▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION
LUTETIUM (^{177}Lu) CHLORIDE RADIOPHARMACEUTICAL PRECURSOR, SOLUTION

1 NAME OF THE MEDICINE

Lutetium (^{177}Lu) chloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lutetium (^{177}Lu) chloride (lutetium chloride) is a clear, colourless solution, free of impurities in 0.04M hydrochloric acid. Each vial may contain between 10 GBq/mL to 200 GBq/mL lutetium chloride at Calibration DATE AND TIME (radioactive concentration) in required volume of 0.04 M hydrochloric acid to make the final solution volume of 0.5 mL.

Lutetium emits both medium-energy beta particles and imageable gamma photons and has a half-life of 6.647 days. The primary radiation emissions of lutetium are shown in Table 1 below.

Table 1: Lutetium (^{177}Lu) principle radiation emission data

Radiation	Energy (keV)*	Abundance (%)
Beta (β^-)	47.66	11.61
Beta (β^-)	111.69	9.0
Beta (β^-)	149.35	79.4
Gamma	112.9498	6.17
Gamma	208.3662	10.36

* mean energies are listed for beta particles

3 PHARMACEUTICAL FORM

Lutetium chloride is a clear, colourless solution, free of impurities supplied as a radiopharmaceutical precursor.

Lutetium chloride has no therapeutic application in clinical medicine. It is intended to be used only when bound to a specific biological carrier as part of peptide receptor radionuclide therapy (PRRT).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor, and it is not intended for direct use in patients. For the treatment of non resectable or metastatic neuroendocrine tumours (NETS) expressing somatostatin subtype 2 receptors when coupled with a suitable carrier molecule.

4.2 DOSE AND METHOD OF ADMINISTRATION

Lutetium chloride is intended for *in vitro* radiolabelling of medicinal products which are subsequently administered by the approved route. It should not be administered directly to the patient.

Lutetium chloride is only to be used by specialists experienced with PRRT.

Dosage

The quantity of lutetium (^{177}Lu)-labelled PRRT that is subsequently administered will depend on the carrier molecule to be radiolabelled and its intended use.

The radiation dose received by various organs following intravenous administration of a lutetium (^{177}Lu)- labelled PRRT is also dependent on the specific molecule being radiolabelled.

Dosimetry

The dosimetry table below is presented in order to evaluate the contribution of non-conjugated lutetium chloride to the radiation dose following the administration of a lutetium chloride labelled PRRT or resulting from an accidental intravenous injection of lutetium chloride.

The dosimetry estimates were based on a rat biodistribution study performed according to MIRD pamphlet no.16, and the calculations were performed using the OLINDA 1.1 software package. Time points for measurements were 5 minutes, 1 hour, 12 hours, 2 days, 7 days and 28 days.

Table 2: Estimated organ absorbed radiation doses and effective doses (mSv/MBq) after inadvertent intravenous administration of $^{177}LuCl_3$ for various human age classes, based on data collected in rats (n = 24)

Organ	Absorbed dose per unit radioactivity administered (mSv/MBq)				
	Adult (73.7 kg)	15 years old (56.8 kg)	10 years old (33.2 kg)	5 years old (19.8 kg)	1 year old (9.7 kg)
Adrenals	0.2130	0.3070	0.4450	6.0400	0.9120
Brain	0.0056	0.0068	0.0089	1.3500	0.0197
Breasts	0.0107	0.0134	0.0239	0.0377	0.0697
Gallbladder Wall	0.1090	0.1240	0.1610	0.2530	0.4500
LLI Wall	0.0104	0.0097	0.0167	0.0292	0.0522
Small Intestine	0.1090	0.0244	0.0434	0.0731	0.1260
Stomach Wall	0.0556	0.0381	0.0648	0.1040	0.1860
ULI Wall	0.0297	0.0334	0.0609	0.1050	0.1830
Heart Wall	0.0415	0.0535	0.0805	0.1190	0.2090
Kidneys	0.3720	0.4490	0.6460	0.956	1.7200
Liver	5.5600	7.5600	11.900	17.900	35.700
Lungs	0.0574	0.0808	0.1140	0.1720	0.3230
Muscle	0.0143	0.0180	0.0260	0.0386	0.0697
Ovaries	0.0106	0.0129	0.0224	0.0379	0.0709
Pancreas	0.0663	0.0818	0.1250	0.1900	0.3050
Red Marrow	0.5910	0.6670	1.2300	2.6200	6.6000
Osteogenic Cells	2.1500	2.8100	4.5900	7.8000	18.800
Skin	0.0073	0.0091	0.0140	0.0217	0.0412
Spleen	5.7300	8.5000	13.500	21.600	40.700
Testes	0.0022	0.0029	0.0049	0.0088	0.0188
Thymus	0.0102	0.0128	0.0179	0.0276	0.0469

