Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Lutetium (^{177}Lu) chloride

Active ingredients: Lutetium (^{177}Lu) chloride

Sponsor: Australian Nuclear Science and Technology Organisation (ANSTO)

September 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ANSTO	Australian Nuclear Science and Technology Organisation
ARTG	Australian Register of Therapeutic Goods
AU	Australian
CI	Confidence interval
CMI	Consumer Medicines Information
DLP	Data lock point
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency (European Union)
^{68}Ga	Gallium-68
GBq	Gigabecquerel
GVP	Good Pharmacovigilance Practices
Gy	Gray
E_{max}	Maximum effect attributable to the drug
^{177}Hf	Hafnium-177
HR	Hazard ratio
keV	Kiloelectronvolt
LAR	Long-acting repeatable
^{177}Lu	Lutetium-177
Lu^{3+}	Lutetium III
mCi	Millicurie
MeV	Megaelectronvolt
MSAC	Medical Services Advisory Committee
NET	Neuroendocrine tumour
ORR	Objective response rate

Abbreviation	Meaning
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PFS	Progression-free survival
PI	Product Information
PRRT	Peptide receptor radionuclide therapy
PSMA	Prostate-specific membrane antigen
PSUR	Periodic safety update report
RECIST	Response Evaluation Criteria In Solid Tumours
RMP	Risk management plan
SAS	Special Access Scheme
SSTR	Somatostatin receptor
SSTR1	Somatostatin type 1 receptor
SSTR2	Somatostatin type 2 receptor
SSTR5	Somatostatin type 5 receptor
µSv	Microsievert
T3	Triiodothyronine
T4	Thyroxine
TGA	Therapeutic Goods Administration
WHO	World Health Organization
^{176}Yb	Ytterbium-176
^{177}Yb	Ytterbium-177

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Lutetium (^{177}Lu) chloride
Active ingredient:	Lutetium (^{177}Lu) chloride
Decision:	Approved
Date of decision:	8 December 2021
Date of entry onto ARTG:	11 January 2022
ARTG number:	352151
, *Black Triangle Scheme:*	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Australian Nuclear Science and Technology Organisation (ANSTO) Locked Bag 2001 Kirrawee DC, NSW 2232
Dose form:	Radiochemical solution
Strengths:	Between 10 and 200 gigabecquerel (GBq)/mL at date and time of calibration
Container:	Vial
Pack size:	One (2 mL)
Approved therapeutic use:	*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.*
Route of administration:	Intravenous
Dosage:	Lutetium (^{177}Lu) chloride should not be administered directly to the patient. Lutetium is intended for *in vitro* radiolabelling of medicinal products which are subsequently administered by the approved route. Lutetium chloride is only to be used by specialists experienced with peptide receptor radionuclide therapy (PRRT).

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. See Table 2 of the Product Information for dosimetry information.

Before each administration and during the treatment, biological tests for liver, kidney and haematological function are required to re-assess the patient's condition and adapt the therapeutic protocol if necessary (dose, infusion interval, number of infusions). See Section 4.2 Method of Administration for further information.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: X

Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Australian Nuclear Science and Technology Organisation (ANSTO; the sponsor) to register lutetium (^{177}Lu) chloride as a radiochemical solution for the following proposed indication:

> *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.*

This submission for is for lutetium (^{177}Lu), a radioisotope of lutetium, supplied in the form of lutetium (^{177}Lu) chloride. Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor. In itself, it has no therapeutic application in clinical medicine and is not intended for direct use in patients and should not be administered directly.

When reacted with an appropriate medicinal product (a specific carrier molecule), it is intended for *in vitro* radiolabelling of that medicinal product which are subsequently administered by the approved route.

Each vial may contain between 10 gigabecquerel (GBq)/mL to 200 GBq/mL of lutetium (^{177}Lu) chloride at the date and time of calibration depending on the requirement. Each vial is dispensed individually; from the same batch, various finished product vials could

have different activities, based on the customer requirement. Each vial is individually labelled with the radioactive content inside. For the finished product, the radioactivity concentration for the customer order varies between 5 to 100 GBq in 0.5 mL.

