Lutetium (^{177}Lu) oxodotreotide (Lutathera®) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10*	Regimen Code	Reimbursement Status
Treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive-gastroenteropancreatic neuroendocrine tumours (GEP- NETs) in adults.	C16-20, C25, C26	00642a	ODMS 01/02/2021

*Neuroendocrine tumours can occur in a variety of anatomical locations, C16-20 & C25 refer to gastroenterohepatic tumours, where exact location cannot be determined C26 can be used.

TREATMENT:

Lutetium (^{177}Lu) oxodotreotide is administered IV, **once every 8 weeks for 4 infusions.** The infusion interval maybe extended up to 16 weeks in case of dose modifying toxicity (DMT) (See dose modifications).

It should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings which satisfy radiation safety and regulation requirements.

Facilities to treat anaphylaxis MUST be present when lutetium (^{177}Lu) oxodotreotide is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Lutetium (^{177}Lu) oxodotreotide[a]	7,400 MBq	IV infusion	Over approximately 30 to 40 minutes[b]	Every 8 weeks[c]
[a]For renal protection, an intravenous amino acid solution must be administered intravenously over 4 hours, starting 30 minutes before infusion of lutetium (^{177}Lu) oxodotreotide. Please see pre-medication section for suggested amino acid solutions.					
[b]Lutetium (^{177}Lu) oxodotreotide infusion should start 30 minutes after the beginning of the amino acid solution infusion, with an infusion rate of approximately 400 mL/h (this infusion rate is the reference rate; the infusion should start at a lower rate of <100mL/h for the first 5 to 10 minutes and should then be increased depending on the patient's venous status).					
[c]The infusion interval maybe extended up to 16 weeks in case of DMT.					

ELIGIBILITY:

- Indications as above
- Patients ≥18 years
- Well differentiated locally advanced or metastatic mid-gut neuroendocrine tumours that had progressed on standard octreotide treatment
- Previous treatment with long acting somatostatin analogue at a fixed dose for at least 12 weeks prior
- Confirmation of tumour somatostatin receptor overexpression by imaging (scintigraphy or positron emission tomography [PET])
- ECOG 0-2

- Adequate renal, hepatobiliary, cardiac and haematological function

CAUTION:

- Given the mechanism of action and the tolerance profile of lutetium (^{177}Lu) oxodotreotide, caution is recommended in the following cases:
    - Previous external beam radiotherapy involving more than 25% of the bone marrow
    - Severe heart failure defined as class III or IV in the New York Heart Association (NYHA) classification
    - Kidney failure with creatinine clearance < 40 mL/min
    - Impaired haematological function with either Hb < 8 g/dL, platelets < 75 x 10^9/L or leucocytes < 2 x 10^9/L (except lymphopenia)
    - Liver impairment with either total bilirubin > 3 times the upper limit of normal (ULN), regardless of AST level
    - Uncontrolled diabetes mellitus

EXCLUSIONS:

- Hypersensitivity to lutetium (^{177}Lu) oxodotreotide or any of the excipients.
- Patients who are candidates for curativesurgery
- CrCl<30ml/min
- Pregnancy and breastfeeding

PRESCRIPTIVE AUTHORITY:

Therapy Plan:

The therapy plan must be determined by the patient's primary consultant following discussion and agreement with the patient and their carer(s) if required. The primary consultant for this indication is a consultant with specialist interest in the management and treatment of NETs* where the treatment is to be administered in RPII licensed sites where appropriate supporting infrastructure is in place. Consideration should also be given to the broader care and management of patients associated with the use of radionuclides including:

1. The recommendation to treat as agreed at the relevant MDM for NETs.
2. The prescription, administration and oversight of the radionuclide treatment itself.
3. Follow up during/after treatment to ensure safety and to evaluate treatment response and the patient's capacity to continue with the next course of treatment.

*This may be the nuclear medicine consultant/ medical oncologist or other consultant with expertise in the management and treatment of NET with radionuclides.

