# **Medical Services Advisory Committee (MSAC) Public Summary Document**

Application No. 1744 – 177Lutetium-DOTA-octreotate treatment for advanced neuroendocrine neoplasms with high somatostatin receptor expression

**Applicant: Applied Molecular Therapies (AMT) Pty Ltd**

**Date of MSAC consideration: 1-2 August 2024**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

## 1. Purpose of application

An application was received from Applied Molecular Therapies (AMT) Pty Ltd by the Department of Health and Aged Care, requesting Medicare Benefits Schedule (MBS) listing of 177Lutetium (no carrier added)-DOTA-octreotate (177Lu (nca)-DOTA-octreotate) for the treatment of advanced neuroendocrine neoplasms (NETs) with high somatostatin receptor (H-SSTR) expression. As noted in the ratified PICO (Population, Intervention, Comparator, Outcomes), NETs have been recently reclassified as neuroendocrine neoplasms (NENs), and these terms are used interchangeably in the assessment report. In general, the term NEN is preferred except when referring to a specific reference, study, or trial inclusion/exclusion criteria, where the term NET may be used.

The application also requested a new MBS listing for 68Gallium (Ga)-DOTA-octreotate SSTR-positron emission tomography (PET)/computed tomography (CT)—68Ga-DOTA-octreotate PET/CT—to determine eligibility for 177Lu (nca)-DOTA-octreotate treatment, as well as for monitoring the post-treatment effect of 177Lu (nca)-DOTA-octreotate treatment.

The original application requested a restriction to the ‘nca’ product. However, as noted by the PICO Advisory Sub-Committee (PASC) there is no available evidence to support the superior safety and effectiveness of the nca product compared to the ‘carrier added’ (ca) product to justify restriction of the benefit to the nca product. Therefore, , the intervention described in this assessment report refers to the more generic 177Lu-DOTA-octreotate.

Furthermore, the original application included the requirement for an additional test, 18F-FDG (fluorodeoxyglucose) PET/CT (FDG PET/CT), to assist in therapeutic decision-making for some patients. The application requested the amendment of existing MBS item 61612 for whole body FDG PET study to include assessing eligibility for 177Lu-DOTA-octreotate treatment. This item is used for initial staging of rare or uncommon cancers for a patient considered suitable for active therapy. PASC considered that existing item MBS 61612 would not require amendment, as NENs are considered rare or uncommon cancers.

## 2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its advice on the public funding of 1) 177Lutetium Octreotate (177Lu-DOTA-octreotate) treatment of advanced neuroendocrine neoplasms (NENs) with high somatostatin receptor (H-SSTR) expression and 2) whole body 68Gallium (Ga)-DOTA-octreotate SSTR-positron emission tomography (PET)/computed tomography (CT) (68Ga-DOTA-octreotate PET/CT) to identify those eligible for 177Lu-DOTA-octreotate.

MSAC accepted the high clinical need for this population with advanced disease. MSAC also noted there is an equity of access issue as the proposed intervention is standard of care in Australian practice and some patients are currently paying privately for the treatment or are receiving the treatment funded through the Department of Veterans' Affairs.

MSAC considered the evidence base and the additional perspectives comparing 177Lu-DOTA-octreotate and Lutathera® (177Lu-DOTATATE). MSAC noted that the assessment assumed noninferiority of 177Lu-DOTA-octreotate and Lutathera® (177Lu-DOTATATE), and therefore assumed that the randomised controlled trial (RCT) data presented for Lutathera® (177Lu-DOTATATE) would be relevant to 177Lu-DOTA-octreotate. MSAC considered that whilst it appeared that the products may be two formulations of the same active compound [(Tyr3)Octreotate-Dota-Lu, i.e., 177Lu-DOTATATE], no reliable data were presented in the assessment to establish whether or not the products have similar chemical structures and/or biodistribution - characteristics which are expected to affect the relative efficacy and safety of the products.

MSAC deferred its advice and requested that further consultation is required to ascertain the extent of similarity of the chemical structure of 177Lu-DOTA-octreotate and Lutathera® (177Lu-DOTATATE) as this has implications for whether the two products have similar biodistribution and therefore similar efficacy and safety. MSAC advised that if the similarity of chemical structure between the two products is not adequately established, then additional evidence is required to establish similar biodistribution, efficacy and safety between the two products. If the chemical similarity of the two products cannot be established, MSAC requested that a more comprehensive assessment of the efficacy and safety of 177Lu-DOTA-octreotate and Lutathera® (177Lu-DOTATATE) be conducted in order to demonstrate that the two products are noninferior in terms of health outcomes. Specifically, MSAC noted that published observational data (including studies from Australia) of these products were not included in the assessment and that this evidence was likely to be relevant to the Committee in providing its advice.

MSAC foreshadowed it was of a mind to support public funding if the noninferiority between 177Lu-DOTA-octreotate and Lutathera® (177Lu-DOTATATE) products was subsequently accepted. This was because MSAC concluded from the evidence presented that 177Lu-DOTATATE, and thus 177Lu-DOTA-octreotate if noninferiority was subsequently accepted, was acceptably safe and effective compared with standard care and despite limitations in the economic evaluation, 177Lu-DOTA-octreotate was acceptably cost-effective.

MSAC noted the patent related issues raised during the consultation process. MSAC referred to its Terms of Reference and concluded that patent related matters would require consideration by Government prior to any decision to list the MBS items as a result of this application.

| Consumer summary |
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| This is an application from Applied Molecular Therapies requesting Medicare Benefits Schedule (MBS) listing of 177Lutetium (no carrier added [nca])-DOTA-octreotate (177Lu [nca]-DOTA-octreotate) for the treatment of advanced neuroendocrine neoplasms with high somatostatin receptor expression. This application also requests amendment of existing MBS item 61647 (68Gallium[Ga]-DOTA-octreotate SSTR positron emission tomography [PET] / computed tomography [CT]) to determine eligibility for therapy and/or to monitor response to therapy.  Neuroendocrine neoplasms or tumours are a rare type of cancer that form in neuroendocrine cells, which are found throughout the body. Neuroendocrine cells are part of the neuroendocrine system, a network of glands and nerve cells that make hormones and release them into the bloodstream. Neuroendocrine tumours cause the cells to release more hormones than normal, which can worsen the person’s quality of life and, with high-grade tumours, affect organ function and lead to death.  Some neuroendocrine tumour cells have specific spots on their surface called somatostatin receptors. The receptors can be detected by a special type of scan (PET/CT scan). If the scan finds that a patient’s tumour cells are found to have a high number of somatostatin receptors, they may be eligible for a new treatment containing Lutetium. Lutetium is a radioactive chemical. The treatment containing Lutetium is designed to stick to the somatostatin receptors on the surface of the tumour cells. The Lutetium is then able to enter the tumour cell and kill it. The number of doses of the treatment a person needs depends on the grade or severity of their cancer.  The applicant’s product is called 177Lutetium(nca)-DOTA-octreotate. After the Lutetium in the product name, you may notice the wording ‘(nca)’. This is an abbreviation for “no carrier added” which means that the treatment is free from byproducts of the production process. However, whether a carrier is added or not does not affect how well the treatment works.  177Lu-DOTA-octreotate treatment has been used in Australia for the past 10 years. It is currently funded for certain people through the Department of Veterans’ Affairs, or other people pay for it privately.  MSAC acknowledged the high clinical need for this therapy, and that it has been used for several years in Australia and is considered standard of care for patients with neuroendocrine tumours. However, all the evidence presented in the application was for 177Lu-DOTATATE, not 177Lu-DOTA-octreotate (the applicant’s product). Although the evidence suggested that 177Lu-DOTA-octreotate is more effective and just as safe as other treatments and is good value for money, this was based on the assumption that 177Lu-DOTA-octreotate was chemically similar to 177Lu-DOTATATE or has the same impacts in terms of the uptake and delivery of Lutetium in the human body and MSAC could not be sure that this assumption was warranted. MSAC wanted to be certain that 177Lu-DOTATATE and 177Lu-DOTA-octreotate are chemically similar and/or have the same effects on the body before it can be assumed that the evidence presented for 177Lu-DOTATATE is also applicable to the applicant’s product. Therefore, MSAC could not make a decision without first seeking advice from an expert such as a radiochemist. Also, MSAC noted that some studies had been omitted from the assessment report. This included studies which were focused on the applicant’s product rather than 177Lu-DOTATATE, so it requested that all such evidence be included for consideration before it made its decision.  MSAC’s advice to the Commonwealth Minister for Health and Aged Care  MSAC deferred its advice on MBS listing of 177Lu (nca)-DOTA-octreotate treatment for advanced neuroendocrine neoplasms with high somatostatin receptor expression. The evidence presented was for another product, 177Lu-DOTATATE. Although 177Lu-DOTA-octreotate appeared to be more effective and just as safe as other treatments and has good value for money, this was based on the assumption that it is chemically similar and/or has the same effects on the body as 177Lu-DOTATATE. Therefore, MSAC could not make a decision without first seeking advice from a radiochemist. MSAC also requested that all published studies be included in the application.  If the products are found to be chemically similar and/or have the same effects on the body and MSAC approves MBS listing, MSAC advised that uptake and usage should be reviewed after 12 months. Patient out-of-pocket costs should also be monitored. |

## 3. Summary of consideration and rationale for MSAC’s advice

MSAC noted that this application from Applied Molecular Therapies Pty Ltd was requesting Medicare Benefits Schedule (MBS) listing of 177Lutetium (no carrier added)-DOTA-octreotate (177Lu (nca)-DOTA-octreotate) for the treatment of advanced neuroendocrine neoplasms (NENs) with high somatostatin receptor (H-SSTR) expression. The application was also requesting amendment of existing MBS item 61647 (68Gallium [Ga]-DOTA-octreotate SSTR positron emission tomography [PET] / computed tomography [CT]) to determine eligibility for therapy and/or to monitor response.

MSAC noted that NENs are a heterogenous tumour type with varied behaviour. Some are functional and release hormones (e.g. insulin, serotonin, catecholamines) that can be life-threatening. The only cure is surgical resection, but NENs often present late when the disease is unresectable (e.g. due to metastatic disease). MSAC noted that treatment of NENs is not “one size fits all” especially regarding the timing of different treatments.

MSAC noted that consultation feedback, received from eight professional organisations and one consumer organisation, was generally supportive. The consumer feedback highlighted the strong clinical need for this therapy, due to the condition being rare and often diagnosed late. The treatment has been successfully performed in Australia for the past 10 years and is currently funded through the Department of Veterans’ Affairs on a case-by-case basis, while other patients pay privately for the service. The feedback noted that both the “no carrier added” and “carrier added” treatment options are currently being used, and that having both options subsidised would enable clinicians to manage radiopharmaceutical shortages. MSAC also noted and considered the consultation input from those who were not supportive of the application. MSAC noted that Novartis considered that the proposed 177Lu-DOTA-ctreotate and 177Lu-DOTATATE (Lutathera®) may be two different drug products and there is no evidence to support the therapeutic equivalence between the two products. Novartis also noted that its 177Lu-DOTATATE drug product is protected by a granted patent.

MSAC noted the patent-related issues raised during the consultation process. MSAC noted that it was not within its Terms of Reference to reach a conclusion about the extent of the patent or the rights under it and concluded that these matters would require consideration by government and in particular the Minister prior to and in the course of any decision in relation to whether to list new MBS items as a result of this application. Accordingly, MSAC conducted its analysis in relation to the comparative safety, clinical effectiveness, cost-effectiveness and total cost of the applicant’s product on the basis of the information and evidence before it, and on the premise that providers will have a legal right to use it in Australia if the application is approved.

MSAC noted the clinical management algorithm. The proposed population is those with histologically confirmed, locally advanced or metastatic inoperable NENs with documented disease progression or uncontrolled NEN-related symptoms despite standard therapy. Patients first undergo whole-body 68Ga-DOTA-octreotate SSTR PET/CT to determine if there is high SSTR expression. Patients with a positive result (i.e. modified Krenning score >3) are potential candidates for peptide receptor radionuclide therapy (PRRT), which is proposed to be 177Lu (nca)-DOTA-octreotate. Approximately 30% of patients require an additional FDG PET/CT scan (already covered by MBS item 61612) to assess for concordance of lesions with the first scan. Discordance indicates a poorer prognosis and hence that the patient is unsuitable for PRRT.