Neuroendocrine tumours

Neuroendocrine tumours are a heterogeneous group of malignancies that can arise from neuroendocrine cells through the body. Common sites include the lung, large bowel, small intestine, pancreas and stomach. The gastrointestinal and pancreatic sites of neuroendocrine tumours represent around 60 to 65% of these tumours.

Neuroendocrine tumours are known for their ability to over-express somatostatin receptors (SSTRs). Neuroendocrine tumours express SSTRs in 70 to 90% of tumours. Over-expression of somatostatin type 2 receptor (SSTR2) is the most common followed by types 1 and 5 (SSTR1 and SSTR5).[1]

According to the World Health Organization (WHO) classification, tumours are classified into one of four types based on their size, proliferation, localisation, differentiation, and hormone production.[2] This classification is as follows:

- Type 1: well-differentiated neuroendocrine tumour (benign behaviour);
- Type 2: well-differentiated neuroendocrine tumour (uncertain behaviour);
- Type 3: well-differentiated neuroendocrine carcinoma (low grade malignancy); and
- Type 4: poorly differentiated neuroendocrine carcinoma (high grade malignancy).

A further pathological grading system has been applied using antigen Ki-67 as a cellular marker of cell proliferation:

- Grade 1: neuroendocrine tumours with a proliferative antigen Ki-67 of < 2%: well-differentiated, slow-growing and exhibit a poor response to chemotherapy;
- Grade 2: neuroendocrine tumours with a Ki-67 of 3 to 20%: have an intermediate and unpredictable rate of progression and unclear optimal treatment options; and
- Grade 3: neuroendocrine tumours with a Ki-67 > 20%: progress rapidly, progressively lose differentiation and have a higher but transient response to chemotherapy.

Management of gastroenteropancreatic neuroendocrine tumours depends on operability, symptoms, tumour type, stage and grade and the overall medical condition. These treatment options include:

- surgical resection and ablative therapy;
- somatostatin analogues such as octreotide;
- interferons and molecular-targeted therapy;
- cytotoxic chemotherapy; and
- peptide receptor radionuclide therapy (PRRT).

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) involves linking a radiopharmaceutical precursor such as lutetium (^{177}Lu) to a somatostatin analogue to target neuroendocrine tumour cells with a high density of SSTR. PRRT facilitates delivering tumouricidal doses of

[1] Chang et al. Cancer Forum, 2015; 39(1): 13.
[2] Modlin, I.M. et al. Gastrointestinal Neuroendocrine (Carcinoid) Tumours: Current Diagnosis and Management, *Med J Aust*, 2010; 193(1): 46-52.

radiation to neuroendocrine tumours. Ligands used to treat neuroendocrine tumours in this context include DOTATATE, DOTATOC and DOTANOC. After ^{177}Lu-somatostatin analogue binds to SSTRs, the ^{177}Lu-somatostatin analogue-receptor complex is internalised by tumour cells and the beta particles emitted from the ^{177}Lu atom produce a tumouricidal effect.

Lutetium

Lutetium (^{177}Lu) is said to be a radioisotope of choice due to the following properties:[3,4]

- Low energy beta-emitter (maximum effect attributable to the drug (E_{max}) = 0.498 megaelectronvolts (MeV)) allowing specific energy deposition in tumour lesions and low dose delivery to the surrounding healthy tissue.
- Maximum penetration range in tissues of 2.2 mm (mean 0.67 mm) facilitating precise dose localisation during therapy.
- Half-life of 6.64 days.
- Low kidney toxicity.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

This product received orphan drug designation on 22 January 2020 for the following indication:

> *For the treatment of non-resectable or metastatic neuroendocrine rumours (NETS) expressing somatostatin subtype 2 receptors when coupled with a suitable carrier molecule.*

At the time the TGA considered this submission, the sponsor has not submitted an application to register lutetium (^{177}Lu) chloride in any other countries.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 1: Timeline for Submission PM-2020-06691-1-4