TESTS:

Baseline tests:

- FBC, renal and liver profile, blood glucose
- Cardiac function (ECHO or MUGA)
- Pregnancy test

Regular tests:

- FBC, renal and liver profile at least once in the 2-4 weeks prior to administration, and shortly before administration. These tests should also be performed every 2 weeks between treatments, every 4 weeks for at least 3 months after the last infusion of lutetium (^{177}Lu) oxodotreotide, and every 3 months for the following year. Renal function as determined by serum creatinine and calculated creatinine clearance must be assessed at baseline, during and at least for the first year after treatment

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Management of severe or intolerable adverse drug reactions may require temporary dose interruption, extension of the dosing interval from 8 weeks up to 16 weeks, dose reduction, or permanent discontinuation of treatment with lutetium (^{177}Lu) oxodotreotide

Haematological:

Table 3: Dose modification lutetium (^{177}Lu) oxodotreotide for haematological toxicity

Toxicity	Severity		Dose Modification
Thrombocytopenia	**Grade**	**Platelets (x10^9/L)**	Withhold dose until complete or partial resolution (Grade 0 to 1). Resume treatment at 3,700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, administer treatment at 7,400 MBq (200 mCi) for next dose. Permanently discontinue treatment for Grade ≥2 thrombocytopenia requiring a treatment delay of 16 weeks or longer
	2	-50-75[a]	
	3	25-49	
	4	<25	
	Recurrent Grade 2, 3 or 4		Permanently discontinue treatment.
Neutropenia	**Grade**	**ANC (x10^9/L)**	
	3	0.5 – 0.99	Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume treatment at 3,700 MBq (100 mCi) in patients with complete or
	4	<0.5	

			partial resolution. If reduced dose does not result in Grade 3 or 4 neutropenia, administer treatment at 7,400 MBq (200 mCi) for next dose. Permanently discontinue treatment for Grade ≥3 neutropenia requiring a treatment delay of 16 weeks or longer.
	Recurrent grade 3 or 4		Permanently discontinue treatment.
Anaemia	**Grade**	**Hgb (g/dL)**	
	3	<8.0[a]	Withhold dose until complete or partial resolution (Grade 0, 1, or 2). Resume treatment at 3,700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 anaemia, administer treatment at 7,400 MBq (200 mCi) for next dose. Permanently discontinue treatment for Grade ≥3 anaemia requiring a treatment delay of 16 weeks or longer.
	4	Life threatening consequences	
	Recurrent Grade 3 or 4		Permanently discontinue treatment.
[a]The same thresholds are also applicable to baseline values at the time of treatment initiation			

Renal and Hepatic Impairment:

Careful consideration to the administration of lutetium (^{177}Lu) oxodotreotide is required since an increased radiation exposure is possible in patients with renal and hepatic impairment.

Table 4: Dose modification of lutetium (^{177}Lu) oxodotreotide in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
The pharmacokinetic profile and safety of lutetium (^{177}Lu) oxodotreotide in patients with severe renal impairment or end-stage renal disease have not been studied. Treatment with lutetium (^{177}Lu) oxodotreotide in patients with severe kidney failure (CrCl <30 mL/min) is contraindicated. Treatment with lutetium (^{177}Lu) oxodotreotide in patients with CrCl <40 mL/min at baseline is not recommended. No dose adjustment is recommended for renally impaired patients with CrCl ≥40 mL/min. Renal function should be more frequently monitored during treatment as these patients may be at greater risk of toxicity. For additional details about the treatment of patients with renal toxicity, see Table 5	No dose adjustment is recommended for patients with mild or moderate hepatic impairment The pharmacokinetic profile and safety of lutetium (^{177}Lu) oxodotreotide in patients with severe hepatic impairment (bilirubin >3x ULN, regardless of AST) have not been studied therefore these patients should only be treated with lutetium (^{177}Lu) oxodotreotide after careful benefit-risk assessment. For additional details about the treatment of patients with mild to moderate hepatic toxicity, please see Table 5.

Table 5: Dose Modification of Lutetium (^{177}Lu) oxodotreotide for non-haematologic toxicity

Toxicity	Severity	Dose Modification
Renal toxicity	Defined as: • CrCl < 40 mL/min[a,b] or • 40% increase in baseline serum creatinine	Withhold dose until complete resolution or return to baseline. Resume treatment at 3,700 MBq (100 mCi) in patients with complete resolution or return to baseline. If reduced dose does not result in renal toxicity, administer treatment at 7,400 MBq (200 mCi) for next dose.

