Cost-effectiveness of lutetium (^{177}Lu) oxodotreotide (Lutathera®) for the treatment of unresectable or metastatic, progressive, well differentiated (Grade 1 and Grade 2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.

The NCPE has issued a recommendation regarding the cost-effectiveness of lutetium (^{177}Lu) oxodotreotide (Lutathera®). Following assessment of the Applicant's submission, the NCPE recommends that lutetium (^{177}Lu) oxodotreotide (Lutathera®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Advanced Accelerator Applications) economic dossier on the cost effectiveness of lutetium (^{177}Lu) oxodotreotide (Lutathera®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists, and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe, and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health, or social care services.

National Centre for Pharmacoeconomics **February 2020**

Summary

In May 2019, Advanced Accelerator Applications submitted a dossier of clinical, safety, and economic evidence for lutetium (^{177}Lu) oxodotreotide (Lutathera®) for the treatment of unresectable or metastatic, progressive, well-differentiated (Grade 1 and Grade 2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NET) in adults.

In clinical practice, GEP-NETs are anatomically classified according to their location as either gastrointestinal (GI-NET) or pancreatic (P-NET). Patients with midgut-NETs comprise a subcohort of the population with GI-NETs. GEP-NETs can also be classified as either functional or non-functional. Non-functional GEP-NETs are generally symptomless but may present with symptoms related to tumour mass. Functional GEP-NETs may cause clinical conditions due to the discharge of specific hormones. For patients with unresectable, progressive GI-NETs, treatment guidelines, supported by clinical opinion, recommend first-line treatment with a somatostatin analogue (SSA) followed by subsequent treatment with either peptide receptor radionuclide therapy (PRRT) or everolimus. For patients with unresectable, progressive P-NETs, clinical opinion suggests that in Irish clinical practice, PRRT would be reserved as a third-line option following treatment with a SSA and either everolimus or sunitinib.

Lutetium (^{177}Lu) oxodotreotide is the first approved PRRT and is a radiopharmaceutical product. It has a high affinity for subtype 2 somatostatin receptors and is thus able to target, and bind to, malignant cells overexpressing these receptors. Lutathera® is available as a 370MBq/ml solution for intravenous (IV) infusion; the total amount of radioactivity per single dose vial is 7,400MBq. The recommended treatment regimen consists of four infusions of 7,400MBq each. The recommended interval between each administration is eight weeks. Patients receiving lutetium (^{177}Lu) oxodotreotide require premedication with an antiemetic; they also require concomitant treatment with an IV amino acid solution to protect their kidneys.

1. Comparative effectiveness of lutetium (^{177}Lu) oxodotreotide

Clinical trial evidence supporting product registration was derived from two main studies: NETTER-1 and ERASMUS. NETTER-1 was a phase III randomised, controlled clinical trial comparing lutetium (^{177}Lu) oxodotreotide to high dose octreotide long-acting release (LAR) in patients with inoperable, progressive, midgut-NET tumours of the small bowel. Patients (n=229) were randomised to receive either lutetium (^{177}Lu) oxodotreotide (n=116) at a dose of 7,400MBq every eight weeks (four intravenous infusions, plus best supportive care including octreotide LAR administered intramuscularly at a dose of 30mg) (treatment arm), or octreotide LAR 60mg (n=113) via intramuscular injection once every four weeks (control arm) until the final overall analysis of progression-free survival (PFS), unless the patient progressed or died. A statistically significant increase in PFS was observed in the treatment arm compared to the control arm (hazard ratio (HR) 0.21 95% CI 0.14 to 0.33; p<0.0001). The median PFS in the treatment arm was 28.4 months (95% CI 25.4 to not reached) versus 8.5 months (95% CI 5.8 to 11) in the control arm. Overall survival (OS) data remains immature. The population of interest in the NETTER-1 trial was patients with midgut-NET tumours, which is a subcohort of the population with GI-NETs. The Review Group noted that the populations eligible for treatment under the product license for lutetium (^{177}Lu) oxodotreotide are patients with GI-NETs and P-NETs; it does not distinguish patients with midgut-NETs as a separate population.