The effective dose to a 73.7 kg adult resulting from an inadvertently injected intravenous activity of 1 GBq would be 534 mSv.

Method of administration

Lutetium chloride should not be administered directly to the patient.

Before each administration and during the treatment, biological tests are required to re-assess the patient's condition and adapt the therapeutic protocol if necessary (dose, infusion interval, number of infusions).

The minimum laboratory tests needed before each infusion are:

- Liver function (alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], albumin, bilirubin)

- Kidney function (creatinine and creatinine clearance)
- Haematology (Haemoglobin [Hb], white blood count, platelet count)

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 lutetium-based PRRT and every 6 months thereof, in order to be able to detect possible delayed adverse reactions (see section 4.8). Dosing may need to be modified based on the tests results.

Dose modification

In some circumstances, it might be necessary to temporarily discontinue treatment with lutetium-based PRRT, adapt the dose after the first administration, or even discontinue the treatment**.**

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of excipients.
- Severe hepatic impairment, i.e., total bilirubin >3 upper limit of normal or both an albumin <25 g/L and prothrombin time increased >1.5 upper limit of normal, indicating biosynthetic liver failure should be an absolute contraindication.
- Severe cardiac impairment (New York Heart Association grade III or IV) should be an absolute contraindication.
- Pregnancy or ongoing lactation.
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6 Fertility, Pregnancy and Lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by a nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agency authorised to license the use of radionuclides.

Care should be taken to minimise radiation exposure to patients consistent with proper patient management.

There have been reports of extravasation of lutetium-labelled ligands in the post-marketing setting in Europe. In case of extravasation, infusion of the medicinal product should be

immediately ceased, and the nuclear medicine physician and the radiopharmacist should be promptly informed. Management should be in accordance with local protocols.

As with other radioactive drugs, lutetium chloride must be handled with care and appropriate safety measures should be used to minimise radiation exposure to clinical personnel. Disposal of all radioactive wastes should be carried out in accordance with local requirements.

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. A patient presenting with any of the conditions below is more prone to develop adverse reactions. Therefore, it is recommended to monitor those patients more frequently during the treatment, with modification of dosing considered as appropriate by the treating physician.

- Moderate to severe renal impairment (i.e., creatinine clearance <50 ml/min). For patients with severe baseline renal dysfunction, lutetium chloride based PRRT should be used only in exceptional circumstances in consultation with a nephrologist.
- Impaired haematological function, i.e., Hb <5 mmol/L (8 g/dL); platelets <75 X 10^9 /L; white blood cell count <2 X 10^9 /L.
- Moderate to severe right heart valvular disease.
- Significant sites of active disease as determined by unequivocal, contrast-enhancing lesions on CT or MRI that lack somatostatin receptor expression.

Myelosuppression

Anaemia, thrombocytopenia, leucopenia, lymphopenia, and less commonly neutropenia may occur during lutetium chloride based PRRT.

In a study with lutetium chloride based PRRT, Grade 3 or 4 haematological toxicity occurred in 61 of 582 patients (10%; 95%CI,8%–13%), Grade 3 or 4 toxicity of platelets occurred in 30 of 582 patients (5%; 95% CI, 4%–7%), total WBC count Grade 3 or 4 toxicity in 32 of 582 patients (5%; 95% CI,4%–8%), haemoglobin Grade 3 toxicity in 22 of 582 patients (4%; 95% CI, 2%–6%). No Grade 4 haemoglobin toxicity was observed.

At first follow-up visit after 3 months, these values normalised in 77% of patients. Grade 3 or 4 of the lymphocytes was observed in 288 of 582 patients (50%; 95% CI, 46%–54%). At 3 months follow-up, 74 of 287 patients and at 30 months follow-up 6 of 108 patients had persistent Grade 3 or 4 lymphocyte toxicity and 53 of 108 patients had Grade 1 or2 lymphocyte toxicity.

