contraindicated in patients with severe kidney failure (see section 4.3).

Hormonal crises
Hormonal crises related to release of bioactive substances (probably due to lysis of the neuroendocrine tumor cells) have rarely been observed and resolved after appropriate medical treatment (section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/, and to S.R.Y Medical Services Ltd. via email to: contact@sryms.com.

4.9 Overdose

Overdose is unlikely with LuNET-SRY as this medicinal product is supplied as a single-dose and ready-to-use product containing a predefined amount of radioactivity. In the event of overdose, an increase in the frequency of the adverse reactions related to radiotoxicity is expected.

In the event of administration of a radiation overdose with LuNET-SRY, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding during the first 48 hours after infusion. It might be helpful to estimate the effective dose that was applied.

The following laboratory tests should be carried out every week, for the next 10 weeks:
- Hematologic monitoring: white blood cells, platelets and hemoglobin
- Blood chemistry monitoring: serum creatinine and glycemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10XX04

Mechanism of action
Lutetium-177-labeled oxodotreotide ([^{177}Lu]DOTA-TATE) has a high affinity for subtype 2 somatostatin receptors (sst2). It binds to malignant cells which overexpress sst2 receptors.
Lutetium-177 is a β^- emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted tumor cells with a limited effect on neighboring normal cells.

Pharmacodynamic effects

At the concentration used (about 10 µg/mL in total, for both free and radiolabeled forms), the peptide oxodotreotide does not exert any clinically relevant pharmacodynamic effect.

Clinical efficacy and safety

LuNET-SRY has been produced in Israel for over four years, enabling treatment of several hundred patients with various NETs on compassionate grounds. Under these circumstances, non-clinical and clinical studies were not performed. Non-clinical and clinical studies evaluating the pharmacokinetic, pharmacodynamic, safety and efficacy characteristics of [^{177}Lu]DOTA-TATE have been reported and are public knowledge. A brief summary of these data is provided herein, followed by clinical information (progression-free survival (PFS), overall survival (OS) and dosimetry data) of patients treated with LuNET-SRY in a single medical center in Israel between May 2018 and Sept 2020.

- In a Phase-III multi-centric, active-controlled randomized clinical trial including GEP-NET patients, [^{177}Lu]DOTA-TATE (7,400 MBq every 8 weeks, four cycles) plus intramuscular long-acting octreotide 30 mg was compared to high dose octreotide LAR (60 mg every 4 weeks). The results of this study demonstrated increased median PFS of 28.4 months in the [^{177}Lu]DOTA-TATE treatment arm, with a hazard ratio (HR) of 0.18 (95% CI 0.11 - 0.29 p<0.0001). Following a median follow-up of 76.3 months, the median OS of the [^{177}Lu]DOTA-TATE treatment arm was higher by 11.7 months, albeit the difference in OS was not statistically significant. Furthermore, improved health related quality of life (HRQoL) was reported for [^{177}Lu]DOTA-TATE up to week 84 from randomization compared to octreotide LAR.
- In another monocentric phase I/II single-arm study, the efficacy of [^{177}Lu]DOTA-TATE (7,400 MBq every 8 weeks, four cycles) was assessed in patients with SSTR-positive bronchial/ pancreatic, foregut, midgut or hindgut tumors. In the full analysis set (FAS), which included 360 patients, the median PFS was 28.5 months (95% CI 24.8 - 31.4 months) and the reported median OS was 61.2 months (95% CI 54.8 - 67.4 months). The median PFS of a subgroup of patients (52%, n = 188) who received concomitant treatment with octreotide LAR was 25.4 months (95% CI 22.8 - 30.6) compared to a median PFS of 30.9 months (95% CI 25.6 - 34.8) in the subgroup of patients, who did not receive concomitant octreotide LAR treatment (p = 0.747).
- LuNET-SRY survival data and tumor responses were reviewed retrospectively after the treatments were given on compassionate grounds, in accordance to the literature and the published guidelines. Patient eligibility for LuNET-SRY treatment included the following: (1) high expression of SSTR in tumors as indicated by [^{68}Ga]DOTA-TATE PET/CT, wherein tumor uptake was greater than the background liver activity, (2) evidence of progressive disease in the past 12 months, as assessed by combination of increasing biochemical marker (chromogranin A), and new or enlarging lesions on SSTR PET/CT imaging, contrast-enhanced CT, or magnetic resonance imaging (MRI), or (3) persistence of symptoms despite conventional management. Treatment was excluded in case of: (i) low SSTR expression in tumor, (ii) renal impairment (CrCL <50 mL/min), (iii) hypoalbuminemia (<25 g/L), (iv) thrombocytopenia (<70 × 10^9/L), (v) pancytopaenia (hemoglobin <10 g/dL and white cell count <3 × 10^9/L), (vi) Eastern Cooperative Oncology Group (ECOG) performance status score of 4, (vii) expected survival of less than 3 months, or (viii) in case of confirmed pregnancy.