	or • 40% decrease in baseline CrCl[b]	Permanently discontinue treatment for renal toxicity requiring a treatment delay of 16 weeks or longer
	Recurrent renal toxicity	Permanently discontinue treatment
Hepatotoxicity	Defined as: • Bilirubinaemia > 3 times the upper limit of normal (Grade 3 or 4)[c] or • Albuminaemia[c] less than 30 g/L with international normalised ratio (INR) >1.5	Withhold dose until complete resolution or return to baseline. Resume treatment at 3,700 MBq (100 mCi) in patients with complete resolution or return to baseline. If reduced treatment dose does not result in hepatotoxicity, administer treatment at 7,400 MBq (200 mCi) for next dose. Permanently discontinue treatment for hepatotoxicity requiring a treatment delay of 16 weeks or longer.
	Recurrent hepatotoxicity	Permanently discontinue treatment
Any other CTCAE* Grade 3 or Grade 4 toxicity	Grade 3 or 4	Withhold dose until complete or partial resolution (Grade 0 to 2). Resume treatment at 3,700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in Grade 3 or 4 toxicity, administer treatment at 7,400 MBq (200 mCi) for next dose. Permanently discontinue treatment for Grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer
	Recurrent Grade 3 or 4	Permanently discontinue treatment
[a]The same thresholds are also applicable to baseline values at the time of treatment initiation		
[b]calculate using Cockcroft-Gault with actual body weight		
[c]If the same thresholds are seen at baseline, treatment initiation to be considered after benefit risk assessment		
*CTCAE: Common Terminology Criteria for Adverse Events, National Cancer Institute		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate **(Refer to local policy).**

PREMEDICATIONS:

- Premedication with 5-HT_3 antagonist should be used to help prevent nausea/vomiting associated with the amino acid infusion, should be commenced at least 30 minutes prior to the start of amino acid solution infusion to reach the full antiemetic efficacy.
  Depending on the amino acid solution, additional antiemetics including NK1 inhibitors and H_2 receptor antagonists may be required.
  Note: Corticosteroids should not be used as first-line anti-emetics (see drug interactions section below) but may be used in cases of refractory nausea/vomiting.
- For renal protection, an intravenous amino acid solution must be administered intravenously over 4 hours, starting 30 minutes before infusion of lutetium (^{177}Lu) oxodotreotide. The composition of the standard amino acid solution is detailed in Table 6. Alternatively, some commercially available amino acid solutions can be used if compliant with the specification described in Table 7 below.
- An amino acid solution containing just lysine and arginine in the amounts specified in Table 6 is considered the medicinal product of choice, due to the lower total volume to be infused and lower osmolality.

Table 6: Composition of the standard amino acid solution

Compound	Amount
L-Lysine HCl	25g*
L-Arginine HCl	25g**
NaCl 0.9% solution for injection, or water for injection	1L
*equivalent to 20g lysine **equivalent to 20.7g arginine	

Table 7. Specification of commercially available amino acid solutions

Characteristic	Specification
L-Lysine HCl content	Between 18 and 25g*
L-Arginine HCl content	Between 18 and 25g**
Volume	1L to 2L
Osmolality	<1,200 mOsmol/kg
*equivalent to 14.4 to 20g lysine **equivalent to 14.9 to 20.7g arginine	

OTHER SUPPORTIVE CARE:

- Concomitant use of somatostatin analogues may be needed for disease symptom control. Administration of long acting somatostatin analogues (SSAs) should be avoided within 30 days prior to the administration of lutetium (^{177}Lu) oxodotreotide. If necessary to control carcinoid syndrome, patients may be treated with short acting somatostatin analogues during the 4 weeks preceding lutetium (^{177}Lu) oxodotreotide administration, until 24 hours before the administration of lutetium (^{177}Lu) oxodotreotide. Long acting SSA can be administered 24 hours after administration of lutetium (^{177}Lu) oxodotreotide, can also be given on the same evening following luterium (177Lu) oxodotreotide if patient is treated as a day case.
- Local Radiation Protection rules should be followed when administering lutetium (^{177}Lu) oxodotreotide.
- In patients with functioning NETs, particularly with high tumour burden, administration of lutetium (^{177}Lu) oxodotreotide may precipitate carcinoid crisis or other neuroendocrine hormonal crisis. Treating clinicians should be aware of this risk and local guidelines for carcinoid crisis management should be followed.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings **(Refer to local policies).**
- **Risk from radiation exposure:** 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.