A systematic review of the published literature on lutetium chloride based PRRT found that acute haematological toxicity manifested as modest self-limited Grade 3 or 4 toxicity (CTCAE or WHO classification) most often affecting platelets, then WBC and finally hemoglobin, and was commonly observed during the first cycle of treatment, with the lowest nadir predictive of time taken for recovery. Toxicity manifesting early was managed with dose modification or therapy cessation and was ameliorated by appropriate patient selection based on age, prior therapies, comorbidities, and adequate baseline myeloid function.

Myelodysplastic syndrome and acute myeloid leukaemia

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been observed after treatment with lutetium chloride based PRRT for neuroendocrine tumours (see section 4.8).

The prevalence of therapy-related persistent haematological dysfunction (PHD), defined as MDS, AML, myeloproliferative neoplasm (MPN), or MDS/MPN or unexplained Grade 34 haematologic toxicity (> 6 months) in haemoglobin, platelets, or white blood cells) after lutetium chloride based PRRT in GEP NET patients was 4%, implying a relative risk of 2.7 compared to the untreated population.

In a study designed to evaluate the incidence of persistent haematological dysfunction (PHD) after lutetium chloride based PRRT in GEP NET patients, 11 of the 274 patients (6 women and 5 men) had PHD after lutetium chloride based PRRT (4%). Eight patients developed a hematopoietic malignancy (4 myelodysplastic syndrome (MDS), 1 acute myeloid leukaemia (AML), 1 myeloproliferative neoplasm (MPN), and 2 MDS/MPN), and 3 patients developed bone marrow (BM) failure characterized by cytopenia and BM aplasia.

The median latency period from initiation of PRRT to diagnosis of PHD in the 11 of 274 GEP NET patients was 41 months (range, 15–84 m). In 5 of the 11 patients, PRRT was interrupted. The median cumulative estimated BM dose was 2.0 Gy (range, 0.2–4.0 Gy) in the 263 patients without PHD and 1.8 Gy (range, 1.0 22.0 Gy) in the 11 patients with PHD. Seven of the 11 patients received a BM dose of less than 2.0 Gy.

Of patients treated with a median cumulative radionuclide administered activity of 40.5 GBq (range 24.4–74.8), 19 (3.6% of entire cohort) developed MDS and six patients (1.2% of entire cohort) developed AML. No patient developed acute lymphoblastic leukaemia.

Factors associated with development of significant short and long-term myelotoxicity included age >70 years, impaired renal function, baseline cytopenias, prior number of therapies, prior chemotherapy (especially alkylating agents), and prior radiation therapy.

This should be taken into account when considering the benefit/risk, especially in patients with possible risk factors like prior exposure to chemotherapeutic agents (such as alkylating agents).

Renal irradiation

In 323 patients treated with lutetium chloride based PRRT in a median cumulative activity of 29.6 GBq (range 7.4 – 29.6 GBq), 14 (4 %) had a (sub)acute toxicity Grade 1 (creatinine increase >26.5 µmol/L). Three patients (1 %) developed (subacute) toxicity Grade 2 (creatinine increase >1.5 – 3.0 × baseline or upper limit of normal). No Grade 3 or 4(sub)acute nephrotoxicity was observed.

Hormone release syndromes

There have been reports of carcinoid crisis and other syndromes associated with release of hormones from functional neuroendocrine tumours following lutetium chloride based PRRT. The reported incidence ranges from 0.6% to 3.5% of patients. Patients at greater risk are those with a high tumour load, liver metastases, high chromogranin A (CgA)/urinary 5-Hydroxyindoleacetic acid (5-HIAA) ratio, established carcinoid syndrome or known carcinoid heart disease.

Reported symptoms include flushing and diarrhoea associated with hypotension. Observation of patients by overnight hospitalisation should be considered in some cases (e.g. patients with poor pharmacologic control of symptoms). In case of hormonal crises, treatments may include intravenous high dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and/or vomiting.