Description	Date
Designation (Orphan)[5]	22 January 2020

[3] de Jong, M. et al. (177Lu-DOTA(0),Tyr3) Octreotate for Somatostatin Receptor-Targeted Radionuclide Therapy, *Int J Cancer*, 2001; 92(5): 628-633.
[4] Bergamasco, A. et al. Prevalence of Gastroenteropancreatic and Lung Neuroendocrine Tumours in the European Union, *Ann Oncol*, 2016; 27 (suppl_6): 424PD.
[5] **'Orphan drugs'** are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset

Description	Date
Orphan extension	26 August 2020
Submission dossier accepted and first round evaluation commenced	20 January 2021
First round evaluation completed	16 July 2021
Sponsor provides responses on questions raised in first round evaluation	1 September 2021
Second round evaluation completed	7 October 2021
Delegate's Overall benefit-risk assessment	1 December 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	8 December 2021
Completion of administrative activities and registration on the ARTG	11 January 2022
Number of working days from submission dossier acceptance to registration decision*	189

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Quality

Lutetium (^{177}Lu) is a radioisotope of lutetium. Non-carrier added lutetium (^{177}Lu) chloride is produced by the irradiation of highly enriched ytterbium (^{176}Yb) in neutron sources with a thermal neutron flux. The produced isotope ytterbium (^{177}Yb) with a half-life of 1.9 hours decays to lutetium (^{177}Lu). The accumulated lutetium (^{177}Lu) is then separated chemically from the original target material chromatographically.

orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application, and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

The finished product is in 0.04 M hydrochloric acid solution, each vial containing, according to the sponsor, 10 to 200 gigabecquerel (GBq)/mL. The sponsors rational for including a range in lutetium (^{177}Lu) chloride activity is provided below:

- The stock solution has a target activity concentration of approximately 225 GBq/mL lutetium (^{177}Lu) chloride.
- For the finished product, the radioactivity concentration for the customer order varies between 5 to 100 GBq in 0.5 mL.

The radioactivity concentration range supplied by the sponsor is to meet customer requirements. The sponsor is able to reliably and reproducibly manufacture lutetium (^{177}Lu) chloride stock (in 0.04 M hydrochloric acid), which is then dispensed as per activity required by the customer.

Each vial is dispensed individually; from the same batch, various finished product vials could have different activities, based on the customer requirement. Each vial is individually labelled with the radioactive content inside.

The European Medicines Agency (EMA) have likewise registered a lutetium (^{177}Lu) chloride solution for radiolabelling under EndolucinBeta, available as a solution corresponding to 3 to 150 GBq ^{177}Lu (at activity reference time). This approach is considered to be acceptable.

The lutetium is bound to a suitable carrier peptide in a nuclear medicine facility prior to being administered to the patient.

The product is packaged into a glass vial and placed into a lead pot for protective shielding.

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the Therapeutic Goods Administration (TGA). After several rounds of evaluations, the quality evaluator was satisfied that this product met acceptable standards.

Nonclinical

The nonclinical module was a literature-based submission. The literature search strategy was developed and approved in consultation with the TGA. The data provide limited information relevant to the proposed use of lutetium (^{177}Lu) chloride in PRRT.

Lutetium (^{177}Lu) is a medium energy beta-emitter with a maximum energy of 0.5 megaelectronvolts (MeV), a maximal tissue penetration of 2 mm and a half-life of 6.7 days, making it suitable for small tumours. Lutetium (^{177}Lu) also emits low energy gamma-rays (113 to 208 kiloelectronvoluts (keV)), which allows scintigraphy and subsequent dosimetry with the same therapeutic compound. Lutetium (^{177}Lu) decays to the stable isotope hafnium-177 (^{177}Hf) with a half-life of 6.647 days.

Lutetium (and other rare earth metal ions) bind or displace calcium or other divalent metal cations from a variety of binding sites. Lutetium III (Lu^{3+}) relaxed smooth muscle and inhibited agonist or potassium-induced contractions. Interactions with binding sites on actin isolated from rabbit muscle, canine osteocalcin, trypsinogen and human mitochondrial nicotinamide adenine dinucleotide-dependent malic enzyme have been reported. Lutetium enhanced neuronal gamma-aminobutyric acid currents. The concentrations required for these secondary pharmacological activities were well above the concentration likely to be reached during use of lutetium (^{177}Lu) for PRRT.