MSAC noted that access to PET services in Australia is limited based on the location of the PET machines. Most PRRT is currently administered in public hospitals, and nearly all states and territories can provide PRRT to patients with NENs. The exception is the Northern Territory (NT), whose patients receive treatment in Adelaide, which introduces additional costs associated with travel and accommodation for NT patients. MSAC noted that there is a PET department in the Northern Territory that is expected to offer therapeutic nuclear medicine in the near future.

MSAC noted the comparators include long-acting somatostatin analogues (SSAs) (octreotide depot and lanreotide), target therapies (everolimus and sunitinib), chemotherapy and best supportive care (BSC). MSAC noted that 177Lu (nca)-DOTA-octreotate will not displace other therapies but will be used in addition to current treatments. Thresholds for treatment are presented in the clinical algorithm, but in clinical practice, a multidisciplinary team makes treatment decisions, due to the high complexity of individual cases.

MSAC noted that the outcomes for the diagnostic test were based on the clinical utility / diagnostic performance of 68Ga-DOTA-octreotate PET/CT +/– FDG PET/CT, but that there was very limited evidence on sensitivity and specificity for either of these tests compared to the reference standards, and no quantitative data were presented on change in clinical outcomes. However, MSAC noted that 68Ga-DOTA-octreotate PET/CT is more accurate, easier for the patient, less expensive and has a lower radiation dose than the alternative, 111Indium-octreotide single-photon emission CT (SPECT). Also, some trials, including CONTROL NETS (which was omitted from the Department Commissioned Assessment Report [DCAR]) have used 68Ga-DOTA-octreotate PET/CT to assess suitability for therapy. Regarding change in clinical outcomes, MSAC noted that 177Lu-DOTA-octreotate treatment is only given when there is good evidence that most lesions express SSTR.

MSAC noted there was no evidence presented for the safety of the diagnostic test, but as both tests have previously undergone MSAC assessment and are already listed on the MBS, their safety profile has been established.

MSAC noted that although the applicant expressed a preference for the proposed MBS listing to be for 177Lu (nca)-DOTA-octreotate, there is no difference in biodistribution between the “carrier added” and “no carrier added” versions of 177Lu-DOTA-octreotate. The main difference in the version relates to waste disposal rather than biodistribution or effectiveness. Therefore, MSAC agreed with ESC that it is appropriate to not stipulate “no carrier added” in the item descriptor (i.e. that the descriptor be carrier agnostic). MSAC also agreed with ESC that the amended uniform fee of $10,000 for the proposed therapeutic item was appropriate.

MSAC noted that all evidence presented for the treatment related to another product, 177Lu-DOTATATE, and not to 177Lu-DOTA-octreotate (the applicant’s product) and therefore the relevance of this evidence was premised on the assumed non-inferiority between 177Lu-DOTATATE, and 177Lu-DOTA-octreotate. This was because the DCAR identified a lack of randomised controlled (RCT) data available for 177Lutetium Octreotate (177Lu-DOTA-octreotate). MSAC noted that the commercial therapeutic product, 177Lu-DOTATATE, Lutathera® (Novartis) against which a claim of non-inferiority is being made, is not currently registered in Australia.

MSAC noted the assumption of non-inferiority between 177Lu-DOTATATE (Lutathera®) and 177Lu-DOTA-octreotate which was based on a comparison of pharmaceutical forms only was highlighted as a key uncertainty in the DCAR and was based solely on information provided in the product package inserts of the two products. No reliable data were presented in the DCAR itself to establish whether or not the products have similar chemical structure or similar biodistributions, characteristics which are expected to affect the assessment of non-inferiority of the two products in terms of safety and efficacy. MSAC noted the pre-MSAC response, in which the applicant noted that the active ingredients of 177Lu-DOTA-octreotate and 177Lu-DOTATATE are the same, the European Medicines Agency (EMA) accepted the evidence using different formulations of the active substance in Erasmus Phase I/II study and NETTER-I trial, and there are multiple trials demonstrating improved patient outcomes with 177Lu-DOTA-octreotate. In addition, MSAC noted the applicant tendered expert opinion from a biochemist that the structure of the peptides in 177Lu-DOTATATE and 177Lu-DOTA-octreotate information were similar. MSAC considered that whilst it appeared that the products may be two formulations of the same active compound [(Tyr3)Octreotate-Dota-Lu, i.e., 177Lu-DOTATATE], further independent expert radiochemist advice was needed before non-inferiority between the two products could be accepted, either on the basis of establishing chemical similarity or establishing similarity in biodistribution.

Additionally, MSAC noted that the NENs are a heterogenous group of rare tumours, which limits the RCT data that are available. The evidence base presented to MSAC only included RCT data, however, MSAC noted that there was both available published observational studies and Australian RCTs that had been omitted from the DCAR, including studies which used the applicant’s product rather than 177Lu-DOTATATE (as noted above in the pre-MSAC response).

MSAC noted it was aware of at least one observational study and one RCT from Australia that could have been considered for inclusion in the evidence base presented in the DCAR. The first was a clinical audit of 177Lu-DOTATATE services at the Royal Brisbane and Women’s Hospital (RBWH)[[1]](#footnote-2), consisting of 123 patients with a median follow up of 51 months. The second study was the CONTROL NETS trial which used the nca product, 177Lu- Octreotate [Lutate].

MSAC noted that a claim of noninferiority needs to be accepted in order for the evidence for the Lutathera® product (177Lu-DOTATATE; unspecified, used in the NETTER-1 trial), to be considered relevant for the applicant’s product (177Lu-DOTA-octreotate) or other 177Lu PRRT products, and for subsequent acceptance of the results of the modelled economic evaluation. MSAC considered that a significant limitation was that available data regarding the safety and efficacy of the applicant’s product (177Lu-DOTA-octreotate) was not assessed in the DCAR, including to inform the claim of noninferiority of 177Lu-DOTA-octreotate versus 177Lu-DOTATATE. However, MSAC assessed the comparative safety and effectiveness of 177Lu-DOTATATE and left for later consideration (as discussed below), the implications of this evidence for the clinical safety and effectiveness and cost effectiveness of 177Lu-DOTA-octreotate.

Regarding comparative safety, MSAC noted that a high number of patients (all pooled proportions and across all studies) experienced AEs, but the rates of serious AEs (SAEs) varied across treatments (including the comparators). The rates of SAEs for octreotide + everolimus (59%) were more than double those for 177Lu-DOTATATE (26%). The frequency of SAEs was no worse with PRRT treatment than other comparator treatments. The long-term side effects of PRRT included myelodysplastic syndrome, occurring in 2% (*n* = 2) of patients in the NETTER-1 key pivotal trial. Limited evidence was presented demonstrating that 177Lu-DOTATATE had:

* non-inferior safety compared with octreotide monotherapy, everolimus monotherapy, sunitinib, lanreotide or placebo/BSC
* superior safety compared to octreotide + everolimus combination therapy.

MSAC noted that 177Lu-DOTATATE is a specialised form of therapy using unsealed radiopharmaceuticals, which are longer-acting beta-emitters. Consequently, the therapy carries risks to the patient, and to a lesser extent, staff, carers and other members of the community, as well as the environment (waste disposal). There is also a small risk of carcinoid crises during 177Lu-DOTATATE therapy. However, MSAC considered that these risks can be mitigated if therapy is administered in appropriately equipped centres with resuscitation capacity and with appropriately trained supervision. MSAC noted that a NEN multidisciplinary team is needed to advise on management of therapy on a case-by-case basis.

MSAC noted that comparative effectiveness evidence against 177Lu-DOTATATE was only found for two comparator treatments (octreotide and sunitinib). A network meta-analysis (NMA) was conducted to generate indirect evidence. Based on the NMA, 177Lu-DOTATATE was associated with:

* statistically significant improvements in progression-free survival (PFS) versus all examined comparators (however, this was based on indirect evidence)
* non-significant improvement (i.e. no evidence of change) in overall survival (OS) compared to four comparators, and inferior improvement compared with sunitinib.

However, MSAC noted that there were significant transitivity issues with the NMA that made the findings highly uncertain, including:

* only one of two trials informed each pairwise connection, resulting in imprecision
* the key assumption of similarity and transitivity was breached
* there were methodological issues associated with the individual studies, resulting in selection and measurement bias in individual studies, with an unknown magnitude or direction of the biases.

MSAC noted that the transitivity and potential biases associated with the indirect treatment comparisons resulted in inconsistency between OS and PFS results across comparators. The uncertainty in the indirect evidence of comparative effectiveness had flow-on effects to the reliability of the inputs used in the economic model.

MSAC noted that the economic evaluation was a cost-utility analysis considering lifetime quality-adjusted life years (QALYs) and healthcare costs. It used a partitioned survival approach, which MSAC considered appropriate. MSAC also considered the model structure to be reasonable. However, the model relied on acceptance of the clinical evaluation assuming efficacy and safety of 177Lu-DOTA-octreotate is noninferior to 177Lu-DOTATATE, as well as acceptance of the results of the NMA. The economic evaluation used 177Lu-DOTA-octreotate as a first-line treatment against the six comparators, but MSAC considered it is more likely to be used as a second-line treatment in clinical practice.

MSAC noted that the incremental cost-effectiveness ratio (ICER) was highly uncertain and variable against the comparators. However, ICERs were <$50,000 (most <$35,000) per QALY for the majority of modelled scenarios, which is in the range typically considered acceptable by MSAC. One scenario showed 177Lu-DOTATATE to be dominated by sunitinib, which MSAC considered surprising from a clinical perspective as there is a lack of evidence that sunitinib prolongs OS in small bowel NENs; MSAC noted that the DCAR model appeared to have applied the same sunitinib efficacy to all NENs, overestimating likely response. Additionally, MSAC noted that the only head-to-head trial of sunitinib vs 177Lu-DOTATATE ([OCCLURANDOM](https://clinicaltrials.gov/study/NCT02230176)) showed that 177Lu-DOTATATE had better PFS and fewer AEs. MSAC also questioned the conclusion that domination by sunitinib was related to better OS, as OS was not yet reported in the OCCLURANDOM trials; in recent published abstracts, there was only one death and that was in the sunitinib arm. However despite these limitations, MSAC considered that, due to the complexity of the clinical presentation of NENs and the low likelihood of better-quality RCT evidence to reduce the uncertainty of the economic analysis, the current model is sufficient for exploring the likely cost-effectiveness of therapy with 177Lu-DOTA-octreotate (assuming noninferiority between the applicant’s product and 177Lu-DOTATATE), and the ICERs appear acceptable.

The key drivers of the model were the comparative effectiveness relative to the six comparators (high impact), the choice of the health state utility values (high impact) and the choice of the parametric distribution for PFS and OS (moderate impact).

MSAC noted that additional scenarios requested by ESC were included in the addendum. These were:

* converting the base case from average time on treatment based on 3.5 administrations to time based on dosing regimen in the NETTER-1 trial (4 infusions at 1 infusion every 8 weeks)
* including a scenario of 4 cycles over 8 months, which may be more realistic due to treatment being unrestricted
* including an additional two consolidation cycles of therapy following progression of disease.

MSAC noted that these scenarios had little impact on the ICER.

MSAC noted that the estimated financial impacts to the MBS under the scenario defined by ESC were $12,561,865 in Year 1 increasing to $14,053,288 in Year 4 (total of $53.2 million over 4 years), with the PRRT fee set at $10,000. The figures were based on approximately 80% of patients diagnosed with NENs receiving 68Ga-DOTA-octreotate PET/CT, with 30% of these undergoing FDG PET/CT (as stated previously, this is already covered by MBS item 61612). It also assumed patients undergoing PRRT would require at least one follow-up 68Ga-DOTA-octreotate PET/CT to determine treatment response or recurrence, as well as assuming no change in the use of comparator therapies. MSAC noted from ESC that the uptake rate and number of cycles of 177Lu-DOTA-octreotate are uncertain, and small changes affect the financial estimates. However, MSAC considered that the financial estimates presented in the addendum were likely to constitute the upper limit of the financial impacts of listing.

MSAC considered it unlikely that 80% of the incident population will be assessed for therapy: MSAC noted that the RBWH currently treats in the order of 35 new patients/year with 177Lu-DOTATATE therapy, which would equate to approximately 175 patients/year in Australia. MSAC also considered that there should be no restrictions on the number of treatment cycles, as neuroendocrine tumours behave differently depending on their subtype and grade. Including potential retreatment and additional 68Ga-DOTA-octreotate PET/CT for response monitoring, using a treatment fee of $10,000 and excluding FDG PET/CT, MSAC noted that the estimated financial impact to the MBS is more likely to be approximately $8–10 million/year over 6 years.