ERASMUS was a single-centre, open-label, non-randomised phase I/II study. It investigated the efficacy of lutetium (^{177}Lu) oxodotreotide in patients with somatostatin receptor positive tumours. Individuals with neuroendocrine tumours other than GEP-NETs were eligible for inclusion in the study. Although 1,214 patients were recruited, efficacy results were reported only for the Dutch cohort (n=811) because of loss to follow-up with patients of other nationalities (n=403). For this evaluation, efficacy analyses pertain to a subgroup of the Full Analysis Set (FAS). This subgroup (FAS Dutch population with GEP-NETs; n=360) represents the Dutch cohort of patients enrolled with GEP-NETs, and who had tumour measurements documented at baseline. A proportion of these patients (n=19) also had bronchial NETs. Median PFS and OS in the FAS Dutch population with GEP-NETs were 28.5 months (95% CI 24.8 to 31.4) and 61.2 months (95% CI 54.8 to 67.4), respectively.

As no direct clinical trial evidence was available comparing lutetium (^{177}Lu) oxodotreotide with either everolimus or sunitinib in the relevant populations of GI-NETs and P-NETs, evidence synthesis was undertaken. Matching adjusted indirect treatment comparisons (MAICs) were conducted by the Applicant to compare treatment efficacy of lutetium (^{177}Lu) oxodotreotide and everolimus in both the populations with GI-NETs and P-NETs, and also to compare lutetium (^{177}Lu) oxodotreotide with sunitinib in the population with P-NETs. Data from ERASMUS was used to inform treatment efficacy of lutetium (^{177}Lu) oxodotreotide for all comparisons. Data from the RADIANT-3 (everolimus vs. placebo; population with P-NETs) and RADIANT-4 (everolimus vs. placebo; population with GI-NETs) trials was used to inform everolimus efficacy in the populations with P-NETs and GI-NETs, respectively. Data from the NCT00428597 trial (sunitinib vs. placebo; population with P-NETs) was used to inform the efficacy of sunitinib in the population with P-NETs. The results of the MAICs suggested that lutetium (^{177}Lu) oxodotreotide demonstrated improvements in survival compared to everolimus and sunitinib. However, important limitations to the clinical evidence synthesis were identified by the Review Group. Limitations that were of considerable concern included the small effective sample sizes following reweighting of data, high residual risk of bias, issues of heterogeneity between patient populations, and omission of prognostic factors such as tumour grade and functionality as covariates for matching. The outcomes of the MAICs are highly uncertain and it is, therefore, not possible to definitively conclude that lutetium (^{177}Lu) oxodotreotide confers true survival benefits over everolimus and sunitinib in patients with GEP-NETs.

2. Safety of lutetium (^{177}Lu) oxodotreotide

Safety data pertaining to lutetium (^{177}Lu) oxodotreotide is based on combined data from the NETTER-1 (lutetium (^{177}Lu) oxodotreotide group [n=134]) and ERASMUS (n=811) trials (including all patients who received at least one dose of study drug). In the pooled safety analysis, very common adverse events (>1/10) reported include thrombocytopenia (25%), lymphopenia (22.3%), anaemia (13.4%) and pancytopenia (10.2%), decreased appetite (13.4%), nausea (58.9%), vomiting (45.5%), and fatigue (27.7%). The European Medicines Agency (EMA) has mandated continued monitoring and collection of safety data with particular emphasis on specific identified and potential risks. A post authorisation safety study, to investigate the risk of secondary malignancies, has also been requested.