The pharmacokinetics of lutetium (^{177}Lu) during PRRT will be dependent on the carrier molecule that is to be radiolabelled with the isotope. The pharmacokinetics of uncomplexed lutetium (^{177}Lu) chloride are only of interest in case of accidental intravenous administration.

The toxicity of the peptide receptor radionuclide therapy will be dominated by that of the carrier molecule to be labelled with lutetium (^{177}Lu). Lutetium (^{177}Lu) chloride is of low acute toxicity. No pharmacological effects on respiration and cardiovascular function were observed in cats following cumulative intravenous doses up to 10 mg/kg, approximately 5 orders of magnitude higher than the anticipated intake of lutetium during PRRT. There were no adverse effects observed in a 90-day dietary administration study with lutetium chloride in rats at dietary doses of up to 1.0%. It is concluded that there are no concerns over the toxicity of the lutetium ion, and the only concerns relate to the radioactivity of the isotope.

Target organs for lutetium (^{177}Lu)-mediated toxicity in animal studies were bone (accumulation of the radionuclide, resulting in osteosarcoma formation), kidney (radiation damage following tubular reabsorption of the radiopeptide) and bone marrow (myelosuppression). Potential strategies to mitigate these toxicities include infusing chelators like trisodium calcium diethylenetriaminepentaacetate or calcium disodium ethylenediaminetetraacetate. Amino acid infusions have often been used to protect the kidneys during clinical use. Potential strategies to mitigate the myelotoxicity include extracorporeal affinity adsorption treatment.

Genotoxicity studies have not been conducted. Radiation emission from radionuclides such as lutetium (^{177}Lu) is expected to cause deoxyribonucleic acid (DNA) damage. Osteosarcomas were observed in mice following intraperitoneal administration at lutetium (^{177}Lu) doses of 185 to 1480 megabequerel (MBq)/kg (28 to 224 gray (Gy)). Osteosarcoma formation was associated with single doses of lutetium (^{177}Lu) ≥ 7.8 Gy and is of potential clinical relevance in the case of inadvertent intravenous administration of non-carrier added lutetium (^{177}Lu) chloride.

No data on reproductive and developmental toxicity are available. The sponsor has proposed Pregnancy Category X,[6] which is appropriate as radiation emission from radionuclides such as lutetium (^{177}Lu) is a known hazard to individuals of reproductive potential.

Clinical

This was a literature-based submission.

Pharmacology

Lutetium chloride is a clear, colourless solution, free of impurities supplied as a radiopharmaceutical precursor. Lutetium (^{177}Lu) is a radioisotope of lutetium, which has no intrinsic pharmacodynamic properties and it should never be administered as a standalone therapy.

Radioactive properties

Lutetium (^{177}Lu) decays to stable hafnium (^{177}Hf), with a half-life of 6.647 days. The decay is via low energy beta and gamma emissions.

[6] **Pregnancy Category X**: Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Pharmacokinetics

The sponsor included a number of dosimetry studies, most of these were using lutetium (^{177}Lu) reacted with the ligand DOTATATE, also known as DOTA-octreotate.