  Data of 70 patients (42 males) who received 212 LuNET-SRY treatments between May 2018 and Sept 2020 in a single medical center were available for the efficacy (PFS and OS) analyses (Table 4). Of these, 45 (64%) had GEP-NETs, whilst 25 (36%) had other NETs (including neuroblastoma, pheochromocytoma/ paraganglioma, and/or NET of unknown origin). The average age of patients was 62.1 ± 14.8 years, including three adolescents (12, 13, and 18 years old). The total number of treatments per patient ranged between 1 and 6 (Table 4), and the average time between treatments was 49 ± 19 days.

Table 4. Efficacy of LuNET-SRY in NET patients treated at a single medical center

Patient No.	No. of treatments	Average dose per treatment (MBq)	Response to treatment	PFS (months)	OS (months)
1	4	7262.9	SD	18.1	18.1
2	3	7396.3	LFU	-	-
3	1	7217.8	LFU	-	-
4	1	7015.1	PD	0.0	13.8
5	4	6959.6	SD	8.9	8.9

6	4	6974.2	LFU	-	-
7	4	7327.9	SD	3.0	3.0
8	3#	7949.7	PD	5.2	8.4
9	3	6996.1	PD	1.9	1.9
10	3#	7217.5	LFU	-	-
11	1#	6847.9	PD	3.5	3.5
12	4	7254.3	SD	2.8	2.8
13	4	7357.6	PD	7.5	7.5
14	2#	7297.1	SD	19.1	19.1
15	4#	7703.6	LFU	-	-
16	4	7291.3	PD	15.7	15.7
17	3	7514.8	LFU	-	-
18	4	7311.8	SD	9.1	9.1
19	4	7293.5	SD	3.2	3.2
20	1#	7309.7	PD	8.4	8.4
21	4	7434.7	SD	28.0	28.0
22	3	7333.0	SD	23.3	23.3
23	4	7479.1	SD	22.3	22.3
24	3	7073.9	SD	20.0	20.0
25	4	7461.1	SD	4.1	4.1
26	4	7180.4	SD	7.1	7.1
27	1	7511.6	PD	1.3	1.3
28	4#	7320.5	SD	11.8	11.8
29	2	7378.3	SD	18.8	21.8
30	5	7484.4	OT	-	0.0
31	2	3364.0	SD	0.0	0.0
32	4	7360.9	LFU	-	-
33	4#	7200.4	PR	4.4	4.4
34	5	7444.2	SD	20.2	20.2
35	3	7232.5	SD	11.5	11.5
36	1	7504.3	SD	7.8	7.8
37	3#	7579.9	PR	2.3	2.3
38	4	7337.9	SD	24.6	24.6
39	1	7602.5	SD	2.6	2.6
40	3	7495.8	LFU	-	-
41	1	7208.3	SD	9.5	10.5
42	1	6791.6	LFU	-	-
43	4 (3+1#)	7411.4	ST	2.8	8.3
44	3	7660.2	ST	3.4	6.9
45	2	7450.2	SD	28.9	28.9
46	1	7085.2	LFU	-	-
47	6#	7656.4	PD	6.1	12.6
48	4	7193.7	SD	15.5	15.5
49	3	7331.3	SD	26.1	26.1
50	2	7425.8	ST	10.1	10.1
51	4#	7486.8	LFU	-	-
52	1#	7573.5	ST	1.6	1.6
53	3	7363.7	SD	21.3	21.3