Overall, MSAC deferred its advice on MBS listing of 177Lu-DOTA-octreotate treatment for advanced NENs with H-SSTR expression. MSAC acknowledged the high clinical need for a therapy for NENs, and that the rarity of the disease presents challenges for collecting high-quality evidence. MSAC also acknowledged that 177Lu-DOTA-octreotate has been used for the past 10 years in Australia and is considered standard of care for NEN patients. However, the evidence presented in the DCAR for comparative effectiveness and safety was for another product, 177Lu-DOTATATE. Although MSAC considered that this product appeared to have superior clinical effectiveness and non-inferior safety, the assumed non-inferiority between 177Lu-DOTATATE and the proposed product, 177Lu-DOTA-octreotate, upon which the assessment of comparative safety, effectiveness and cost-effectiveness was premised was uncertain.

MSAC was of the view that independent radiochemist advice is needed to establish either the degree of chemical similarity or similarity of biodistribution between the two products in order to establish non-inferior safety and efficacy. In particular, MSAC considered that in order to establish the similarity of chemical structure between the two products, expert independent radiochemist opinion would be needed to verify the similarity of the following in the two products:

* targeting moiety (peptides)
* the chelators binding 177Lu-DOTATATE to the peptides
* the linker which joins the chelator to the targeting part of the peptides.

If chemical similarity cannot be established, similarity of biodistribution between the two products would need to be established based on the following questions:

* Are the molecular kinetics (tissue uptake and washout) of these agents equivalent in human tissues?
* Is the measured radiation dose delivered equivalent in “at risk” healthy tissues?
* Is the measured radiation dose delivered to the tumour tissue equivalent?

MSAC noted that information on the above biodistribution questions may be available from pre-clinical studies.

MSAC advised that if the similarity of chemical structure between the two products is not established, then additional evidence is required to establish similar biodistribution, efficacy and safety between the two products. In this case, MSAC requested that a more comprehensive assessment of the efficacy and safety of 177Lu-DOTA-octreotate and Lutathera® (177Lu-DOTATATE) be conducted in order to demonstrate that the two products are noninferior in terms of health outcomes. MSAC noted that there was both available published observational studies and Australian RCTs that used the applicant’s product (177Lu-DOTA-octreotate) rather than 177Lu-DOTATATE (Lutathera®) but that these studies were not evaluated in the DCAR.

MSAC also noted that there appeared to be several names used for the same product, so suggested consulting the applicant and appropriate clinicians and clinician organisations (e.g. the Australasian Association of Nuclear Medicine Specialists) to appropriately define the product terminology to ensure appropriate wording in the proposed agnostic item descriptor for the proposed therapeutic service (177Lutetium-somastatin receptor agonist treatment) if this service is subsequently supported for MBS listing.

MSAC considered that in drafting the item descriptor, the Department should ensure that patients with phaeochromocytoma and paraganglioma are also eligible for this service. Due to the uncertainty in uptake and usage (i.e. number of cycles per patient), MSAC advised that, if the service is subsequently listed, usage should be reviewed after 12 months. In addition, MSAC also supported the Department in monitoring the out-of-pocket costs for patients.

## 4. Background

MSAC has not previously considered 177Lu-DOTA-octreotate for the treatment of advanced NENs with H-SSTR expression, nor has a similar technology been considered for use in this treatment indication.

PASC ratified the PICO for 177Lu-DOTA-octreotate at its meeting in August 2023.

## 5. Prerequisites to implementation of any funding advice

177Lu chloride was approved by the Therapeutic Goods Administration (TGA) on 8 December 2021, and was included on the Australian Register of Therapeutic Goods (ARTG) on 11 January 2022 (ARTG number: 352121). Its approved therapeutic use is as a radiopharmaceutical precursor; it is not intended for direct use in patients. The registered use is: ‘For the treatment of non-resectable or metastatic NETs expressing somatostatin subtype 2 receptors when coupled with a suitable carrier molecule.’

The 177Lu-DOTA-octreotate product is supplied as an extemporaneously manufactured medicine for individual patient use as prescribed by a medical practitioner. The product is exempt from ARTG entry. The product that will be supplied by the applicant is produced by a TGA-licensed manufacturer following good manufacturing practice (GMP). According to TGA guidance on GMP information for manufacturers of compounded medicines and dose administration aids, a person with a TGA-issued manufacturing licence can supply a medicine that has been extemporaneously compounded for a particular person for therapeutic application to that person.[[2]](#footnote-3)

## 6. Proposal for public funding

The proposed funding arrangement is via the MBS, with listing of 2 new MBS items being sought.

### New MBS item for 68Ga-DOTA-peptide PET

PASC recommended that the existing MBS item descriptor for 68Ga-DOTA-peptide PET imaging (item 61647) (Table 1), would require revision or replacement to accommodate the 68Ga-DOTA-octreotate PET/CT imaging proposed in this application. Specifically, the relevant radiopharmaceutical product should be a 68Ga-DOTA-octreotate or SSTR agonist (excludes SSTR antagonists) and indications should be amended to include:

* 1. localisation of functioning (hormonally active) NEN when conventional imaging is negative/equivocal
  2. staging of histologically confirmed NEN considered surgically curable on conventional imaging
  3. evaluation of somatostatin analogue (SSA) avidity (SSTR-2 expression) of NEN under consideration for peptide receptor radionuclide therapy (PRRT)
  4. evaluation of response to therapy
  5. evaluation of suspected recurrent/metastatic disease in known SSA-avid (H-SSTR) NEN.

PASC also noted that a revised item for whole body 68Ga-DOTA-peptide PET study should allow referral by a specialist or consultant physician rather than restrict referrals to a multidisciplinary team (MDT).

Item 61647 is often billed with item 61505 (Table 1) for a CT scan performed at the same time and covering the same body as PET. The wording for item 61505 will not require amendment.

The proposed new MBS item for 68Ga DOTA-peptide PET to determine SSTR expression, suggested by PASC at the August 2023 meeting, is below (Table 2). The proposed new MBS item has the same fee as existing item 61647.

Table 1 Current MBS item for 68Ga DOTA-peptide PET

| Category 5 – Diagnostic Imaging Services |
| --- |
| MBS item 61647  Whole body 68Ga DOTA-peptide PET study, if:  (a) a gastro entero pancreatic neuroendocrine tumour is suspected on the basis of biochemical evidence with negative or equivocal conventional imaging; or  (b) both:  (i) a surgically amenable gastro entero pancreatic neuroendocrine tumour has been identified on the basis of conventional techniques; and  (ii) the study is for excluding additional disease sites (R) |
| Fee: $953.00 |
| Category 5 – Diagnostic Imaging Services |
| MBS item 61505  CT scan performed at the same time and covering the same body area as single photon emission tomography or positron emission tomography for the purpose of anatomic localisation or attenuation correction if no separate diagnostic CT report is issued and performed in association with a service to which an item in Subgroup 1 or 2 of Group I4 applies (R) |
| Fee: $100.00 |

Abbreviations: CT = computerised tomography; Ga = Gallium; MBS = Medicare Benefits Schedule; PET = positron emission tomography

Source: MBS online

Table 2 Proposed item descriptor for 68Ga DOTA-peptide PET Study to determine SSTR expression

|  |
| --- |
| Category 5 – Diagnostic Imaging Services |
| MBS item [item number]  Whole body 68Ga-DOTA-octreotate or somatostatin receptor agonist PET study of patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine neoplasms (NENs) with   1. Localisation of functioning (hormonally active) NEN when conventional imaging negative or equivocal; or 2. Staging of histologically confirmed NEN considered surgically curable on conventional imaging, or 3. Evaluation of somatostatin analogue (SSA) avidity (SSTR-2 expression) of NEN under consideration for peptide receptor radionuclide therapy (PRRT); or 4. Evaluation of response to PRRT therapy; or 5. Evaluation of suspected recurrent/metastatic disease in known SSA-avid (H-SSTR) NEN.   when referred by a specialist or consultant physician. |
| Fee: $953.00 |

Abbreviations: Ga = Gallium; MBS = Medicare Benefits Schedule; NEN = neuroendocrine neoplasm; PRRT = peptide receptor radionuclide therapy; PET = positron emission tomography; SSA = somatostatin analogue; SSTR = somatostatin receptor

Source: Ratified PICO

### New MBS item for 177Lu-DOTA-octreotate

Table 3 presents the item descriptor suggested by PASC for the proposed new MBS item for 177Lu-DOTA-octreotate. It is proposed that the various service elements of 177Lu-DOTA-octreotate treatment administration be bundled together into the per-cycle fee for 177Lu-DOTA-octreotate treatment (Table 4). If this item is recommended for MBS listing, the item descriptor should be accompanied by an explanatory note that provides guidance to clinicians regarding the use of the item, including the provider’s qualifications (i.e. a theranostic specialist). The credentialing requirements of service providers and facilities will be developed in consultation with stakeholders and will further develop how a ‘theranostic specialist’ should be defined. The fee for the proposed new MBS item should reflect the final definition of the provider’s qualifications.

The bundled fee elements for the proposed MBS item provided in the ratified PICO includes a theranostic specialist pre-treatment consult fee aligned with MBS item 110 ($167.75), which represents the fee for the initial attendance of a consultant physician (Table 4). Alternatively, the fee for this service element could be aligned to MBS item 104 ($95.60) for the initial attendance of a specialist. Furthermore, the fees for MBS item 116 ($84.35) for the subsequent attendance of a consultant physician, and for MBS item 105 ($48.05) for the subsequent attendance of a specialist, are also relevant in this context. The most relevant MBS item for this service element depends on who is most likely to be delivering this item, as nuclear medicine physicians (classified as consultant physicians) could claim items 110/116 whereas items 104/105 are more relevant if radiologists (classified as specialists) are involved.

Table 3: Proposed item descriptor for 177Lu-DOTA-octreotate

| Category T3-Therapeutic Nuclear Medicine |
| --- |
| MBS item [item number]  177Lutetium-somastatin receptor agonist treatment for patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine neoplasms (NENs) with documented disease progression or uncontrolled symptoms related to their NEN despite standard therapy who:   1. have high tumour somatostatin receptor expression demonstrated on whole body 68Ga DOTA somatostatin agonist PET study; and 2. are considered suitable for 177Lu-somatostatin agonist therapy by a formally convened neuroendocrine neoplasm multidisciplinary board.   The item fee is inclusive of necessary patient preparation such as:   1. patient preparation (including cost of amino acid infusion), 2. radiopharmaceutical preparation and administration, 3. immediate patient aftercare; and 4. post-infusion single photon emission tomography (SPECT) if performed (recommended after every 2nd cycle)   NOTE: To be finalised but will specify the provider’s qualifications |
| Fee: $10,431.05 (nca) / $10,031.05 (ca) |

Abbreviations: ca = carrier added; Ga = Gallium; Lu = Lutetium; nca = no carrier added; PET = positron emission tomography.

Source: Ratified PICO

Table 4: Bundled fee elements for the proposed MBS item for 177Lu-DOTA-octreotate

| Service Element | Suggested Fee | Comments from applicant |
| --- | --- | --- |
| GMP 177Lu (nca)-DOTA-octreotate supply | $8,000.00 | AMT cannot supply for a lower cost |
| GMP 177Lu (ca)-DOTA-octreotate supply | $7,600.00 | AMT cannot supply for a lower cost |
| Delivery | $450.00 | Derived directly from fee suggested by AANMS for 177Lu DOTA PSMA i&t therapy |
| Theranostic specialist pre-treatment consult fee | $167.75 | Aligned with item 110 but no wording modification of that item number would be required if the 177Lu DOTA-octreotate fee bundled a number of essential service elements. Higher fee than suggested by AANMS for 177Lu DOTA PSMA i&t therapy reflects differences in clinical complexity of patients. A lower fee could be applied if the theranostic specialist is also a member of the MDT recommending treatment and receives a fee for that attendance |
| Theranostic specialist treatment supervision and follow-up fee | $118.30 | Aligned with item 13950 but no wording modification of that item number would be required if the 177Lu DOTA-octreotate fee bundled a number of essential service elements |
| Non-admitted patient facility fee (facility cost) | $900.00 | Derived directly from fee suggested by AANMS for 177Lu DOTA PSMA i&t therapy |
| Nuclear medicine technologist | $200.00 | Derived directly from fee suggested by AANMS for 177Lu DOTA PSMA i&t therapy |
| Amino acid infusion | $120.00 | Cost to Peter MacCallum Cancer Centre from one commercial provider |
| Post-administration SPECT/CT scan | $400.00 | Derived directly from fee suggested by AANMS for 177Lu DOTA PSMA i&t therapy |
| Radiation safety officer/physicist | $75.00 | Derived directly from fee suggested by AANMS for 177Lu DOTA PSMA i&t therapy. Probable this function could be supplied without additional cost by the nuclear medicine technologist |
| Total  GMP 177Lu (nca)-DOTA-octreotate | $10,431.05 |  |
| Total  GMP 177Lu (ca)-DOTA-octreotate | $10,031.05 |  |

Abbreviations: AANMS = Australasian Association of Nuclear Medicine Specialists; AMT = Applied Molecular Therapies; ca = carrier added; CT = computed tomography; GMP = Good Manufacturing Practice; i&t = imaging and therapy; Lu = Lutetium; MDT = multidisciplinary team; nca = no carrier added; PSMA = prostate-specific membrane antigen; SPECT = single photon emission tomography.