3. Cost effectiveness of lutetium (^{177}Lu) oxodotreotide

A partitioned-survival model was developed to investigate the cost-effectiveness of lutetium (^{177}Lu) oxodotreotide. Data from NETTER-1, ERASMUS, and the MAICs were used to inform the model. A time horizon of 36 years was applied. The model comprised three mutually exclusive health states: progression-free, progressed disease, and death. Patients entered the model in the progression-free state and their transition to the other health states was unidirectional. The Applicant conducted separate cost-effectiveness analyses for three different populations, depending on location of the GEP-NET:

1. Midgut-NET
2. GI-NET and
3. P-NET

The Applicant considered the relevant comparators to lutetium (^{177}Lu) oxodotreotide to be high dose octreotide LAR 60mg for the population with midgut-NETs, everolimus for the population with GI-NETs, and everolimus and sunitinib for the population with P-NETs. The Review Group had concerns regarding the choice of relevant comparator for the population with midgut-NETs. Midgut-NETs are included within the anatomical classification of GI-NET and are not treated as a separate population in the product license for Lutathera®. It is likely, that in clinical practice, patients with midgut-NETs would be treated according to GI-NET guidelines, which recommends a SSA first-line followed by treatment with either everolimus or PRRT. Therefore, the Review Group considered that everolimus was the more relevant comparator to lutetium (^{177}Lu) oxodotreotide in the population with midgut-NETs, and not octreotide LAR 60mg.

Model outcomes included costs per quality adjusted life year (QALY). All costs were estimated based on the proportion of patients in each health state at a given time. The Applicant included drug acquisition, administration, monitoring, and adverse event costs in their analyses. Costs for subsequent treatment were not included. A once-off terminal care cost was applied to patients on entry to the death state. EQ-5D-3L utility values were derived by mapping data obtained from a GEP-NET specific patient register, and also from the ERASMUS study, using an algorithm by Longworth et al.

For each population, treatment effectiveness was informed by parametric extrapolation of survival outcomes taken from the clinical evidence. The limitations associated with the clinical evidence synthesis compounded the uncertainty associated with projected long-term survival outcomes. Final costs and outcomes for each treatment were determined by these projected outcomes. The Review Group advises that the incremental cost-effectiveness ratios (ICERs) generated by the economic model be interpreted with caution, and this uncertainty should be considered in the decision-making process.

The Review Group made several changes to derive their adjusted base case:

1. Incorporation of age-related mortality
2. An assumption that, for the comparison of lutetium (^{177}Lu) oxodotreotide versus octreotide LAR 60mg in the population with midgut-NETs, 30% of patients (representing the estimated proportion of patients with functional NETs) in the lutetium (^{177}Lu) oxodotreotide arm receive concomitant octreotide LAR 30mg every four weeks.

The product license for Lutathera® contains a special warning advising against concomitant use of somatostatin analogues. However, patients in the lutetium (^{177}Lu) oxodotreotide arm of the NETTER-1 trial were permitted to receive octreotide LAR 30mg every four weeks for symptom alleviation. Clinical opinion to the Review Group also suggests that it is likely that a proportion of patients, most likely those with functional NETs, will receive concomitant treatment with a long-acting SSA.

The NCPE Review Group's adjusted ICERs and the Applicant's base-case ICERs are presented in Table 1 and Table 2, respectively. The Review Group highlights the significant uncertainty, and its low confidence in these estimates, as a true reflection of the likely expected relative-effectiveness and cost-effectiveness of lutetium (^{177}Lu) oxodotreotide in Irish clinical practice.