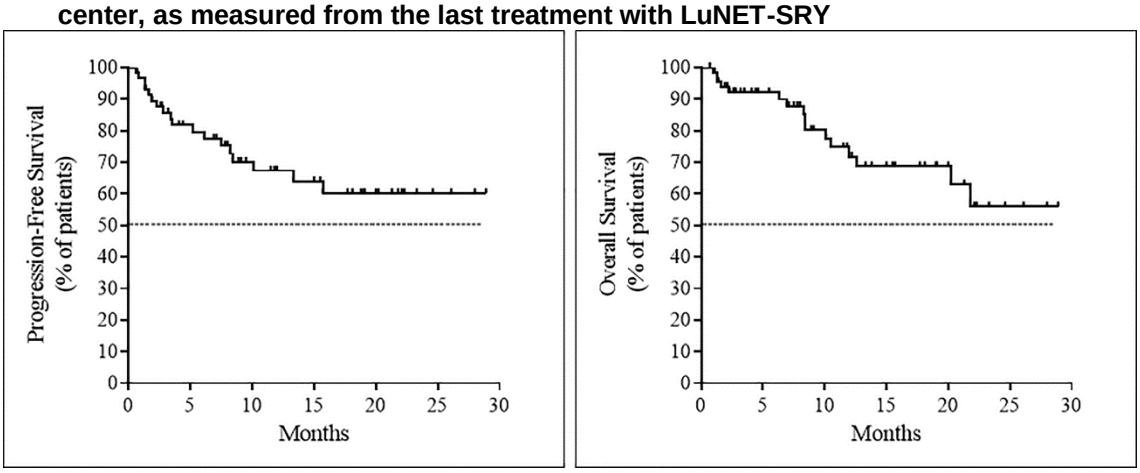
54	4	7227.3	SD	12.0	12.2
55	6	7528.6	SD	8.2	20.2
56	4	7324.6	SD	13.3	13.3
57	3	7307.8	SD	6.9	6.9
58	1	7209.2	LFU	-	-
59	4	7062.7	SD	22.1	22.1
60	3[#]	7345.8	SD	7.5	12.0
61	4	7493.8	SD	0.0	0.0
62	4	7537.8	LFU	-	-
63	3	7338.1	SD	21.8	21.8
64	3	7596.1	SD	10.1	10.1
65	3	7677.9	LFU	-	-
66	1	7054.0	LFU	-	-
67	3	7205.8	SD	17.7	17.7
68	1	7386.6	PD	0.6	1.0
69	4	7453.8	PR	8.0	8.0
70	1	7177.7	PD	0.8	6.3
	Assessed patients: 70/70 Total treatments: 212 [#]Salvage treatments: 40	Assessed patients: 70/70 7400 MBq ±10%: 69 3700 MBq ±10%: 1	Assessed patients: 50/70 Tumor response: CR 0 (0%) SD: 36 (72%) PR: 3 (6%) PD: 11 (22%) Excluded: 20/70 LFU: 15[*] ST: 4[**] OT: 1[***]	Assessed patients: 54/70 Censored: 35 Events: 16 Excluded: 3	Assessed patients: 55/70 Censored: 38 Events: 14 Excluded: 3

SD: stable disease, PR: partial response, NR: no response, PD: progressive disease, LFU: lost to follow-up, ST: stopped treatment, OT: ongoing treatment, PFS: progression-free survival, OS: overall survival.

The analyzed data contained 212 treatments given to 70 patients. Of those, [*]15 patients were lost to follow-up (LFU) and excluded from further PFS and OS analyses. [**]4 patients had died and treatment was stopped (ST) before the 4th cycle. In all cases death was related to NET, but unrelated to PRRT. [***] Treatment was ongoing (OT) in one patient, for whom the reference date for calculating OS was that of the first treatment. This patient was excluded from the PFS analysis.