Source: Ratified PICO: Attachment 1

## 7. Population

The proposed population for 68Ga-DOTA-octreotate PET/CT testing to assess eligibility for 177Lu-DOTA-octreotate therapy is patients referred by a specialist or consultant physician, with histologically confirmed, locally advanced or metastatic, inoperable NENs with documented disease progression or uncontrolled NEN-related symptoms despite standard therapy, who have suspected H-SSTR expression. A proportion of patients who have received 68Ga-DOTA-octreotate PET/CT revealing H-SSTR may also require FDG PET/CT to assess for high intra- and inter-tumour heterogeneity that may not be revealed on receptor-based imaging alone.

Patients who have demonstrated H-SSTR expression following imaging are then eligible for treatment. This population is aligned with the TGA-registered use of 177Lu chloride as a radiopharmaceutical precursor ‘for the treatment of non-resectable or metastatic NETs expressing somatostatin subtype 2 receptors when coupled with a suitable carrier molecule’.

177Lu-DOTA-octreotate will be used in addition to existing therapies. 177Lu-DOTA-octreotate is already in use in multiple locations within Australia and the clinical management algorithms in Figure 1 and Figure 2 demonstrate how current best practice guidance recommends the integration of 177Lu-DOTA-octreotate treatment (i.e. PRRT) with other potentially effective treatments for patients with advanced NEN and H-SSTR malignancies and for patients with carcinoid syndrome.[[3]](#footnote-4) Given the complexity in patient management due to the heterogeneity of tumour progression, symptoms and response to different tumoricidal or tumourostatic treatments, treatment with 177Lu-DOTA-octreotate should not be viewed as a fixed line in any patient’s therapy. The most appropriate line of therapy for 177Lu-DOTA-octreotate treatment should be considered on an individual patient basis by an MDT experienced in the management of advanced NENs and other H-SSTR tumours.

Figure 1 ESMO clinical management algorithm for advanced/metastatic gastroenteropancreatic NENs

**Figure 7 ESMO Clinical management algorithm for advanced/metastatic GEP-NETs
Source: Figure 4, p854 from ESMO guidelines (Pavel 2020)
**

Source: Figure 4, p854 from European Society of Medical Oncology (ESMO) guidelines[[4]](#footnote-5)

Figure 2 ESMO clinical management algorithm for advanced/metastatic NENs with carcinoid syndrome

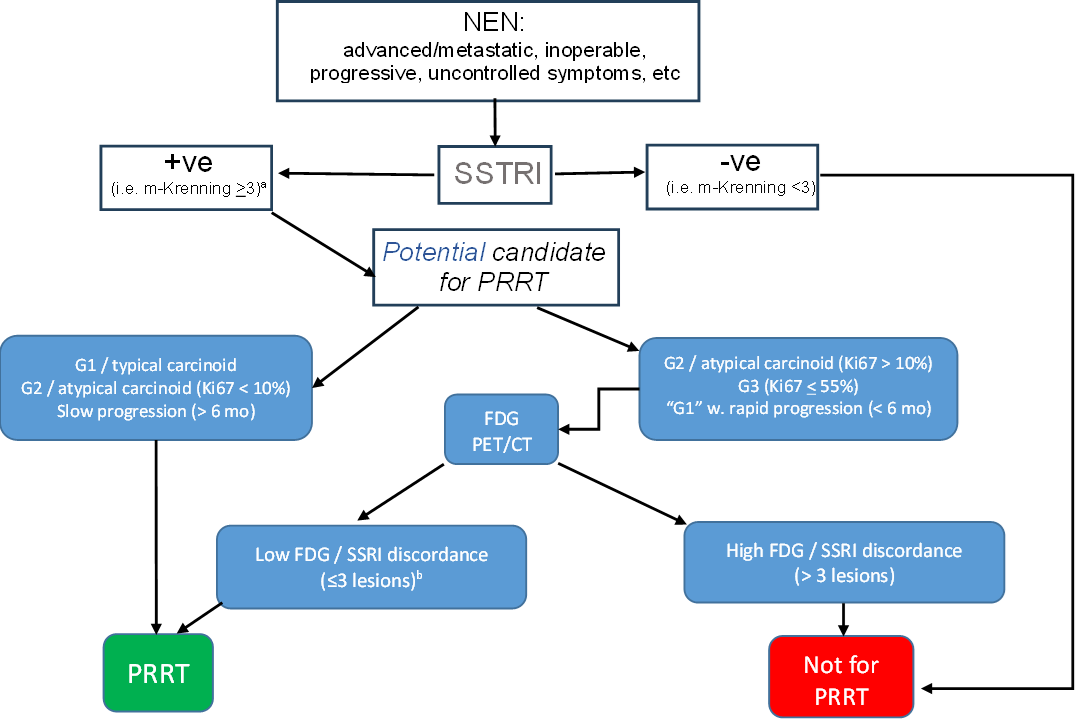
**Figure 8 ESMO Clinical management algorithm for advanced/metastatic NETs with carcinoid syndrome2
Source: Figure 3, p851 from ESMO guidelines (Pavel 2020)
**

Source: Figure 3, p851 from ESMO guidelines[[5]](#footnote-6)

PASC suggested a clinical management algorithm that highlights the population likely to be considered for an additional FDG/PET scan, as well as exemplar thresholds for eligibility for PRRT. (Figure 3). This includes a modified Krenning score of ≥3 and a maximum of 3 sites of FDG/SSRI discordance. It is important to note that these thresholds are for guidance only and that in clinical practice, decisions regarding eligibility for 177Lu-DOTA-octreotate will be made by an MDT.

As most patients will receive both 177Lu-DOTA-octreotate and comparator treatments during their advanced incurable malignancy, it is anticipated that there will be little difference in healthcare resource utilisation.

Figure 3 Reduced clinical management algorithm for G1 and G2 carcinoids and G3 pulmonary neuroendocrine carcinomas



Abbreviations: CT = computed tomography; G1 = grade 1; G2 = grade 2; G3 = grade 3; FDG = fluorodeoxyglucose; m-Krenning = modified Krenning score; NEN = neuroendocrine neoplasm; PET = positron emission tomography; PRRT = peptide receptor radionuclide therapy; SSTR = somatostatin receptor; SSTRI = somatostatin receptor imaging.

a Patients with demonstrated high concentration of SSTR expression at all, or the majority of, tumour sites

b No more than 3 sitesof discordance where the tumour is ≥2 cm in size

Source: Developed by PASC

### Alignment with PICO confirmation

This Department contracted assessment report (DCAR) of 177Lu-DOTA-octreotate addresses some of the PICO elements prespecified in the PICO confirmation ratified by PASC.

The original application and ratified PICO confirmation were restricted to the nca product; however, there is no available evidence to support the superior safety and effectiveness of the nca product compared to the ‘ca’ product to justify restriction of the benefit to the nca product. Therefore, in line with PASC considerations, the intervention described in this assessment report refers to the more generic 177Lu-DOTA-octreotate.

Furthermore, the original application included the requirement for an additional test, FDG PET/CT, to assist in therapeutic decision-making for some patients. The application requested the amendment of existing MBS item 61612 for whole body FDG PET study to assess eligibility for 177Lu-DOTA-octreotate treatment. However, PASC considered that existing MBS item 61612 would not require amendment, as NENs are considered rare or uncommon cancers and would therefore meet the eligibility criteria for item 61612.

The ratified PICO stated that ‘no outcomes for the 2 tests (68Ga-DOTA-octreotate PET/CT or FDG PET/CT) were nominated’. At its April 2023 meeting, PASC agreed that the relevant outcomes for 68Ga-DOTA-octreotate PET/CT and FDG PET/CT were intra-/inter-observer variability; however, it was further noted in the ratified PICO that these would be difficult to evaluate and therefore may not be relevant to determining test outcomes and suitability for PRRT treatment. A systematic literature review was performed to assess the diagnostic performance/accuracy and clinical utility of 68Ga-DOTA-octreotate PET/CT and FDG PET/CT in the population of interest. There were no reviews identified which restricted their investigation of the performance and utility of the diagnostic tests to the population with progressive, advanced, metastatic, or inoperable NENs with suspected/demonstrated H-SSTR expression. Efficacy/effectiveness outcome results concerning the intra-/inter-observer agreement across SSTR-PET/CT and FDG PET/CT tests, the proportion of patients who meet the nominated thresholds for SSTR-PET/CT imaging and the proportion who also proceed to FDG PET/CT imaging and subsequently receive 177Lu-DOTA-octreotate treatment were also not retrieved from the studies identified; therefore, this information has not been addressed in this report.

## 8. Comparator

177Lu-DOTA-octreotate is proposed as an add-on therapy rather than a replacement for comparator management strategies, thus it is considered that best supportive care (BSC) is the most relevant comparator for 177Lu-DOTA-octreotate. This is particularly appropriate given the complexity of optimal management strategies for patients with advanced NEN and H-SSTR malignancies who may exhibit a wide variety of individual and changing clinical circumstances. Furthermore, no guidelines considerPRRT as first-line treatment (versus alternative first-line treatments such as unlabelled SSA, targeted treatment [everolimus, sunitinib] or chemotherapy). Therefore, 177Lu-DOTA-octreotate therapy would most likely be offered after the failure of any nominated comparator treatments.

## 9. Summary of public consultation input

Consultation input was welcomed from 8 professional organisations, 1 consumer organisation and 2 individuals who are clinical experts and provide peptide receptor radionuclide therapy (PRRT) in Australia.

The organisations who submitted input were:

* The Urological Society of Australia and New Zealand (USANZ)
* Australian Diagnostic Imaging Association (ADIA)
* Novartis Pharmaceuticals Australia Pty Ltd (Novartis)
* The Royal Australian and New Zealand College of Radiologists (RANZCR)
* Australian Association of Nuclear Medicine Specialists (AANMS)
* Telix Pharmaceuticals Limited (Telix)
* Medical Oncology Group of Australia (MOGA) and the Clinical Oncology Society of Australia (COSA)
* Australian and New Zealand Society of Nuclear Medicine (ANZSNM)
* NeuroEndocrine Cancer Australia (NECA)

The consultation feedback received was mostly supportive of the application.

**Benefits**

* Clinical need, as NETs (neuroendocrine tumours) are rare and an area of need for novel therapies such as the proposed medical service
* The treatment delivers prolonged disease-free periods with minimal toxicity and good clinical tolerance (better tolerated than chemotherapy)
* It is single day treatment, making it more feasible for patients and requires little travel for patients who live remotely
* It is a cost-effective targeted therapy, in particular when compared to the cost of other treatments
* Equity of access (financial) as treatment has been available for 10 years and is currently funded through the Department of Veterans’ Affairs or State-specific funding models or paid for privately.
* Many NET patients suffer from debilitating symptoms such as facial flushing, diarrhea, asthma, nausea, and heart palpitations due to the NETs secreting hormones, and in addition to tumour shrinkage the treatment can be effective in managing these symptoms
* Successful treatment would reduce reliance on carers
* Economic benefit, including savings from patients coming off somatostatin analogue treatments and avoiding costly admissions/tumour de-bulking surgeries.

**Disadvantages**

* The cost of the treatment
* Side effects such as bone marrow suppression and renal injury, although these can be managed and minimised
* Patient would be disadvantaged if the treatment is ordered without the decision being made by an expert NET Multidisciplinary Team.

**Additional Comments**

Two nuclear medicine physicians advised that both non carrier added (nca) and carrier added (ca) options are currently being used and that having both options subsidised would enable clinicians to manage radiopharmaceutical shortages.