Table 1: NCPE Review Group adjusted base case analysis*

Treatment	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Midgut-NET population			
Octreotide LAR 60mg Lutetium (^{177}Lu) oxodotreotide	60,219	1.21	49,812
GI-NET population			
Everolimus Lutetium (^{177}Lu) oxodotreotide	39,822	1.17	34,012
P-NET population			
Everolimus Lutetium (^{177}Lu) oxodotreotide	56,697	1.87	30,360
Sunitinib Lutetium (^{177}Lu) oxodotreotide	45,698	2.58	17,745

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2: Applicant base case ICERs*

Treatment	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Midgut-NET population			
Octreotide LAR 60mg Lutetium (^{177}Lu) oxodotreotide	49,139	1.23	40,035
GI-NET population			
Everolimus Lutetium (^{177}Lu) oxodotreotide	40,062	1.18	33,810
P-NET population			
Everolimus Lutetium (^{177}Lu) oxodotreotide	56,970	1.88	30,275
Sunitinib Lutetium (^{177}Lu) oxodotreotide	45,804	2.60	17,640

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio
* A discount rate of 4% on costs and outcomes is applied. The Review Group identified a number of errors in the submitted model, which were rectified to produce the results shown. Figures in the table are rounded and so calculations will not be directly replicable.

Probabilistic sensitivity analyses (PSA) were conducted, by both the Applicant and the Review Group, to investigate parameter uncertainty. Whilst both sets of analyses suggested that the probability of cost-effectiveness of lutetium (^{177}Lu) oxodotreotide is favourable in both populations, the Review Group considers that the high level of uncertainty associated with the outcomes of the MAICs is not sufficiently captured within the economic model. The

results of the PSA should be interpreted with caution as the probability of cost-effectiveness is likely being overestimated. The PSA conducted by the Review Group suggested that the probability of cost-effectiveness of lutetium (^{177}Lu) oxodotreotide at the cost-effectiveness threshold of €45,000 per QALY in the population with GI-NETs is 98%. The probability of cost-effectiveness at the cost-effectiveness threshold of €45,000 per QALY, in the population with P-NETs for lutetium (^{177}Lu) oxodotreotide versus everolimus, and lutetium (^{177}Lu) oxodotreotide versus sunitinib, is 95% and 99.9%, respectively.

4. Budget impact of lutetium (^{177}Lu) oxodotreotide

Lutetium (^{177}Lu) oxodotreotide is formulated as a 370MBq/ml solution for intravenous infusion. One single use vial contains 7,400MBq. The total cost to the HSE (incorporating mandatory rebate) per single use vial is €23,500 including VAT; the total cost to the HSE per treatment course is €94,000 including VAT.

The Review Group amended the Applicant's estimated number of eligible patients by applying Irish incidence and prevalence rates for GEP-NETs, and altering the assumption relating to the proportion of GEP-NET patients with somatostatin receptor positive tumours. The Applicant assumed that this would apply to 60% of patients. However, literature indicates that this figure is closer to 90%. The eligible patient population was subsequently estimated to be 121 patients in year one increasing to 124 patients by year five. Using these updated figures, and applying predicted market share values provided by the Applicant, the Review Group estimates the gross budget impact to be €5.6million in year one increasing to €9.1 million by year five. The five-year cumulative gross budget impact is estimated to be €37.7 million. The Applicant estimated a five-year cumulative gross budget impact of €31.4 million.

The net budget impact assumes lutetium (^{177}Lu) oxodotreotide will replace other drugs as potential second and third line treatment options. The Review Group estimate the net budget impact to be €2.76 million in year one increasing to €4.8 million in year five. The five-year cumulative net budget impact is estimated to be €19.4 million. The Applicant estimated a five-year cumulative net budget impact of €16.4 million.

Administration of lutetium (^{177}Lu) oxodotreotide is associated with additional costs including the cost of concomitant administration of amino acid solution and anti-emetic therapy, and the expertise of a nuclear medicine specialist. Concomitant octreotide is not included. The Review Group estimates that when these additional costs are incorporated, the cumulative five-year net budget impact increases to €20.7 million. The Applicant had estimated this figure to be €17.5 million.

5. Patient Organisation submissions

A patient organisation submission was received from NET Patient Network Ireland, and is included in the full report to the HSE.

6. Conclusion

The NCPE recommends that lutetium (^{177}Lu) oxodotreotide (Lutathera®) not be considered for reimbursement*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.