At the time of data analysis, the median PFS and OS of LuNET-SRY-treated patients were not yet reached. However, the estimated rates of PFS and OS at 25 months were 60.3% and 56.0%, respectively (Figure 2). This suggests that the LuNET-SRY survival rates are in line with those reported in the literature. It should be noted that the calculated PFS and OS rates for LuNET-SRY were slightly underestimated, as they were determined from the time of the last treatment rather than the time of the first treatment or time of randomization (as in the aforementioned clinical studies). Moreover, LuNET-SRY treatment was given for treating NETs of all types and of all grades, in adults and in adolescents. In a similar manner, tumor responses following LuNET-SRY treatment were also determined from the time of the last treatment. The calculated response rates of complete response (CR): 0 (0%), stable disease (SD): 36 (72%), partial response (PR): 3 (6%) and PD: 11 (22%) were in line with those reported in the literature.

Figure 2. Kaplan-Meier survival plots for PFS and OS of a patient cohort treated at a single medical center, as measured from the last treatment with LuNET-SRY



- LuNET-SRY treatments were also administered in a second medical center, wherein 38 patients with high SSTR-expressing were given a total of 80 treatments between May 2018 and Feb 2019. The various patients have received between 1-4 treatments, and the average time between treatments was 77 ± 39 days. Only distribution and dosimetry data were available in this patient population, as described under section 8.

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) properties of LuNET-SRY have not been studied. The PK characteristics of a similar [^{177}Lu]DOTA-TATE drug product have been investigated *in vitro* and *in vivo*, including evaluation of distribution, metabolism and excretion, and are publically available. A brief summary of the PK of [^{177}Lu]DOTA-TATE is provided herein.

- [^{177}Lu]DOTA-TATE is administered intravenously and is fully bioavailable upon administration.
- [^{177}Lu]DOTA-TATE is rapidly cleared from blood and accumulates in the kidneys, tumor lesions, liver and spleen, and in certain cases, in the pituitary and the thyroid. Co-administration of the amino acid infusion decreases the uptake in kidneys and enhances the renal clearance of the drug product. About 50% of the product is bound to plasma proteins.
- [^{177}Lu]DOTA-TATE is poorly metabolized, and most of the activity excreted in the urine up to 48 h after administration represents the unchanged drug product. These findings are in line with *in vitro* studies using human hepatocytes, in which no metabolites of [^{177}Lu]DOTA-TATE were detected.
- The primary elimination route of [^{177}Lu]DOTA-TATE is renal clearance, with about 60% and 65% of the injected dose being eliminated unchanged in the urine within 24 h and 48 h, respectively. No data are available regarding the PK profile in elderly patients (>75 y).

5.3 Preclinical safety data

Preclinical safety data for LuNET-SRY are not available.
Safety pharmacology studies using non-radioactive [^{175}Lu]DOTA-TATE were performed in rats and dogs, and their results are publically available. Briefly, these studies indicate that:

- [^{175}Lu]DOTA-TATE has no effect on behavior or body temperature of male Wistar rats following a single intravenous bolus administration up to 20 mg/kg. The no observed event limit (NOEL) of the non-labelled drug was reported as ≥20 mg/kg.
- Following a single intravenous administration of [^{175}Lu]DOTA-TATE to dogs at doses up to 800 µg/kg, no effect on blood pressure, heart rate, body temperature or electrocardiogram were observed.

Overall, [^{175}Lu]DOTA-TATE was well tolerated in both rats and dogs, and no deaths had occurred, and the preclinical data using the non-radioactive reference reveal no particular hazard as indicated by safety pharmacology, dose toxicity and genotoxicity studies.

- Toxicological studies in rats following a single intravenous administration of 4,550 MBq/kg [^{177}Lu]DOTA-TATE (roughly 100-fold higher than the human infused dose) indicated the administration was well tolerated, and no deaths had occurred.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium ascorbate
Ascorbic acid
Sodium chloride
Water Ultrapure

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned insection 4.2.

6.3 Shelf life

The expiry date and time of LuNET-SRY is indicated on the packaging materials, and is limited to 72 hours from the end of its synthesis.