Hormone release syndromes may develop again following subsequent cycles of lutetium chloride based PRRT. It is recommended that additional precautions are taken before the administration of further therapy cycles in patients who develop a hormonal crisis after their first therapy cycle, including continuation of somatostatin analogues, corticosteroids, prolonged observation in hospital, and reduction in dose.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported following lutetium chloride based PRRT. The reported incidence associated with ^{177}Lu-ligand PRRT is 0.74% of PRRT cycles administered. Patients with a history of renal insufficiency and high tumour burden may be at greater risk of TLS.

Patients who develop TLS should be treated symptomatically according to TLS guidelines.

Pituitary and related endocrine effects

In patients undergoing lutetium chloride based PRRT treated with 7.4GBq per cycle (3 to 9 cycles), a small number patients developed hypothyroidism or elevated levels of HbA1c. the study also found that in men, lutetium chloride based PRRT induced transient inhibitory effects on spermatogenesis, but non-SHBG bound T levels remained unaffected. Gonadotropin levels decreased significantly in postmenopausal women.

A further study, using similar dosage regimens of lutetium chloride based PRRT found a statistically significant decrease in insulin like growth hormone IGF-1 levels, which was significantly correlated with the number of cycles of lutetium chloride based PRRT received as well as to the radiation dose.

Calcium Homeostasis

In 47 patients who received a cumulative 29.6 GBq dose of lutetium chloride, the mean serum calcium level decreased significantly from 2.29 ± 0.01 mmol/l to a nadir of 2.24 ± 0.01 mmol/l at 6 weeks after treatment (p=0.02). The decline in plasma calcium concentration was confirmed in a larger, retrospectively analysed, patient group, in which 22 % of patients developed hypocalcaemia. Calcium supplementation may be required in patients who develop hypocalcaemia.

Parathyroid hormone

A small, but significant reduction in parathyroid hormone was observed in men but not women.

Bowel obstruction

Patients with midgut NETs and underlying peritoneal and mesenteric metastases are at increased risk of developing bowel obstruction during PRRT.

Use in hepatic impairment

Liver function should be monitored regularly during treatment. Dose reduction may be necessary in affected patients.

In patients treated with lutetium chloride based PRRT in doses up to a cumulative intended dose of 750 to 800 mCi (27.8–29.6 GBq), an increase of aminotransferases (aspartate transaminase and/or alanine transaminase) grade 3/4 was observed (3%; 95% CI, 2%–5%). After 3 months follow up, there were three patients with persistent grade 3/4 toxicity of the aminotransferases. No hepatic failure was observed during or after therapy.

Use in renal impairment

Renal function including glomerular filtration rate (GFR) should be assessed at baseline and during treatment and renal protection should be considered, in accordance with clinical guidance of the radiolabelled medicinal product.

A retrospective study assessing renal function over time, reported the incidence of nephrotoxicity in patients treated with lutetium chloride based PRRT primarily for NETs. The intended cumulative activity was 29.6 GBq (800 mCi). The interval between treatments was 6 – 16 weeks.

A total of 14 patients (4 %) had a (sub)acute toxicity Grade 1 (creatinine increase >26.5 µmol/l). Three patients (1 %) developed (subacute) toxicity Grade 2 (creatinine increase >1.5 – 3.0 × baseline or upper limit of normal). These changes were judged not related to therapy. No Grade 3 or 4 (sub)acute nephrotoxicity was observed.

With all other factors held constant, the estimated average baseline CLR showed a significant decrease in patients older than 70 years or with baseline CTCAE grade 2 (both p <0.0001). None of the risk factors considered for inclusion in the model (hypertension, diabetes, age >70 years, cumulative injected activity >22.2 GBq, high radiation dose to the kidneys and CTCAE grade at baseline) had a significant effect on the estimated rate of change in CLR over time.

In a study of patients treated with lutetium chloride based PRRT, with primary NETs in the gastrointestinal tract, or NETs of unknown primary origin, patients who had ^{51}Cr-EDTA GFR measured prior to and at the end of induction therapy (n=64), showed a change in mean GFR after administration of a mean activity of 24.6 GBq over 2.8 cycles of 1.2 ml/min (95 % CI –6.9 to 4.4 ml/min). This change not statistically significant.