NECA provided deidentified cases from multiple patients who had received PRRT highlighting that the therapy is well tolerated without side effects, near complete resolution of flushing and diarrhoea, significant improvement in blood pressure control, significant reduction in prior metastases and improvement in quality of life.

MOGA and COSA stated the recent NETTER-1 trial has established Peptide Receptor Radionuclide Therapy (PRRT that includes 177Lutetium Octreotide therapy) as the treatment of choice in this second-line setting for patients with midgut NENs and is supported by the forthcoming COSA NEN guidelines. Additionally, it was estimated that approximately 100-150 patients would be eligible for treatment per year.

USANZ queried whether the clinical efficacy of Lu-Ocreotate can be fully ascertained using the mixture of evidence from Lu-dotate and Lu-ocreotate studies given that the sensitivities of these two radiotracers are different.

Novartis noted that its 177Lu-DOTATATE drug product is protected by a granted patent.

Novartis requested that the MSAC refrains from making a determination of noninferiority based on assumed biosimilarity of the two products 177Lu DOTA Octreotate and 177Lu-DOTATATE (Lutathera®) because they may be two different drug products and there is no evidence to support the therapeutic equivalence between the two products. Novartis also requested that the MSAC Application identify the specific active ingredient including radionuclide-chelator moiety and linker instead of referring to generic 177Lutetium (n.c.a) Octreotate” therapy and commented that the Applicant has not conducted a prospective randomised clinical trial comparing the clinical efficacy and safety of 177Lu- DOTATATE and any 177Lutetium(n.c.a.) Octreotate (with or without a DOTA chelating agent), meaning they could not be described as therapeutically equivalent. Novartis also raised questions about whether there were inconsistencies between National Medicines Policy and the proposed reimbursement of 177Lu DOTA Octreotate, prior to its registration on the ARTG and what sort of post-market pharmacovigilance would apply to non-ARTG listed products.

ADIA stated the proposed requirements in the AANMS Position Statement would severely limit the range of prospective providers of theranostics services, including the requirement for therapeutic radiopharmaceuticals to be manufactured by a qualified radiopharmaceutical scientist/radiochemist as well as the accreditation requirements which will be unattainable for many well-qualified nuclear medicine specialists. RANZCR also did not support reference to the Position Statement in developing the proposed requirements for theranostic service providers.

Feedback noted the MBS fee should be set to allow the provider to recover the cost of 177Lutetium(nca) Octreotate, otherwise patients are likely to incur substantial out of pocket costs. There was one comment disagreeing with the proposed fee and stating that the true cost of 177Lutetium(nca) Octreotate was closer to the $12,000 to $15,000 range.

The AANMS stated that all patients considered for this treatment must have a whole body DOTA-peptide PET/SPECT scan and suggested a new item number be created for this purpose. They added that a new item for FDG PET in the context of Lutate treatment should be created and that the post-treatment SPECT scan should have its own item number for tracking.

LuTATE therapy is best provided by a multidisciplinary team with oncologists, nuclear medicine physicians, endocrinologists, surgeons, palliative care specialists, medical physicists and nuclear medicine technologists as well as nursing, social work and dietician support services.

There are current restrictions around the use of Rare Cancers FDG PET imaging (61598) (i.e. limited to one per lifetime), and it was suggested to create a new item number for FDG PET in the context of providing LuTATE treatment.

Additionally, the AANMS noted the findings of the May 2024 Senate inquiry report into *Equitable access to diagnosis and treatment for individuals with rare and less common cancers, including neuroendocrine cancer* should be considered in light of the concern with reducing out-of-pocket (OOP) costs associated with 68Ga-DOTATATE and 18FDG PET/CT scans and ensuring those with rarer non-gastro-entero-pancreatic (GEP) NET SSTR-avid malignancies also receive access to 177Lu-DOTATATE theranostics.

## 10. Characteristics of the evidence base

As noted in the ratified PICO, the applicant provided no studies assessing the safety and/or efficacy of the proposed intervention (177Lu-DOTA-octreotate) and no randomised controlled trials (RCTs) were identified in the systematic literature review supporting this assessment. Instead, the applicant claimed that 177Lu-DOTA-octreotate appears to be a very close biosimilar to the Lutathera® product (referred to as 177Lu-DOTATATE). An evidence-based assessment of non-inferiority efficacy and safety between 177Lu-DOTATATE and 177Lu-DOTA-octreotate could not be performed due to the current lack of available data for the applicant’s intervention. However, a comparison of the pharmaceutical form of the 2 products, based on the Summary of Product Characteristics for 177Lu-DOTATATE[[6]](#footnote-7) and information provided by the applicant on 177Lu-DOTA-octreotate, is presented in Table 5. In lieu of an alternative approach, and despite the apparent differences between the 2 products, especially in the use of different excipients for the prevention of radiolysis, it is assumed that the efficacy and safety of 177Lu-DOTA-octreotate is equivalent to 177Lu-DOTATATE. Therefore, the clinical claim for 177Lu-DOTA-octreotate presented in this assessment report is based on the relative effectiveness and safety of 177Lu-DOTATATE. As such, this assumption is a key area of uncertainty in the assessment report.

Table 5: Comparison of pharmaceutical form of 177Lu-DOTATATE (Lutathera®) and 177Lu-DOTA-octreotate (applicant’s proposed intervention)

|  | **177Lu-DOTATATE (Lutathera®) (European Medicines Agency 2024)** | **177Lu-DOTA-octreotate (applicant’s proposed intervention)** |
| --- | --- | --- |
| Radioactivity concentration | 370 MBq/mL at time of calibration; 7,400 MBq at time of infusion (in 20.5–25.0mL) | ≤1,768 MBq/mL at time of synthesis |
| Form | Clear, colourless to slightly yellow solution | Clear, colourless-to-slightly yellow solution |
| Excipients | Acetic acid  Sodium acetate  Gentisic acid  Ascorbic acid  Pentetic acid  Sodium chloride  Sodium hydroxide  Water for injections | Sodium ascorbate  Ascorbic acid  Sodium chloride (saline solution) |
| Shelf-life | 72 hours from date and time of calibration | Up to 96 hours post synthesis |

Separate systematic literature reviews were conducted to investigate evidence for the diagnostic tests (68Ga-DOTA-octreotate PET/CT and FDG PET/CT) and for the therapeutic intervention (177Lu-DOTATATE).

### Investigative technologies

An additional systematic literature review investigated 2 research questions including:

* What is the clinical utility of 68Ga-DOTA-octreotate PET/CT for the selection of patients with progressive, advanced, metastatic or inoperable NENs with suspected H-SSTR expression for 177Lu-DOTA-octreotate therapy?
* What is the clinical utility of FDG PET-CT in addition to 68Ga-DOTA-octreotate PET/CT for the selection of patients with progressive, advanced, metastatic or inoperable NENs with known H-SSTR expression for 177Lu-DOTA-octreotate therapy?

Four systematic reviews/meta-analyses including Bauckneht et. al (2020),[[7]](#footnote-8) Carideo et. al (2019),[[8]](#footnote-9) Treglia et al (2012)[[9]](#footnote-10) and Alevroudis et al (2021)[[10]](#footnote-11) met the inclusion criteria to provide information on the diagnostic performance and clinical usefulness of 68Ga-DOTA-octreotate PET/CT and FDG PET/CT in addition to 68Ga-DOTA-octreotate PET/CT in selecting patients with NENs. Most of these reviews (except Carideo et. al (2019)) were judged to be at a low risk of bias (RoB) using the ROBIS tool.[[11]](#footnote-12)

The clinical utility standard for the proposed tests is discussed in the next section.

### Therapeutic intervention

A second systematic literature review investigated the research question:

* What is the safety, effectiveness and cost effectiveness of 177Lu-DOTA-octreotate versus alternative active and supportive care in patients with advanced NENs?

A total of 16 clinical randomised controlled trials (RCTs) met the inclusion criteria for assessing the safety and effectiveness of 177Lu-DOTATATE (via network meta-analysis [NMA]). Following data extraction, 2 studies—van der Zwan (2018)[[12]](#footnote-13) and Sood et al (2023)[[13]](#footnote-14)—were excluded due to unavailability of the full-text article (abstract only publications), as well as clinical trial records detailing study design characteristics, inclusion/exclusion criteria, and participant baseline characteristics. In total, 14 studies formed the evidence base for this submission.

Of the 14 studies identified in the systematic literature review, only 2 provided direct estimates of treatment efficacy for 177Lu-DOTATATE versus a relevant comparator. These were NETTER -1 and OCLURANDOM, comparing 177Lu-DOTATATE to octreotide and sunitinib, respectively. In the NETTER-1 trial, H-SSTR and PRRT therapy eligibility was based on Octreoscan® SPECT/CT (uptake ≥normal liver uptake, which is equivalent to a Krenning score ≥2). Conversely, in OCLURANDOM, eligibility was determined by somatostatin receptor scintigraphy (SRS) (grade of uptake at SRS ≥2, equal to the physiologic liver uptake) (i.e. the clinical utility standard for SSTR-PET/CT). The proposed tests of 68Ga-DOTA-octreotate PET/CT or FDG PET/CT were not used to select patients for PRRT therapy in these trials.

Seven studies were judged to be at low RoB using the Cochrane RoB-2 tool (Table 6).[[14]](#footnote-15) These studies were well reported, with high levels of confidence for all RoB domains. The studies NCT00428597 and NET-01 were judged to be of unclear RoB due to uncertainties concerning the generation of allocation sequences and masking of the outcome assessor. The methods and interim analysis results for the ECOG-ACRIN EA2142 study were published in an abstract, and ECOG-ACRIN E2211, NETTER-1, OCLURANDOM and TOPIC-NEC were open-label studies where both investigators and patients were unmasked to the treatment assignment and outcome assessors remained unblinded. The methodological quality of these studies was thus judged to be at high RoB (Table 6).

Table 6: Key features of the included evidence

| Study | Intervention | Comparator | Number of patients | Design/ duration | Risk of bias | Patient population | Outcome(s) | Used in economic evaluation |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 177Lu-DOTATATE vs comparator(s) | | | | | | | | |
| NETTER-1[[15]](#footnote-16) | 177Lu-DOTATATE | OCT | 231 | Multicentric, randomised, controlled trial | High | Midgut NET | PFS | Yes |
| OCLURANDOM[[16]](#footnote-17) | 177Lu-DOTATATE | SUN | 84 | Multicentric, randomised, open-label study | High | pNET | PFS | No |
| Comparator therapies studies | | | | | | | | |
| CLARINET[[17]](#footnote-18) | LAN | PBO | 204 | Randomised, double-blind, placebo-controlled trial | Low | NEEPT | PFS | Yes |
| PROMID[[18]](#footnote-19) | OCT | PBO | 85 | Randomised, double-blind, placebo-controlled trial | Low | Midgut NET | TTP | Yes |
| ECOG-ACRIN E2211[[19]](#footnote-20) | TEM | CAPTEM | 144 | Open-label, multicentre randomised controlled trial | Low | pNET | PFS | No |
| TOPIC-NEC[[20]](#footnote-21) | Etoposide + cisplatin | Irinotecan + cisplatin | 170 | Randomised, open-label, multicentre clinical trial | High | Gastro-hepato-pNET | OS | No |
| RADIANT-2[[21]](#footnote-22) | OCT + EVO | OCT+ PBO | 429 | Multicentre, double-blind, randomised trial | High | NET with carcinoid syndrome | PFS | Yes |
| ECOG-ACRIN EA2142[[22]](#footnote-23) | CAPTEM | Etoposide + cisplatin / carboplatin | 67 | Multicentre, randomised controlled trial | Low | GEP-NET | PFS | No |
| REMINET[[23]](#footnote-24) | LAN | PBO | 53 | Multicentre, randomised, controlled trial | Low | Duodeno-pNET | PFS | Yes |
| RADIANT-3[[24]](#footnote-25) | EVO + BSC | PBO + BSC | 410 | International, multicentre, quadruple masking, parallel study | Low | pNET | PFS | Yes |
| RADIANT-4[[25]](#footnote-26) | EVO + BSC | PBO + BSC | 302 | International, multicentre, double-blind, phase 3 study | Low | GI and lung NET | ORR | Yes |
| NET-01[[26]](#footnote-27) | CAP + streptozocin | CAP + streptozocin + cisplatin | 86 | Randomised controlled trial | Unclear | GEP-NET | PFS | No |
| SPINET[[27]](#footnote-28) | LAN + BSC | PBO + BSC | 77 | Prospective, multicentre, randomised, double-blind (participant, investigator), parallel study | Low | BP-NET | PFS | Yes |
| NCT00428597[[28]](#footnote-29) | SUN | PBO | 171 | Multinational, randomised, double-blind, placebo-controlled trial | Unclear | pNET | PFS |  |
| Indirect treatment comparisons | | | | | | | | |
| NMA | 177Lu-DOTATATE | OCT, EVR, OCT+ EVR, SUN, LAN, PBO/BSC | k=8  N=1524 | - | - | NETs | PFS | Yes |
| OCT, EVR, OCT+ EVR, SUN, PBO/BSC | K=6  N=1423 | - | - | OS | Yes |

Abbreviations: BP-NET = bronchopulmonary neuroendocrine tumour; CAPTEM = capecitabine and temozolomide; EVO = everolimus; GEP-NET = gastroenteropancreatic neuroendocrine tumour; H-SSTR = high somatostatin receptor; GI = gastrointestinal; LAN = lanreotide; NEEPT = enteropancreatic neuroendocrine tumours; NET = neuroendocrine tumour; NMA = network meta-analysis; OCT = octreotide; ORR = objective response rate; OS = overall survival; PBO = placebo; pNET = pancreatic neuroendocrine tumour; PFS = progression-free survival; SUN = sunitinib; TEM = temozolomide; TTP = time to treatment progression.