Abuqbeitah et al. (2018)[7] examined the blood clearance and occupational exposure following ^{177}Lu-DOTATATE compared to ^{177}Lu-prostate-specific membrane antigen radionuclide therapy. Four and 6 hours following an infusion of 7.4 gigabecquerel (GBq) ^{177}Lu-DOTATATE, the dose rates were 3.0 ± 2.8 and 2 ± 1.9 microsieverts (μSv)/(h GBq), respectively, at a distance of 1 metre. The total effective dose of 17 caregivers was 100 to 200 μSv; and for nurses 5 μSv, radiopharmacists 4 μSv, physicists and physicians were 2 μSv per patient (see Table 2, below). For ^{177}Lu-DOTATATE, the effective half-life in blood and early elimination phase were 0.31 ± 0.13 and 4.5 ± 1 hours. Overall, it was concluded that blood clearance and radiation exposure for ^{177}Lu-DOTATATE and ^{177}Lu-PSMA (prostate-specific membrane antigen) are similar and both treatment modalities are reasonably reliable for outpatient treatment, since the mean dose rate (2.1 μSv/(h GBq) decreased below the dose rate that allows release of the patient from the hospital (20 μSv/h) after 6 hours at a distance of 1 metre. Moreover, given that the Australian radiation protection framework from the Australian Radiation Protection and Nuclear Safety Agency;[8] indicates that the effective radiation dose limit for the general public is 1 mSV/year or that following acute exposure 3 at up to 50 mSv, no radiation related injury or symptoms were detected, exposure levels received by caregivers are well within the acceptable limits.

Table 2: Abuqbeitah et al. (2018) Study effective dose and finger dose (mean and standard deviation) to the medical staff (μSv); ^{177}Lu-DOTATATE, 17 patients; and ^{177}Lu-PSMA therapy, 23 patients

Staff	Mean dose per patient (μSv)		Finger dose per patient (μGy)		Contribution of annual dose from use of ^{177}Lu to the total occupational annual effective dose (%)	
	DOTATATE	PSMA	DOTATATE	PSMA	DOTATATE	PSMA
Radiopharmacist	4±1.6	4±1.9	33±8	31±7.8	8.0	3.1
Physicist	2±0.4	2±0.8	–	–	2.4	3.3
Physician	2±0.9	2±0.5	–	–	1.5	2.6
Nurse	5±1.1	6±1.3	3±0.3	3±0.25	6.0	7.5
Technologist	3±1.0	3±0.5	–	–	2.4	3.0

Abbreviations: μGy = microgray; ^{177}Lu = lutetium; PSMA = prostate-specific membrane antigen; μSv = microsieverts.

Table sourced from: Abuqbeitah et al. (2018).[7]

Pharmacodynamics

It is a low energy beta-emitter (E_{max} = 0.498 megaelectronvolts (MeV)) allowing specific energy deposition in tumour lesions and low dose delivery to surrounding healthy tissue. The maximum penetration range in tissues in 2.2 mm, mean 0.67 mm, facilitating precise dose localisation.

[7] Abuqbeitah, M. et al. Blood Clearance and Occupational Exposure for ^{177}Lu-DOTATATE Compared to ^{177}Lu-PSMA Radionuclide Therapy, *Radiat Environ Biophys*, 2018; 57(1): 55-61.
[8] Australian Radiation Protection and Nuclear Safety Agency (ARPANSA). Further information is available from the ARPANSA website: https://www.arpansa.gov.au/regulation-and-licensing/regulatory-publications/radiation-protection-series/codes-and-standards.

Efficacy

The use in neuroendocrine tumours was supported by a number of studies, most of these used DOTATATE as the carrier molecule.

Strosberg et al. (2017)[9]

This was a randomised, controlled trial evaluating the efficacy and safety of ^{177}Lu-DOTATATE in patients with advanced, progressive, somatostatin-receptor positive midgut neuroendocrine tumours. This Phase III neuroendocrine tumour therapy trial (known as the NETTER-1 trial) compared ^{177}Lu-DOTATATE with best supportive care (octreotide long-acting repeatable (LAR) 30 mg every month) to octreotide LAR 60 mg every month. This trial was conducted in 41 centres in 8 countries worldwide. Patients who had disease progression according to Response Evaluation Criteria In Solid Tumours (RECIST)[10] version 1.1 on either computed tomography or magnetic resonance imaging over the course of a maximum 3 years during treatment with octreotide LAR (20 to 30 mg every 3 to 4 weeks for at least 12 weeks before randomisation) were eligible. Tumours had to have well differentiated histological features and somatostatin receptors present on all target lesions.