In a study of patients with a progressive metastatic neuroendocrine tumour treated with multiple cycles of lutetium chloride based PRRT at a standard activity of 7.4 GBq at 8-12-week intervals, the mean absolute annual change in measured GFR was -4.3 mL/min/1.73 m^2 (range +11 to -30). This compared to the mean annual GFR-loss in a normal population of a similar age range, which is between 0.4 ± 3.6 and 1.8 ± 2.6 mL/min.

During long-term follow-up (median 22 months), in patients who received doses of 6 – 12 GBq as an induction course consisting of four cycles separated by 6 - 8 weeks followed by one or two consolidation cycles in selected patients and one maintenance cycle as needed 12 - 18 months after induction, the mean rate of decline of GFR estimated in patients who had more than two GFR measurements (n=44) was 2.2 mL/min per year (95 % CI, 4.1 to 0.3 mL/min per year).

Use in the elderly

Clinical experience using lutetium chloride based PRRT has not identified differences in

responses between the elderly and younger patients. However, since increased risk of presenting haematotoxicity has been described in elderly patients (≥ 80 years old), a close follow up allowing for prompt dose adaptation (DMT) in this population is advisable.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies of $^{177}LuCl_3$ with other medicines have been performed.

A clinical study which evaluated the effect of concomitant IV infusion of an amino acid solution (22.0 g of lysine and 16.8 g of arginine in 2 L solution, and containing smaller amounts of 18 other amino acids), with a dose of 7.4 GBq lutetium chloride based PRRT, found lutetium chloride based PRRT $AUC_{Day15,}$ decreased by a mean value of 12.6%.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category X

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 doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient. Before the use of lutetium chloride based PRRT, pregnancy should be excluded using an adequate/validated test.

The use of lutetium chloride based PRRT is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded due to the risk of ionizing radiation to the fetus (see section 4.3 Contraindications).

Use in lactation.

The effects in the nursing infant are unknown. Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted and the expressed feeds discarded.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Effects on ability to drive and to use machines have not been studied for lutetium chloride. For effects on ability to drive and use machines following treatment by lutetium chloride based PRRT refer to the Product Information of the medicinal product to be radiolabelled.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Injection of lutetium chloride in animals has produced insoluble precipitates at the site of injection. It is uncertain whether this effect is directly related to the chloride salt, or low pH required to check the radionuclide in solution.

Lutetium chloride has no therapeutic application in clinical medicine. It is intended to be used only when bound to a specific biological carrier as part of PRRT. Consequently, adverse reactions following lutetium chloride based PRRT will be dependent on the specific carrier molecule being used.

The most common treatment emergent adverse events (TEAE) among patients treated with lutetium chloride based PRRT were nausea [59%] and vomiting [47%]. Other common adverse events include fatigue or asthenia, abdominal pain, and diarrhea; however, a majority of the patients in whom these events were reported (≥97%) had events of Grade 1 or 2.

Tabulated list of adverse reactions

The adverse reactions are listed in Table 3 according to the frequency and the MedDRA System Organ Class (SOC).

Table 3. Frequency of adverse reactions reported from clinical trials

System organ class	Any Grade (n/%)	Grade 3 or 4 (n/%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Myelodysplastic syndrome	19 (3.6)	3 (1)

Acute or chronic myeloid leukaemia	6 (1.2)	1 (0.36)
Gastrointestinal disorders		
Nausea	65 (59)	4 (4)
Vomiting	52 (47)	8 (7)
Abdominal pain	29 (26)	3 (3)
Diarrhoea	32 (29)	3 (3)
Distension	14 (13)	0
General disorders		
Fatigue or asthenia	44 (40)	2 (2)
Oedema peripheral	16 (14)	0
Blood and lymphatic system disorders		
Thrombocytopenia	28 (25)	11 (5)
Anaemia	16 (14)	6 (3)
Lymphopenia	20 (18)	
Leukopenia	11 (10)	20 (10)
Neutropenia	6 (5)	3 (1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	32 (29)	2 (2)
Renal and urinary disorders		
Increased creatinine	17 (5)	2 (0.3)
Nephrotoxicity		1 (1)
Metabolism and nutrition disorders		
Decreased appetite	20 (18)	0
Nervous system disorders		
Headache	18 (16)	0
Dizziness	12 (11)	0
Vascular disorders		
Flushing	14 (13)	1 (1)
Skin and subcutaneous tissue disorders		
Alopecia	12 (11)	2 (2)
Respiratory, thoracic and mediastinal disorders		
Cough	12 (11)	6 (5)
Investigations		
Increased liver enzymes		20 (3)
Hypocalcaemia	33 (22)	
Injury, poisoning and procedural complications		