## 11. Comparative safety

The comparative safety of the diagnostic test was not within the scope of systematic review, nor outlined in the included studies within the review.

The pooled proportions of patients experiencing adverse events (AEs) were similar when comparing 177Lu-DOTATATE to each of the comparator therapies (Table 7). However, differences in the rates of serious AEs (SAEs) varied across treatments. Most notably, the rates of SAEs for octreotide plus everolimus (59%) were more than double those for 177Lu-DOTATATE (26%). High rates of SAEs were also observed for everolimus monotherapy (44%).

Table 7: Pooled analysis of the proportions of patients experiencing AEs and SAEs for each treatment

| Treatment | AE | SAE |
| --- | --- | --- |
| 177Lu-DOTATATE | 95% | 26% |
| Octreotide + everolimus | 100% | 59% |
| Octreotide | 85% | 31% |
| Everolimus | 98% | 44% |
| Sunitinib | 96% | 27% |
| Lanreotide | 91% | 22% |
| Placebo/best supportive care | 89% | 34% |

Abbreviations: AE = adverse events; SAE = serious adverse events.

## 12. Comparative effectiveness

### Test outcomes

In general, the pooled results for 68Ga-DOTA-octreotate PET/CT tests demonstrated high accuracy in the detection and diagnosis of NENs (pooled sensitivity and specificity for assessment of primary pancreatic NENs: 79.6% (95% CI: 70.5 to 87) and 95% (95% CI: 75 to 100); pooled sensitivity and specificity for thoracic and GEP-NENs: 93% (95% CI: 91 to 95) and 91% (95% CI: 82 to 97)). These tests also have prognostic implications because they have a relevant advantage in the detection rate of most metastatic sites, as unknown distant bone metastases are considered a negative prognostic factor in NEN management that may possibly require more aggressive treatment regimens. In addition, there is solid scientific evidence confirming the clinical role of the combined use of SSTR-PET/CT and 18F-FDG PET/CT in exploring 2 different aspects of tumour biology: SSTR expression and glucose metabolism. Their combined use may help to better identify patients that can benefit from PRRT and other treatment options (where there is no consensus for surgical therapy). Furthermore, they should be considered in the following clinical scenarios:

* At the time of initial diagnosis, in those patients with intermediate tumour proliferative activity (i.e. G2 tumours); if there is heterogeneous SSTR expression among different tumour lesions; and in non-functioning tumours when patients have tumour-related symptoms (i.e. pain and weight loss).
* During follow-up, in addition to conventional radiological imaging at the time of first disease re-staging after changing antiproliferative medical treatment; at the time of disease progression after prolonged stable disease; and in case of a discrepancy between conventional radiological evaluation and clinical/biochemical assessment.

In the main trial used to inform the efficacy of 177Lu-DOTATATE in the submission (NETTER-1), the detection and diagnosis of NENs was determined by Octreoscan® uptake and evaluated using the Krenning score. In an effort to translate the clinical utility of OctreoScan® uptake to 68Ga-DOTA-ocreotate uptake, the results of the NETTER-1 trial[[29]](#footnote-30) were compared to those published in the abstract by Sood et al. 2023[[30]](#footnote-31), where 68Ga-DOTA-ocreotate PET/CT was used to confirm SSTR presence in patients (Table 8).

At the data cut-off date for the primary analysis of the NETTER-1 trial (median follow-up: 14 months), median progression-free survival (PFS) and overall survival (OS) of patients treated with 177Lu-DOTATATE in the NETTER-1 trial was not reached. The estimated PFS rate at month 20 was 65.2% (95% CI: 50.0 to 76.8) in the 177Lu-DOTATATE group. Within the population of patients who could be evaluated for tumour response (101 patients), the total number of complete and partial responses was 1 and 17, respectively, which corresponded to an objective response rate (ORR) of 18%.

Similar outcomes were observed for patients in the Sood et al (2023) trial. PFS at 24 months was reported to be 96.4% (95% CI: 89.4 to 100) in the 177Lu-DOTATATE + capecitabine group and 67.3% (95% CI 47.3 to 87.3) in the 177Lu-DOTATATE-only group. After a median follow-up of 23.6 months, ORR in the 177Lu-DOTATATE + capecitabine group was 21.4% and 11% in the 177Lu-DOTATATE only group. The results of this naïve indirect comparison of trials based on their clinical utility standard are to be interpreted with caution due to the inherent limitation of comparing health outcomes across different cohorts of patients.

Table 8 Summary of outcomes for patients treated with 177Lu-DOTATATE, by test threshold adopted for H-SSTR

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial/study** | **Treatments** | **H-SSTR positive** | **FDG PET/CT** | **Median follow-up, months** | **ORR** | **PFS** | **OS** |
| NETTER-1 | Intervention: 177Lu-DOTATATE | Positive OctreoScan® imaging; uptake ≥normal liver uptake | No | Primary analysis: 14 | 177Lu-DOTATATE: 18% | Median: NR  PFS at month 20: 65.2% (95% CI: 50.0 to 76.8) | Median: NR |
| Sood et al (2023) | Intervention: 177Lu-DOTATATE  plus CAP.  Comparator: 177Lu-DOTATATE | SRS positive; 68Ga DOTANOC | Yes, 18F-FDG PET/CT | 23.6 [95% CI: 21.1, 26.0] | 177Lu-DOTATATE + CAP: 21.4%  177Lu-DOTATATE: 11% | Median: NR for either group  PFS at 24 months:  177Lu-DOTATATE + CAP: 96.4% [95% CI: 89.4, 100]  177Lu-DOTATATE: 67.3 [95% CI 47.3, 87.3] | NA |

Abbreviations: CAP = capecitabine; FDG = fluorodeoxyglucose, H-SSTR = high somatostatin receptor; NA = not applicable; NR = not reached; ORR = objective response rate; PFS = progression-free survival, PET/CT = positron emission tomography/computed tomography, SRS = somatostatin receptor scintigraphy.

Source: Constructed during evaluation.

### Clinical efficacy outcomes

#### Direct evidence: 177Lu-DOTATATE trials

NETTER-1 and OCLURANDOM were open-label studies where both investigators and patients were unmasked to the treatment assignment and outcome assessors remained unblinded. The methodological quality of these studies was therefore judged to be at high RoB.

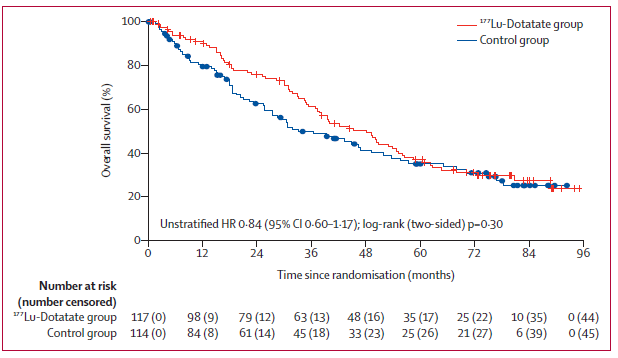
Table 9 Assessment of risk of bias of individual studies- direct RCTs: NETTER-1 and OCLURANDOM

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study reference** | **Random sequence generation** | **Assignment to intervention** | **Incomplete outcome data** | **Blinding of outcome assessment** | **Selective reporting** | **Overall bias** |
| NETTER-1 (ClinicalTrials.gov 2022b) | Low | High | Low | High | Low | **High** |
| OCLURANDOM (Baudin et al. 2022) | Unclear | Unclear | Low | Unclear | Unclear | **High** |

Source: Compiled by department from Table 81, p211 of the DCAR

In NETTER-1 the median OS was 48.0 months (95% CI: 37.4 to 55.2) for the 177Lu-DOTATATE group and 36.3 months (95% CI: 25.9 to 51.7) for the octreotide group (control group), with an HR of 0.84 (95% CI: 0.60 to 1.17), indicating a numerical but non-significant benefit (Figure 4).

Figure 4 Overall survival – NETTER-1



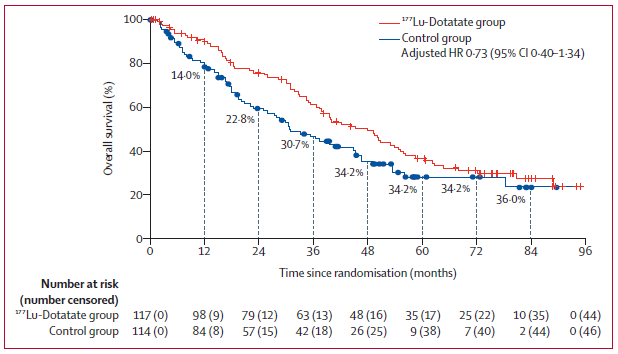
Source: Compiled by department from Figure 2, p1757 of Strosberg 2021

Abbreviations: HR = hazard ratio

Note Kaplan-Meier analysis of overall survival in intention-to-treat population. Crosses and circles represent patients who are censored

The authors of NETTER-1 noted that during long-term follow-up, 14 (12%) of 117 patients in the 177Lu Dotatate group received further treatment with PRRT. Among these 14 patients, eight were treated further with additional cycles of 177LuDotatate (the other six patients received 17LuDotatoc or ⁹⁰YDotatoc). In the octreotide group, 41 (36%) of 114 patients had documented crossover to PRRT. Around a quarter of patients in the control group (26 [23%] of 114 patients) crossed over within 24 months of randomisation. A total of 36 (32%) of 114 patients specifically received ¹⁷⁷LuDotatate (the other five patients received ¹⁷⁷LuDotanoc, ⁹⁰YDotanoc, ⁹⁰YDotatoc, or ⁹⁰YDotatate). During long-term follow up, 55 (24%) of 231 patients in both groups were documented as receiving other antineoplastic agents, including everolimus in 17 (15%) of 117 patients in the 177Lu Dotatate group and 20 (18%) of 114 patients in the control group. The results of a sensitivity analysis using the rank-preserving structural failure time method, which adjusted survival of those patients in the control group who crossed over to PRRT is presented in Figure 5. Consistent with the unadjusted OS results, the adjusted OS results showed a numerical but non-statistically significant benefit.

Figure 5 Rank -preserving structured failure time analysis of overall survival accounting for crossover to any PRRT in control group during long-term follow-up – NETTER 1

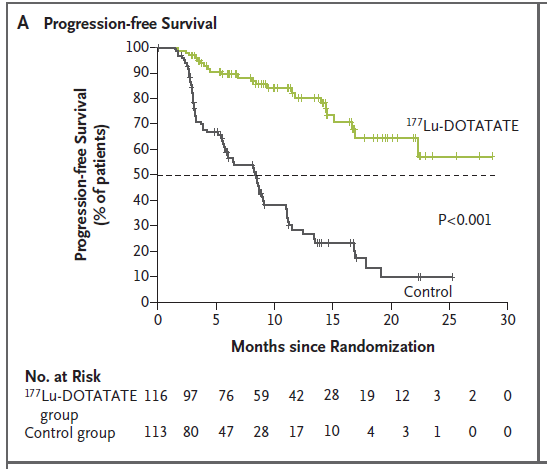


Source: Compiled by department from Figure 2, p1757 of Strosberg 2021

Abbreviations: HR = hazard ratio

In NETTER -1 the median PFS was not reached in the 177Lu-DOTATATE arm, while for patients on octreotide it was 8.4 months (95% CI: 5.8 to 9.1). The HR for PFS was 0.21 (95% CI: 0.13 to 0.33), indicating superiority of 177Lu-DOTATATE over octreotide. Treatment with 177Lu-DOTATATE was also associated with more favourable PFS outcomes than sunitinib. In OCLURANDOM, median PFS was longer in patients treated with 177Lu-DOTATATE (20.7 months; 95% CI: 17.2 to 23.7) compared to sunitinib (11.0 months; 95% CI: 8.8 to 12.4).