In the ^{177}Lu-DOTATATE group, 7.4 GBq (200 millicurie (mCi)) of ^{177}Lu-DOTATATE was infused intravenously over a period of 30 minutes. Infusions were received every 8 weeks (cumulative radiotherapy 29.6 GBq (800 mCi)) unless there was unacceptable toxicity, centrally confirmed disease progression according to RECIST, the patient was unwilling or unable to continue in trial procedures, the patient withdrew consent, or the patient died.

Of the 229 patients undergoing randomisation, 221 patients received at least one dose of trial treatment (111 in the ^{177}Lu-DOTATATE group and 110 in the control group). The ileum being the primary tumour site in the majority of patients (73%) and most patients (83%) had hepatic metastases, lymph node metastases (62%) or both.

At the time of data cut-off for the primary analysis, 23 events of disease progression or death occurred in the ^{177}Lu-DOTATATE group and 68 such events occurred in the control octreotide only groups. The estimated rate of progression-free survival (PFS) at Month 20 was 65.2% (95% confidence interval (CI): 50.0%, 76.8%) in the ^{177}Lu-DOTATATE group and 10.8% (95% CI: 3.5%, 23.0%) in the control group. There was a 79% lower risk of disease progression or death in the ^{177}Lu-DOTATATE group versus control group.

Strosberg et al. (2018)[11]

This was a follow up study describing the quality of life in subjects from the NETTER-1 trial (see Section: Strosberg et al. (2017), above). Time to deterioration was significantly longer in the ^{177}Lu-DOTATATE arm compared to the octreotide alone arm for global health, physical functioning, role functioning, diarrhoea, pain, body image, disease-related worries and fatigue. The hazard ratio (HR) for global health favouring ^{177}Lu-DOTATATE was 0.41 (95% CI: 0.24, 0.69; $p < 0.001$), with a 22.7-month difference in median time to deterioration between both arms. The HR for physical functioning was 0.52 (95% CI: 0.30,

[9] Strosberg, J.S. et al. Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors, *N. Engl. J. Med*, 2017; 376: 125-135.

[10] The **Response Evaluation Criteria In Solid Tumours (RECIST)** is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

[11] Strosberg, J. et al. Health-Related Quality of Life in Patients with Progressive Midgut Neuroendocrine Tumors Treated with ^{177}Lu-Dotatate in the Phase III NETTER-1 Trial, *J Clin Oncol*, 2018; 36(25): 2578-2584.

0.89; p = 0.015) with a 13.7-month difference. The HR for all functioning was 0.58 (95% CI: 0.35, 0.96; p = 0.030), the HR for diarrhoea was 0.47 (95% CI: 0.26, 0.85; p = 0.011), the HR for pain was 0.57 (95% CI: 0.34, 0.94; p = 0.025).

This author published a number of other studies reporting the outcome in relation to renal insufficiency, impact on liver tumour burden and alkaline phosphatase and target lesion size on outcome.

Paganelli et al. (2020)[12] studied late PFS and overall survival (OS) in a cohort of 43 patients with progressive metastatic neuroendocrine tumours. This was an uncontrolled study, patients received 5 cycles of therapy at intervals of 6 to 8 weeks with either a dose of 18.5 GBq or 27.5 GBq. The median follow-up time was 118 months (range 12.6 to 139.6), the overall median PFS was 59.8 months (95% CI: 29.8, 76.4) and median OS was 82 months (95% CI: 64, 125.6). There was very little difference in outcome between the two different doses. OS decreased with greater tumour burden.

Brabander et al. (2017)[13] reported the efficacy and safety of ^{177}Lu-DOTATATE in 1214 patients treated at the Erasmus Medical Centre in Rotterdam, Netherlands. Patients had neuroendocrine tumour of the primary tumours of the midgut, foregut, hind gut and other sources. An efficacy and survival analysis of 443 patients was provided. The dose was at least 600 mCi (22.2 Gbq). The median follow-up was 78 months from the first day of treatment and most patients were treated with somatostatin analogues. The best objective response rate (ORR) defined as complete response plus partial response according the RECIST 1.1 criteria. The ORR in this patient cohort was 39%, standard deviation was found in 43% of patients and pharmacodynamics was seen in 12% of patients. In patients with midgut neuroendocrine tumours and pancreatic neuroendocrine tumours with pharmacodynamics at Baseline, radiologic disease control was seen in 84% and 81% respectively. For the total group of 443 neuroendocrine tumour patients, the median OS was 63 months (95% CI: 55, 72), the median PFS was 29 months (95% CI: 26, 33) and the median time to progression was 36 months (95% CI: 32, 40).