Carcinoid crisis	6 (3)	1 (1)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No data are available regarding the effects of an overdose of ^{177}Lu-DOTATATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate). The usual dosage regimen for ^{177}Lu-DOTATATE PRRT is 7.4 GBq per cycle for 4 cycles. The highest cumulative dose administered to patients in clinical studies was 78.6GBq and the highest number of cycles was 10.

The presence of free lutetium chloride in the body after an inadvertent administration is likely to lead to increased bone marrow toxicity and haematopoietic stem cell damage. Therefore, in case of an inadvertent administration of lutetium chloride, the radiotoxicity for the patient must be reduced by immediate (i e. within 1 hour) administration of preparations containing chelators like Ca-DTPA (trisodium calcium diethylenetriaminepentaacetate) or Ca-EDTA (calcium disodium ethylenediaminetetraacetate) in order to increase the elimination of the radionuclide from the body.

These chelating agents help with the elimination of lutetium chloride radiotoxicity by an exchange between the calcium ion in the complex and the lutetium (^{177}Lu) ion. Due to the capacity of the chelating ligands (DTPA, EDTA) of forming water soluble complexes, the complexes and bound lutetium (^{177}Lu) are rapidly eliminated by the kidneys.

The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to tissue fluids and plasma. However, a post-exposure interval > 1 hour does not preclude the administration and effective action of chelator with reduced efficiency. Intravenous administration should not be protracted over more than 2 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10X

The pharmacodynamic properties of lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with lutetium chloride, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled. Refer to the Product Information of the particular medicinal product to be radiolabelled.

Mechanism of action

Lutetium chloride emits β-particles of moderate maximum energy (0.498 MeV) with a maximum tissue penetration of approximately 2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted tumour cells with a limited effect on neighbouring normal cells, thus minimising potential toxicity.

Clinical trials

The efficacy of lutetium chloride in the treatment of NETs was assessed based on published literature reports. The published reports included three systematic reviews/meta-analyses (Zhang 2020, Wang 2020 and Satapathy 2019); two randomised controlled trials (RCTs) (Australasian Gastrointestinal Trials Groups (AGITG) CONTROL-NETS study, Pavlakis 2020; NETTER-1 study, Strosberg 2017 with two sub-analyses of the initial data or follow up data based on the original study cohort, Strosberg 2018 and Strosberg 2020).

Zhang 2020 reported the outcomes of patients with inoperable or metastatic NETs who were treated with ^{177}Lu-DOTATATE and evaluated the response according to the Response Evaluation Criteria in Solid Tumours (RECIST) or the Southwest Oncology Group (SWOG) criteria or both. Treatment endpoints were the objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). A total of 15 published articles which treated 872 inoperable or metastatic NETs patients were included in the study. The dose of ^{177}Lu ranged from 3.7 to 15.9 GBq, administered in 1 to 8 cycles. The results are presented in Table 4.

Wang 2020 evaluated published clinical trials assessing the efficacy of ^{177}Lu-octreotate/octreotide PRRT in advanced or inoperable NETs patients and evaluated the response according to the RECIST, SWOG or World Health Organisation (WHO) criteria. Disease response rates (DRRs) and disease control rates (DCRs) were calculated according to each response criteria group. The meta-analysis included 22 high-quality published articles which treated 1758 inoperable or metastatic NETs patients. Of the 22 studies included in the analysis, 20 administered ^{177}Lu-DOTATATE and two ^{177}Lu-DOTATOC. The dose of ^{177}Lu ranged from 3.7 to 8.1 GBq, administered in 1 to 10 cycles. The results are presented in Table 4.

Satapathy 2019 evaluated published clinical trials assessing the efficacy of ^{177}Lu-DOTATATE and everolimus in advanced pancreatic NETS (pNET). The meta-analysis included 15 published articles which treated 697 pNET patients with ^{177}Lu-DOTATATE. Twelve studies

treated 946 patients with everolimus. Treatment endpoints were the ORR, DCR and PFS. ORR combined the proportions of patients with complete remission, partial response and/or minor response. The cumulative dose of ^{177}Lu ranged from 3.7 to 29.2 GBq, administered in 1 to 10 cycles. The results are presented in Table 4.