- **Myelosuppression**: Blood counts must be monitored at baseline and during treatment and until resolution of any eventual toxicity. Patients with impaired haematological function and patients who have received prior chemotherapy or external beam radiotherapy may be at higher risk of haematological toxicity during treatment.
- **Myelodysplastic syndrome and acute leukaemia:** Late-onset myelodysplastic syndrome (MDS) and acute leukaemia (AL) have been observed after treatment with lutetium (^{177}Lu) oxodotreotide. 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 protection and renal impairment:** Lutetium (^{177}Lu) oxodotreotide 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 acids solution will help to decrease reabsorption of lutetium (^{177}Lu) oxodotreotide through the proximal tubules, resulting in a significant reduction in the kidney radiation dose. It is not recommended to decrease the amount of amino acid solution in case of lutetium (^{177}Lu) oxodotreotide dose adjustments. Patients should be encouraged to empty their bladder as frequently as possible during the administration of amino acids and the hours after administration.
- **Hepatic toxicity:** Many patients referred for lutetium (^{177}Lu) oxodotreotide therapy have hepatic metastases and it may be common to observe patients with altered baseline liver function. Patients with hepatic metastases 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.
- **Hypersensitivity:** Cases of hypersensitivity reactions (including isolated angioedema events) have been reported. In the event of serious hypersensitivity reactions, treatment should be discontinued immediately.
- **Tumour lysis syndrome: T**umour lysis syndrome has been reported following therapy with medicines containing lutetium (^{177}Lu) oxodotreotide. Patients with a history of renal insufficiency and high tumour burden may be at greater risk and should be treated with increased caution. Renal function as well as electrolyte balance should be assessed at baseline and during treatment.
- **Neuroendocrine hormonal crises:** Crises due to excessive release of hormones or bioactive substances may occur following treatment with lutetium (^{177}Lu) oxodotreotide, therefore 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, recommended treatments are intravenous high dose somatostatin analogues, intravenous fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and/or vomiting.
- **Embryo-fetal toxicity:** Lutetium (^{177}Lu) oxodotreotide can cause foetal harm when administered to pregnant women. During treatment with lutetium (^{177}Lu) oxodotreotide and for a minimum of 6 months after the end of treatment, appropriate measures must be taken to avoid pregnancy; this applies to both male and females.
- **Specific warnings and precautions regarding the co-administered renal protective amino acid solution**
    - **Hyperkalaemia**: 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. Hyperkalaemia must be corrected accordingly before starting the infusion. In case of pre-existing clinically significant hyperkalaemia, a second

monitoring prior to amino acid solution infusion must confirm that hyperkalaemia has been successfully corrected. The patient should be monitored closely for signs and symptoms of hyperkalaemia
    - **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. Patients with severe heart failure 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
- **Sodium content:** This medicinal product contains up to 3.5 mmol (81.1 mg) sodium per dose. This should be taken into consideration in-patient on controlled sodium diet.

DRUG INTERACTIONS:

- Somatostatin and its analogues competitively bind to somatostatin receptors. 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 during the 4 weeks until 24 hours preceding lutetium (^{177}Lu) oxodotreotide administration.
- There is some evidence that corticosteroids can induce down-regulation of SST2 receptors. Therefore, repeated administration of high-doses of glucocorticosteroids should be avoided during lutetium (^{177}Lu) oxodotreotide treatment. Patients with a history of chronic use of glucocorticosteroids should be carefully evaluated for sufficient somatostatin receptor expression. It is not known if there is of interaction between glucocorticosteroids used intermittently for the prevention of nausea and vomiting during lutetium (^{177}Lu) oxodotreotide administration. Therefore, glucocorticosteroids 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 lutetium (^{177}Lu) oxodotreotide infusion.
- The absence of inhibition or significant induction of the CYP450 enzymes, the absence of specific interaction with P-glycoprotein (efflux transporter) as well as OAT1, OAT3, OCT2, OATP1B1, OATP1B3, OCT1 and BCRP transporters in pre-clinical studies suggest that lutetium (^{177}Lu) oxodotreotide has a low probability of causing significant other drug-drug interactions.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Lutathera® Treatment Procedure Guide: https://www.hpra.ie/img/uploaded/swedocuments/81eccd02-ca1c-4df2-b55f-b9a1e69e5ebd.pdf

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2. Strosberg |J et al. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumours Treated With 177Lu-Dotatate in the Phase III NETTER-1 Trial. Journal of Clinical Oncology 2018. 36-25) 2578-2584
3. Lutetium (^{177}Lu) oxodotreotide (Lutathera®) Summary of Product characteristics. Accessed August 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	19/09/2023		Dr Nicola Hughes and Dr Mark Doherty
1a	28/05/2024	Updated ICD-10 code	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.