Two publications were provided to confirm efficacy of ^{177}Lu-DOTATATE when used to retreat patients who relapsed after an initial course.

Safety

An integrated analysis of treatment emergent adverse events from 11 published studies which evaluated safety of ^{177}Lu-DOTATATE given to patients with neuroendocrine tumours was provided in the submission. The most common adverse events amongst patients in the ^{177}Lu-DOTATATE group were nausea (65 patients (59%)) and vomiting (52 patients (47%)). Other common events were fatigue/asthenia, abdominal pain and diarrhoea.

Adverse effects of special interest include:

- myelosuppression 5 to 10% with doses up to 29 GBq, generally short lived;
- myelodysplastic syndrome and acute leukaemia in about 1%;
- decrease in Insulin-like growth factor 1;
- there may be a transient decrease in thyroxine (T4), triiodothyronine (T3) and ovarian function, however these effects were not consistently seen;

[12] Paganelli, G. et al. ^{177}Lu-PRRT in Advanced Gastrointestinal Neuroendocrine Tumors: 10-Year Follow-up of the IRST Phase II Prospective Study, *Eur J Nucl Med Mol Imaging*, 2021; 48(1): 152-160.
[13] Brabander, T. et al. Long-Term Efficacy, Survival, and Safety of [177 Lu-DOTA 0,Tyr 3] OCTREOTATE in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors, *Clin Cancer Res*, 2017; 23(16): 4617-4624.

- high or low serum calcium;
- exacerbation of carcinoid symptoms. In particular in those with high tumour burden;
- intestinal obstruction in those with baseline mesenteric or peritoneal disease.

Additional information

The sponsor included a letter of support from a nuclear medicine expert [information redacted]. In this letter he states that the Peter MacCallum Cancer Centre has been using lutetium obtained through Special Access Scheme (SAS);[14] since 2014. In clinical practice it is combined with DOTATATE or PSMA-617 to treat disseminated gastro-enteropancreatic neuroendocrine tumours, and other tumours with neuroendocrine differentiation including neuroblastoma in children and bronchial carcinoid tumours.

Risk management plan

The sponsor has submitted Australian (AU)-risk management plan (RMP) version 0.1 (dated 18 December 2020; data lock point (DLP) 15 December 2020) in support of this application. In response to a TGA request for information, the sponsor has submitted AU-RMP version 0.1 (dated 3 August 2021; DLP 15 December 2020) in support of its application. At the second round of evaluation, the sponsor has submitted AU-RMP version 0.2 (dated 6 October 2021; DLP 15 December 2020) in support of its application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Use in pregnancy	ü	–	ü	–
	Myelosuppression	ü	–	ü	–
	Myelodysplastic syndrome & acute myeloid leukaemia	ü	–	ü	–
	Renal dysfunction	ü	–	ü	–
	Renal irradiation	ü	–	ü	–
	Hormone release syndromes	ü	–	ü	–
Important potential risks	Tumour lysis syndrome	ü	–	ü	–
	Hepatotoxicity	ü	–	ü	–

[14] The **Special Access Scheme (SAS)** allows certain health practitioners to access therapeutic goods (such as medicines, medical devices or biologicals) that are not included in the Australian Register of Therapeutic Goods (ARTG), for a single patient. Therapeutic goods that are not included in the ARTG (and are not otherwise exempt from being in the ARTG) are described by the TGA as 'unapproved'.