Table 4 - Comparison of the DRR and DCR estimated using the RECIST and SWOG criteria

STUDY	DRR	(% & 95%CI)	DCR	(% & 95% CI)
	RECIST	SWOG	RECIST	SWOG
ZHANG 2020	27.6 (21.0 to 35.5)	20.6 (10.9 to 35.5)	79.1 (75.8 to 82.1)	78.3 (74.4 to 81.7)
WANG 2020	33.0 (25.0 to 42.0)	25.0 (14.0 to 36.0)	79.0 (75.0 to 83.0)	82.0 (75.0 to 89.0)
SATAPATHY 2019	47.0 (36.0 to 58.0)*	59.9 (39.7 to 76.8)*	81.0 (75.0 to 86.0)	84.9 (80.2 to 99.9)

* Note that the response provided in the Satapathy analysis was the ORR rather than the DRR. ORR includes patients with a minor response in addition to those recording complete response (CR) and partial response (PR), as is required in the definition of DRR.

Pavlakis 2020 reported on a non-comparative randomised open label phase 2 study of ^{177}Lu-octreotate (LuTatePRRT) + Capecitabine/ Temozolomide (CAPTEM) for midgut NETs (CONTROL-NETS). The primary endpoint was PFS at 15 months, assuming 15 month PFS of 66.4% in the control arm, aiming for PFS rate >80%. Secondary endpoints were objective tumour response (OTRR), being complete or partial, clinical benefit rate (CBR), being complete or partial, or stable disease and quality of life (QoL). A total of 47 patients were enrolled, 33 receiving PRRT/CAPTEM and 14 PRRT. After a median follow-up of 32 months, the 15 month PFS was 90% (95% CI: 73-97%) compared to 92% (95% CI: 57-99%); the OTRR was 25% compared to 15% and the CBR was 97% compared to 92%, for PRRT/CAPTEM compared to PRRT alone, respectively. This analysis demonstrates similarly high 15 month PFS for CAPTEM/PRRT relative to PRRT alone. OTRR is numerically higher.

Strosberg *et al.* 2017 reported on the Phase 3 NETTER-1 study which was a randomised, controlled trial evaluating the efficacy and safety of ^{177}Lu-DOTATATE in patients with advanced, progressive, somatostatin-receptor-positive midgut NETs and was followed by Strosberg 2018 and Strosberg 2020 with sub analyses. The NETTER-1 study recruited adult patients who had midgut NETs that had metastasised or were locally advanced, that were inoperable, that were histologically confirmed and centrally verified, and that showed disease progression (according to RECIST version 1.11) on either computed tomography (CT) or magnetic resonance imaging (MRI) over the course of a maximum period of 3 years during treatment with octreotide LAR (20 to 30 mg every 3 to 4 weeks for at least 12 weeks before randomisation). A total of 229 patients underwent randomisation, of which 221 received at least one dose of trial treatment, including 111 patients in the ^{177}Lu-Dotatate group and 110 in the control group (safety population).

In the patients randomised to the PRRT arm, 7.4 GBq (200 mCi) of ^{177}Lu-DOTATATE was infused intravenously over a period of 30 minutes. Patients received four infusions every 8 weeks (cumulative radioactivity, 29.6 GBq [800 mCi]) where possible. For renal protection, an intravenous amino acid solution was also administered starting 30 minutes before infusion of the radiopharmaceutical. Patients in the octreotide arm received octreotide LAR at a dose of 60 mg intramuscularly every 4 weeks.