6.4 Special precautions for storage

Store at room temperature below 25°C.
Store in the original containers to protect from ionizing radiation.
Storage of radiopharmaceuticals should be in accordance with institutional and national regulations on radioactive material.

6.5 Nature and contents of container

Clear Type I glass vial, closed with a butyl rubber stopper and aluminum seal.
Each vial contains a volume of 12.5 mL of solution corresponding to an activity of 7,400 MBq at the date and time of infusion (ART).
The vial is enclosed within a poly(methyl methacrylate) (PMMA) box, stored inside a lead container for protective shielding.

6.6 Special precautions for disposal and other handling

The solution is intended for single use only.

General warning
Radiopharmaceuticals should be received, stored, transferred, administered and disposed of only by authorized personnel and in accordance with the regulations and appropriate licenses of the medical center.
Appropriate aseptic precautions should be taken, and adequate aseptic techniques should be used while handling the product.
Radiopharmaceuticals should be handled in line with radiation safety and pharmaceutical quality requirements. Waterproof gloves and suitable personal protective equipment should be used. Use adequate shielding and minimize the exposure to ionizing radiation as low as reasonably achievable. Healthcare personnel are advised to limit the time of close contact with patients injected with LuNET-SRY.

For instruction on preparation of the medicinal product before administration, see section 9. If the integrity of the vial is compromised, it should not be used.

For additional recommendations on radiation safety, radiation protection and environmental hazards, see section 4.4.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Manufacturer and License Holder:

S.R.Y Medical Services Ltd.
Kiryat Hadassah 1 Kalman Mann St.
POB 12000, 9112001, Jerusalem, Israel
Registration Number: 169 58 36719 99

Revised in April 2023 according to MOHs guidelines.

8. DOSIMETRY

Previously reported absorbed dose estimates for [^{177}Lu]DOTA-TATE indicate that the dose regimen of 7,400 MBq in 4 cycles is safe, provided that the cumulative dose does not exceed the safety limits of 23-27 Gy for the kidneys and 2 Gy for the bone marrow. Notably, no correlation between hematologic toxicity and the total [^{177}Lu]DOTA-TATE administered activity or bone marrow absorbed dose have been observed. Moreover, as long as an appropriate amino acid solution is co-infused for renal protection, kidneys are not considered a critical organ.

The absorbed dose estimates of selected organs after the first LuNET-SRY administration to 77 NET patients in one center and to an additional 38 patients in a second center are illustrated in Table 5 and Table 6, respectively. These data are similar to previously published dosimetric analyses of [^{177}Lu]DOTA-TATE, which conform that the kidneys and bone marrow are the main organs at risk following [^{177}Lu]DOTA-TATE treatment. Nonetheless, the absorbed radiation dose to specific organs might be affected by different pathophysiological conditions, and should be taken into consideration and regularly monitored.

Table 5. Absorbed dose estimates for LuNET-SRY after the first treatment in one medical center

	Injected dose [MBq]	Organ absorbed dose (mGy/MBq injected dose) (n = 77)				
		Tumors	Kidneys	Liver	Spleen	Bone marrow
Mean	7360.1	3.7	0.8	0.4	1.4	0.02
S.D	503.5	3.6	0.4	0.3	1.0	0.01

Table 6. Absorbed dose estimates for LuNET-SRY after the first treatment in a second medical center

	Injected dose [MBq]	Organ absorbed dose (mGy/MBq injected dose) (n = 38)				
		Tumors	Kidneys	Liver	Spleen	Bone marrow
Mean	7455.3	3.5	0.8	0.5	1.0	0.03
S.D	253.7	2.7	0.4	0.3	0.5	0.01

9. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Quality controls

The solution should be visually inspected before use. Only clear and colorless solutions, which are free of visible particles, can be used. The visual inspection of the solution should be performed behind a shielded glass, and the vial must remain sealed.

If the integrity of the vial is compromised, it should not be used.

The amount of radioactivity in the vial must be confirmed prior to infusion using a calibrated dose calibrator.

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