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
	Pituitary and related endocrine effects	ü	–	ü	–
	Use in elderly	ü	–	ü	–
	Hypocalcaemia	ü	–	ü	–
Missing information	Use in lactation	ü	–	ü	–
	Use in children	ü	–	ü	–

- The summary of safety concerns includes 'use in pregnancy' as an important identified risk due to its Pregnancy Category X classification.[6] The safety concerns are acceptable.
- Routine pharmacovigilance activities only are proposed which is acceptable given that the submission is literature-based.
- Routine risk minimisation activities only have been proposed which is acceptable as the medicine will only be administered by specialists in nuclear medicine.

Risk-benefit analysis

Delegate's considerations

Lutetium (^{177}Lu)-DOTATATE (that is, lutetium (^{177}Lu) combined with octreotate) is currently widely used by major public hospitals for the treatment of neuroendocrine cancers.

The use of lutetium for this purpose is well supported by the literature.

The addition of lutetium (^{177}Lu) on the Australian Register of Therapeutic Goods (ARTG) is advantageous over its use under the SAS system as it ensures more tightly controlled systems in place to ensure the product is manufactured accordingly.

Proposed action

In principle, the Delegate is supportive of this application to register lutetium (^{177}Lu) chloride on the ARTG.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Is the sponsor planning to apply for funding through the Medical Services Advisory Committee (MSAC) or Pharmaceutical Benefits Advisory Committee (PBAC)?***

The sponsor and/or affiliate company plan to apply for funding through MSAC within the next 12 months.

2. ***How are patients assessed to determine if their tumours express somatostatin type 2 receptor (SSTR2)? Is having the presence of SSTR2 an absolute requirement for treatment?***

- Patients are assessed through a gallium-68 (^{68}Ga) positron emission tomography scan to see if they have somatostatin receptors (SSTRs). This scan looks at not only the extent of the disease but grade as well (with biopsy). Grade 1 and Grade 2 with metastatic disease are usually considered for peptide receptor radionuclide therapy (PRRT) depending also on symptom burden. Patients with a high symptom burden would be prioritised first (relevant clinical trials are: the NETTER 1 trial;[9] and the CONTROL NETS trial;[15]). Please note that ^{68}Ga treatment is reimbursed via Medical Benefits Scheme.
- Yes, the presence of SSTRs is a requirement for treatment. Without the presence of SSTRs the ^{177}Lu will not bind to the tumours. Patients with high Grade 3 neuroendocrine carcinoma (neuroendocrine carcinoma) generally don't have these receptors and their disease is assessed through fluorodeoxyglucose positron emission tomography scan.

  Furthermore, a new clinical trial is about to be commenced that includes Australian sites (Isotopen Technologien München-the COMPOSE trial) to look at high Grade 2 and high Grade 3 neuroendocrine tumours with SSTR.

  The most relevant guidelines to such treatments are the Clinical Oncology Society of Australia guidelines, which are undergoing a review and current update.[16]

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of lutetium (^{177}Lu) chloride 10 to 200 GBq/mL, radiochemical solution, vial, indicated for:

> *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.*

Specific conditions of registration applying to these goods

- ANSTO lutetium (^{177}Lu) chloride is to be included in the Black Triangle Scheme. The PI and CMI [Consumer Medicines Information] for ANSTO lutetium (^{177}Lu) chloride must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Lutetium (^{177}Lu) AU-risk management plan (RMP) (version 0.2, dated 6 October 2021, data lock point 15 December 2020), included with Submission

[15] CONTROL NETS trial: A parallel group randomised, controlled, multi-centre phase II open label trial with two cohorts testing the combination of capecitabine and temozolomide (CAPTEM) and peptide receptor radionuclide therapy (PRRT) for the treatment of advanced pancreatic or midgut neuroendocrine tumours that are not suitable for surgery. Australian New Zealand Clinical Trials Registry registration number: ACTRN12615000909527. Available at: https://ctc.usyd.edu.au/our-research/research-areas/cancer/cancer-divisions/gastro-intestinal-cancers/in-follow-up/control-nets/.

[16] Clinical Oncology Society of Australia guidelines. Available at: https://www.cosa.org.au/publications/guidelines.aspx.

PM-2020-06691-1-4 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report ([Revision] 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Lutetium (^{177}Lu) chloride approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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