Overall, the NETTER-1 series of study reports found:

- An estimated PFS at month 20 of 65.2% (95% CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group compared to 10.8% (95% CI, 3.5 to 23.0) in the octreotide LAR group.
- An estimated risk of death 60% lower in the ^{177}Lu-Dotatate group compared to the control group (HR for death with ^{177}Lu-Dotatate group compared to control, 0.40; P = 0.004).
- A significant improvement in health related QoL. The HR for global health favouring ^{177}Lu-Dotatate was 0.41 (95% CI, 0.24 to 0.69; P =0.001), with a 22.7-month difference in median time to treatment discontinuation (TTD) between both arms.
- No evidence of nephrotoxicity associated with ^{177}Lu-DOTATATE treatment, even in patients with mild to moderate baseline impairment in renal function.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of Lutetium (^{177}Lu)-labelled medicinal products prepared by radiolabelling with lutetium chloride, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled. The following information on pharmacokinetics of Lutetium (^{177}Lu) is relevant only to the case of inadvertent intravenous administration of the unconjugated radionuclide.

Distribution

Pre-clinical studies indicate that lutetium is bound to plasma albumin and globulin.

The distribution of ^{177}Lu following intravenous administration is time dependent. In the male and female rat, following intravenous administration, Lutetium (^{177}Lu) chloride is rapidly cleared from the blood: at 5 min post injection, only 1.52 % of the injected activity (%ID) is found in blood (corresponding to 0.08 %ID/g) and no activity above background levels remains 1 h post dose. Lutetium (^{177}Lu) chloride distributes mainly to the liver, spleen and bone. After one hour, the amount in the liver is 9.56 % of the injected activity per gram (%ID/g) and in the spleen 5.26 %ID/g. In bone, the content increases from 0.01 %ID/g at 5 min to 0.23 %ID/g after 12 h. For the next 28 days, further uptake of Lutetium (^{177}Lu) can be observed in the bone, which is compensated in part by radioactive decay. Taking into account the radioactive half life of Lutetium (^{177}Lu) of 6.647 days, the radioactivity remaining in the bone after 28 days is only about 0.06 %ID/g.

Excretion

Excretion of lutetium occurs predominantly via the renal route, with clearance from the body being slow following IV administration in rats. After 28 days, approximately 30 % of the injected dose remained in the body (17.8 % in bone, 10.5 % in liver and 1.8 % in the spleen). The remaining radioactivity in the body at this time is about 1.8% of the administered dose, due to radioactive decay (> 4 half lives passed).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

$^{177}LuCl_3$ accumulates in bone, and this has been shown to lead to formation of osteosarcomas in mice following IP administration at ^{177}Lu doses of 185-1480 MBq/kg (28-224 Gy). Osteosarcoma formation was associated with single radiation doses ≥ 7.8 Gy.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Dilute hydrochloric acid
- Water for injections

6.2 INCOMPATIBILITIES

Radiolabelling of medicinal products, such as monoclonal antibodies, peptides, vitamins or other substrates, with lutetium chloride is very sensitive to the presence of trace metal impurities.

It is important that all glassware, syringe needles etc., used for the preparation of the radiolabelled medicinal product are thoroughly cleaned to ensure freedom from such trace metal impurities. Only syringe needles (for example, non-metallic) with proven resistance to dilute acid should be used to minimise trace metal impurity levels.

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

6.3 SHELF LIFE

Up to 14 days from the date of manufacture.

Shelf life of the reconstituted product should be as per instructions provided for the medicinal products to be radiolabelled.

From a microbiological point of view, the product should be used immediately. The product is for single use only.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package in order to avoid unnecessary radiation exposure.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

This medicinal product does not require any special temperature storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Colourless, clear type I glass 2 mL V-vial with a flat bottom, closed, with a silicon stopper, and sealed with an aluminium crimp cap seal.

The vials are placed into a lead pot for protective shielding.

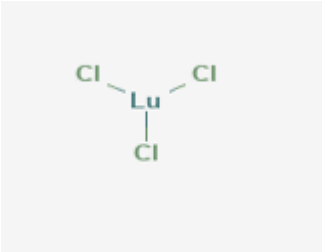
Pack size: 1 vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, disposal of all radioactive wastes should be carried out in accordance with the current Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular Formula: $^{177}LuCl_3$

Molecular Mass: 283.3

CAS number

10099-66-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

Australian Nuclear Science and Technology Organisation T/A ANSTO
Locked Bag 2001
Kirrawee DC
NSW 2232

Telephone: 1800 251 572

9 DATE OF FIRST APPROVAL

11 January 2022

10 DATE OF REVISION

N/A

Summary table of changes

Section changed	Summary of new information
	New Product Information for a new product