Figure 6 Progression free survival – NETTER-1



Source: Figure 1A, p130 of Strosberg 2017

#### Indirect evidence: NMA

Table 10 presents a summary of the results from the comparative effectiveness analyses. Based on the results of the NMA, 177Lu-DOTATATE was associated with statistically significant improvements in PFS over all examined comparators. For OS, 177Lu-DOTATATE was shown to be comparable in efficacy to all examined comparators. Nominally favourable OS outcomes were observed compared with octreotide plus everolimus combination therapy, everolimus monotherapy, octreotide monotherapy and placebo/BSC, and nominally less favourable outcomes compared with sunitinib.

Table 10: Summary of NMA results for PFS and OS (177Lu-DOTATATE reference)

|  |  |  |
| --- | --- | --- |
| Comparator | PFS; HR (95% CrI) | OS; HR (95% CrI) |
| 177Lu-DOTATATE | 1.00 | 1.00 |
| Octreotide + Everolimus | 3.8 (95% Crl: 2.1, 6.3) | 1.5 (95% Crl: 0.9, 2.3) |
| Octreotide | 4.9 (95% Crl: 3.0, 5.6) | 1.2 (95% Crl: 0.9, 1.7) |
| Everolimus | 5.9 (95% Crl: 2.6, 11.5) | 1.5 (95% Crl: 0.4, 3.7) |
| Sunitinib | 6.5 (95% Crl: 2.5, 13.8) | 0.7 (95% Crl: 0.2, 2.2) |
| Lanreotide | 8.6 (95% Crl: 3.5, 17.8) | NE |
| Placebo/BSC | 14.9 (95% Crl: 6.8, 28.6) | 1.7 (95% Crl: 0.5, 4.1) |

Abbreviations: CrI=credible interval; HR = hazard ratio; OS = overall survival, PFS = progression-free survival, NE = not estimable, NMA = network meta-analysis

### Clinical claim

Considering the evidence presented for the diagnostic performance of SSTR-PET/CT tests including 68Ga-DOTA-octreotate PET/CT, they should be considered as an accurate imaging prognostic tool in patients with NENs. The use of dual imaging (68Ga-DOTA-peptides and 18F-FDG) was demonstrated as a useful tool in NEN management by delineating tumour SSTR expression and glycolytic metabolic activity and predicting tumour response and survival outcomes. There was limited evidence available to translate Octreoscan® uptake (Krenning score) to 68Ga-DOTA-ocreotate uptake (modified Krenning score). However, patient outcomes from 2 trials—NETTER-1, which employed Octreoscan® to identify patients for PRRT therapy and Sood et al. 2023, which employed 68Ga-DOTA-ocreotate—appeared consistent. In addition, the decision regarding eligibility for 177Lu-DOTA-octreotate treatment based on SSTR status is proposed to be left to the judgement of the MDT treating the patient, rather than as a trial selection criterion as seen in pivotal trials.

Considering the evidence presented in this assessment report for the relative efficacy and safety of 177Lu-DOTATATE against its comparators, the following conclusions are made:

* Use of 177Lu-DOTA-octreotate is estimated to result in superior effectiveness compared with octreotide plus everolimus combination therapy, octreotide monotherapy, everolimus monotherapy, lanreotide and placebo/BSC; and noninferior effectiveness compared with sunitinib.
* Use of 177Lu-DOTA-octreotate is estimated to result in noninferior safety compared with octreotide monotherapy, everolimus monotherapy, sunitinib, lanreotide and placebo/BSC; and superior safety compared to octreotide plus everolimus combination therapy.

## 13. Economic evaluation

The objective of the analysis is to determine the cost-effectiveness of 177Lu-DOTA-octreotate plus BSC for the treatment of advanced NENs with H-SSTR expression compared with current care. Six comparator therapies against which the effectiveness of 177Lu-DOTA-octreotate could be compared were identified: octreotide, everolimus, octreotide plus everolimus combination therapy, lanreotide, sunitinib, and placebo/BSC.

The target population considers patients with histologically confirmed, locally advanced or metastatic, inoperable NENs with documented disease progression or uncontrolled NEN-related symptoms despite standard therapy, who have demonstrated H-SSTR. As there was no information that could be identified to inform the proportion of the incident NEN population that would be eligible for 177Lu-DOTA-octreotate (i.e. suspected H-SSTR), only the diagnosed and treated population (i.e. demonstrated H-SSTR) has been included in this analysis. The impact of this assumption on the ICER was explored in scenario analysis.

In accordance with the PICO confirmation ratified by PASC, a cost-utility analysis was undertaken considering lifetime quality-adjusted life years (QALYs) and healthcare costs. The model considers the cost-effectiveness of 177Lu-DOTA-octreotate compared with all 6 comparator therapies independently, with the results expressed in terms of incremental cost per QALY gained. A summary of the key features of the analysis is presented in Table 11.

Table 11: Summary of the economic evaluation of 177Lu-DOTA-octreotate treatment

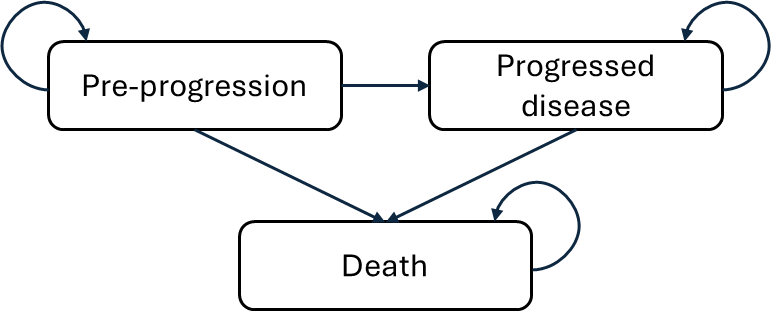
| Component | Description |
| --- | --- |
| Perspective | Healthcare system perspective |
| Population | Patients referred by an MDT, with histologically confirmed, locally advanced or metastatic, inoperable NENs with documented disease progression or uncontrolled NEN-related symptoms despite standard therapy who have demonstrated H-SSTR. |
| Prior testing | The economic model considers 2 diagnostic tests:   * 68Ga-DOTA-octreotate SSTR-PET/CT * 18F-FDG PET/CT   As there are no data on the impact of the diagnostic testing on disease outcomes, diagnostic testing is considered only as an additional cost. |
| Intervention | 177Lu-DOTA-octreotate |
| Comparator | The economic model considers 6 comparator therapies:   * octreotide * everolimus * octreotide + everolimus combination therapy * lanreotide * sunitinib * placebo, considered as best supportive care alone (most relevant comparator) |
| Type(s) of analysis | Cost-utility analysis |
| Outcomes | Outcome measures to be considered:   * treatment-specific efficacy; oncological and patient-relevant quality of life and disease response (objective response rate, disease control rate, biomarkers relevant to patient outcomes, OS and PFS duration) * safety * healthcare resource use * QALYs * total Australian Government healthcare costs |
| Time horizon | Lifetime |
| Computational method | Cohort partitioned survival model |
| Generation of the base case | Trial-based evaluation model |
| Health states | Partitioned survival model with the following health states:   * pre-progression * post-progression * death |
| Cycle length | Monthly |
| Transition probabilities | Health state allocation over time determined by PFS and OS data from NETTER-1 for intervention arm. HRs applied to model health state allocation by PFS and OS in comparator arm |
| Discount rate | 5% for both costs and outcomes |
| Software | Microsoft Excel |

Abbreviations: FDG = fluorodeoxyglucose, MDT = multidisciplinary team; ORR = objective response rate, OS = overall survival, PET/CT = positron emission tomography/computed tomography, PFS progression-free survival, QALYs = quality-adjusted life year, SSTR = somatostatin receptor.

The model was developed in Microsoft Excel using the partitioned survival analysis approach comprising 3 mutually exclusive health states (Figure 4):

* Pre-progression or PFS
* Post-progression survival (PPS)
* Death.

Figure 7 State transition diagram for the economic model used to assess cost-effectiveness of 177Lu-DOTA-octreotate treatment



In the model, all patients start in the PFS state and transition to post-progression and death states according to PFS and OS estimates. At the end of each cycle, patients either remain in their current health state or move to other states. Death is the absorbing state in the model. Health state membership is defined using the partitioned survival approach, which estimates the mean time spent in each health state from the area under the relevant survival curve. The estimates of OS are compared to age- and sex-specific mortality data for the Australian population, with the higher of the 2 estimates used in the model to ensure that the risk of mortality for the modelled population can never be lower than the age-specific general population mortality.

Costs and utilities are estimated for each health state and model cycle and aggregated over the modelled time horizon to estimate total per patient costs and QALYs for each treatment. The economic outcome in the model is the incremental cost-effectiveness ratio (ICER). A model half-cycle correction was applied.

### Model parameterisation

An evidence-based assessment of non-inferiority efficacy and safety between 177Lu-DOTATATE and 177Lu-DOTA-octreotate could not be performed due to the current lack of available data for the applicant’s intervention. In lieu of an alternative approach, and despite the apparent differences between the pharmaceutical form of the 2 products (see Table 5), especially in the use of different excipients for the prevention of radiolysis, it is assumed that the efficacy and safety of 177Lu-DOTA-octreotate is equivalent to 177Lu-DOTATATE. As such, this is a significant area of uncertainty in the proposed analysis. In lieu of an alternative, in this analysis, transitions between health states are based on the time-to-event data reconstructed from published data on the NETTER-1 trial for 177Lu-DOTATATE plus long-acting octreotide.

An indirect treatment comparison was conducted to assess the comparative effectiveness of 177Lu-DOTATATE versus the 6 comparators. As it was infeasible to estimate a hazard ratio for OS for lanreotide, in the model base case this was conservatively set to equal the hazard ratio for octreotide.

Utilities for the PFS and PPS (post-progression survival) health states were included in the model. In lieu of a systematic review of the literature for appropriate sources of health-related quality of life (HRQoL) with which to populate the economic model, data from the National Institute for Health and Care Excellence (NICE) appraisal of 177Lu-DOTATATE for treating unresectable or metastatic NETs was used for this analysis.[[31]](#footnote-32)

Healthcare resource use and costs to the Australian health system are included in the model and are categorised as follows:

* diagnostic testing costs
* treatment acquisition and administration costs
* healthcare resource costs related to monitoring and background treatment costs in PFS and PPS health states
* adverse event management costs.

### Model results

The base case cost-effectiveness analysis results are presented for 177Lu-DOTA-octreotate compared with current care (Table 11). As stated previously, 177Lu-DOTA-octreotate therapy would most likely be offered after the failure of any nominated comparator treatments. The cost-effectiveness of 177Lu-DOTA-octreotate compared with all 6 comparator therapies independently is provided below. All results are presented as a per patient cost or benefit. The presentation of stepped results is not applicable.

Table 12: Summary base case cost-effectiveness results for 177Lu-DOTA-octreotate versus comparators

| Treatment | Total costs | Incremental Costs | Total LYs | Incremental LYs | Total QALYs | Incremental QALYs | ICER (cost per QALY) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 177Lu-DOTA octreotate | $79,036 | reference | 4.73 | reference | 3.59 | reference | reference |
| PBO | $31,456 | $47,580 | 3.26 | 1.47 | 2.09 | 1.50 | $31,792 |
| OCT | $56,160 | $22,876 | 4.15 | 0.58 | 2.78 | 0.83 | $27,676 |
| LAN | $58,797 | $20,239 | 4.15 | 0.58 | 2.69 | 0.89 | $22,621 |
| EVO | $43,799 | $35,237 | 3.61 | 1.13 | 2.39 | 1.20 | $29,439 |
| SUN | $56,111 | $22,925 | 5.75 | -1.02 | 3.75 | -0.16 | Lutetium dominated |
| OCT + EVO | $57,509 | $21,527 | 3.57 | 1.17 | 2.43 | 1.15 | $18,643 |

Abbreviations: EVO = everolimus; ICER = incremental cost-effectiveness ratio; LAN = lanreotide, LY = life year; OCT = octreotide; OCT+EVO = octreotide plus everolimus combination therapy; PBO = placebo; QALY = quality-adjusted life year; SUN =sunitinib

Source: updated by department following ESC advice

For all comparator therapies other than sunitinib, 177Lu-DOTA-octreotate resulted in additional total cost, leading to an incremental cost range of $20,239 to $47,580. This additional cost was associated with substantial improvements in total life years and QALYs, ranging from 0.58 to 1.47 life years and 0.83 to 1.50 QALYs. 177Lu-DOTA-octreotate compared with sunitinib results in additional total costs of $22,924.60 with a reduction of 1.02 life years and 0.16 QALYs. In the base case analysis, 177Lu-DOTA-octreotate cannot be considered cost-effective versus sunitinib.

These cost-effectiveness results directly align to the results of the NMA, which showed that 177Lu-DOTATATE is associated with statistically significant improvements in PFS and comparable OS, with nominally favourable outcomes observed for 177Lu-DOTATATE versus octreotide + everolimus combination therapy, everolimus, octreotide and placebo/BSC; and nominally less favourable outcomes versus sunitinib.

Scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. As the primary driver of the model relates to the comparative efficacy of alternative treatment strategies, scenarios using the upper and lower range estimates of the hazard ratios of OS and PFS were used. The key drivers of the model are discussed in Table 13, and a summary of corresponding one-way sensitivity analyses is presented in Table 14.

Table 13: Key drivers of the economic model for 177Lu-DOTA-octreotate

| Description | Method/Value | Impact |
| --- | --- | --- |
| Treatment effect | HRs associated with treatment for OS and PFS are the main model drivers in terms of cost-effectiveness. Scenarios exploring the upper and lower 95% CrI of estimated HRs from the conducted indirect treatment comparison are applied in sensitivity analyses. | Using the lower limits of estimated HRs can significantly increase the estimated ICER, leading 177Lu-DOTATATE to be dominated by BSC and everolimus monotherapy.  Using the upper limits of HRs resulted in ICERs versus all comparators below $24,000/QALY. |
| Utilities | The model is sensitive to the choice of health state utility values. | Increased utilities in the pre-progression health state or decreased utilities in the progressed disease health state can significantly improve the cost-effectiveness of 177Lu-DOTATATE |

Abbreviations: BSC = best supportive care; CrI = credible interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year.

Table 14: Sensitivity analyses for economic evaluation of 177Lu-DOTA-octreotate; [*plus ESC indicative sensitivity analyses]*

| Scenario | Base case value | ICER result | Lower value | ICER result | Higher value | ICER result |
| --- | --- | --- | --- | --- | --- | --- |
| Discount rate | | | | | | |
| Discount rate costs and benefits | 5.00% | PBO = $31,792  OCT = $27,676  LAN = $22,621  EVO = $29,439  SUN = Lutetium dominated  OCT+EVO = $18,643 | 0.00% | PBO = $24,269  OCT = $19,794  LAN = $17,087  EVO = $22,252  SUN = Lutetium dominated  OCT+EVO = $15,055 | 3.50% | PBO = $29,535  OCT = $25,234  LAN = $20,938  EVO = $27,261  SUN = Lutetium dominated  OCT+EVO = $17,541 |
| Hazard ratios (PFS, OS) | | | | | | |
| PBO | 14.94, 1.68 | $31,792 | 6.81, 0.52 | Lutetium dominated | 28.61, 4.15 | $22,506 |
| OCT | 4.89, 1.21 | $27,676 | 2.97, 0.85 | $467,739 | 7.58, 1.66 | $23,486 |
| LAN | 8.61, 1.21 | $22,621 | 3.51, 0.85 | Lutetium dominant | 17.76, 1.66 | $22,640 |
| EVO | 5.86, 1.47 | $29,439 | 2.58, 0.43 | Lutetium dominated | 11.49, 3.74 | $20,293 |
| SUN | 6.45, 0.74 | Lutetium dominated | 2.48, 0.16 | $3,762 | 13.78, 2.19 | $23,461 |
| OCT+EVO | 3.80, 1.49 | $18,643 | 2.14, 0.93 | $70,643 | 6.26, 2.26 | $16,876 |
| Proportion of patients receiving tests | | | | | | |
| 68Ga-DOTA-octreotate PET/CT, FDG PET/CT | 100%, 30% | PBO = $31,792  OCT = $27,676  LAN = $22,621  EVO = $29,439  SUN = Lutetium dominated  OCT+EVO = $18,643 | N/A | N/A | 150%, 60% | PBO = $31,792  OCT = $27,676  LAN = $22,621  EVO = $30,142  SUN = Lutetium dominated  OCT+EVO = $18,643 |
| Utility (PFS, PPS) | | | | | | |
| Utility from RADIANT-4 | 0.77, 0.61 | PBO = $31,792  OCT = $27,676  LAN = $22,621  EVO = $29,439  SUN = Lutetium dominated  OCT+EVO = $18,643 | 0.78, 0.73 | PBO = $36,719  OCT = $38,532  LAN = $32,807  EVO = $34,855  SUN = Lutetium dominated  OCT+EVO = $21,145 | N/A |  |
| Utility from Erasmus study (from NICE appraisal) | 0.77, 0.73 | PBO = $37,647  OCT = $40,285  LAN = $34,465  EVO = $35,821  SUN = Lutetium dominated  OCT+EVO = $21,643 | N/A |  |
| Time horizon | | | | | | |
| Model time horizon | Lifetime | PBO = $31,792  OCT = $27,676  LAN = $22,621  EVO = $29,439  SUN = Lutetium dominated  OCT+EVO = $18,643 | 10 yearsa | PBO = $38,412  OCT = $34,282  LAN = $27,281  EVO = $36,046  SUN = Lutetium dominated  OCT+EVO = $21,987 | 20 years | PBO = $33,206  OCT = $29,061  LAN = $23,601  EVO = $30,833  SUN = Lutetium dominated  OCT+EVO = $19,349 |
| *Number of cycles of 177Lu PRRT treatment* | | | | | | |
| *Time on treatment* | *6.5 months (3.5 cycles)* | *PBO = $31,792*  *OCT = $27,676*  *LAN = $22,621*  *EVO = $29,439*  *SUN = Lutetium dominated*  *OCT+EVO = $18,643* | *NA* | *NA* | *8 months (4 cycles)* | *PBO = $38,344*  *OCT = $39,539*  *LAN = $33,581*  *EVO = $37,631*  *SUN = Lutetium dominated*  *OCT+EVO = $27,136* |
| *Progression / consolidation cycles* | *0* | *PBO = $31,792*  *OCT = $27,676*  *LAN = $22,621*  *EVO = $29,439*  *SUN = Lutetium dominated*  *OCT+EVO = $18,643* | *NA* | *NA* | *+2 cycles* | *PBO = $41,483*  *OCT = $45,222*  *LAN = $38,831*  *EVO = $41,155*  *SUN = Lutetium dominated*  *OCT+EVO = $31,204* |

Abbreviations: AE = adverse events; CT = computed tomopgraphy; EVO = everolimus; FDG = fluorodeoxyglucose; Ga = gallium; ICER = incremental cost-effectiveness ratio; LAN = lanreotide, N/A = not applicable; OCT = octreotide; OCT+EVO = octreotide plus everolimus combination therapy; OS = overall survival; PBO = placebo; PET = positron emission tomography PFS = progression-free survival; PPS = post-progression survival; SUN =sunitinib.

a 10-year lifetime horizon used in PBAC submission for sunitinib in the treatment of pancreatic NET (pNET); [Sunitinib PSD August 2013](https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2013-08/sunitinib-psd-08-2013.pdf)

## 14. Financial/budgetary impacts

The proposed patient population is patients referred by an MDT, with histologically confirmed, locally advanced or metastatic, inoperable NENs with documented disease progression or uncontrolled NEN-related symptoms despite standard therapy, who have demonstrated H-SSTR. The guideline-recommended line of therapy for PRRT varies depending on the characteristics of the NEN, in particular the primary site, grade, and proliferation of the tumour. In general, given the complexity in patient management due to the heterogeneity of tumour progression, symptoms, and response to different tumoricidal or tumourostatic treatments, treatment with 177Lu-DOTA-octreotate should not be viewed as a ‘fixed’ line in any patient’s therapy. The most appropriate line of therapy for 177Lu-DOTA-octreotate treatment should be considered on an individual patient basis by an MDT experienced in the management of advanced NENs and other H-SSTR tumours.

As 177Lu-DOTA-octreotate is proposed as an add-on therapy rather than a replacement of comparator management strategies, an epidemiological approach to deriving the anticipated financial implications of 177Lu-DOTA-octreotate has been adopted.

To estimate the number of patients eligible for treatment with 177Lu-DOTA-octreotate, data from the Australian Institute of Health and Welfare were used to identify the number of new NEN cases diagnosed between 1982 and 2018, as noted in the ratified PICO.(AIHW 2022) Using these data, an average compound annual growth rate (CAGR) was estimated (3.81%) and used to predict the incidence of NEN diagnoses from years 2018 to 2029.

The applicant advises (Application form 1744) that approximately 200 patients per year would undergo PRRT. Independent expert advice obtained by the Department also suggests that the number of people eligible for this highly specialised treatment will remain small. In lieu of an alternative data source, it was assumed that of the eligible incident NEN cohort, 197 patients would receive treatment with 177Lu-DOTA-octreotate in 2024, which is 3.5% of the estimated incident population for 2024. It was further assumed that this proportion of uptake (3.5%) would remain fixed for the following 5 years until 2029.

The costs of administration, acquisition and diagnosis have been included in the estimate of financial impact and utilise the same costing sources as those provided in the cost-effectiveness model.

The net financial impact of 177Lu-DOTA-octreotate to the health budget is presented in Table 15. The overall net cost to the health budget is $7.43m in Year 1, increasing to $8.96m in Year 6.

It is likely that 177Lu-DOTA-octreotate will result in additional background medication costs given the relative improvement in overall patient survival. However, as these additional costs are expected to be minimal, and given the uncertainty in the costing estimates, these have not been included in the net financial health impact.

Table 15: Net financial impact of 177Lu-DOTA-octreotate to the MBS

| Parameter | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 |
| --- | --- | --- | --- | --- | --- | --- |
| Estimated use and cost of the proposed health technology | | | | | | |
| Incidence of NENs | 5,642 | 5,857 | 6,080 | 6,312 | 6,552 | 6,802 |
| Number of people eligible for 177Lu-DOTA-octreotate | Unknown Assumed 3.5% to match applicant advised treatment population of approximately 200 | | | | | |
| Number of people who receive 177Lu-DOTA-octreotate | 197 | 205 | 213 | 221 | 229 | 238 |
| Number of 177Lu-DOTA-octreotate recipients tested with 68Ga-DOTA-octreotate PET/CT (100%)\* | 197 | 205 | 213 | 221 | 229 | 238 |
| Number of 177Lu-DOTA-octreotate recipients tested with 18F-FDG PET/CT (30%)† | 59 | 61 | 64 | 66 | 69 | 71 |
| Cost to the MBS; treatment drug cost | $7,190,649 | $7,464,649 | $7,749,089 | $8,044,368 | $8,350,899 | $8,669,109 |
| Cost to the MBS; diagnostic test cost | $240,037 | $249,183 | $258,679 | $268,535 | $278,768 | $289,390 |
| Change in use and cost of other health technologies | | | | | | |
| Change in use of comparator and other. | N/A 177Lu-DOTA-octreotate is proposed as an add-on therapy | | | | | |
| **Net financial impact to the MBS** | **$7,430,686** | **$7,713,832** | **$8,007,768** | **$8,312,904** | **$8,629,667** | **$8,958,500** |

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; MBS = Medicare Benefits Schedule; N/A = not applicable; NEN = neuroendocrine neoplasm; PET = positron emission tomography.

\* Confirmation of H-SSTR status is a prerequisite for treatment with 177Lu-DOTA-octreotate, so all patients receiving 177Lu-DOTA-octreotate treatment incur the cost of 68Ga-DOTA-octreotate PET/CT testing.

† It was assumed that approximately 30% of patients would proceed to FDG PET/CT, based on the estimate provided in the ratified PICO.

As there was no information that could be identified to inform the proportion of the incident NEN population that would be potentially eligible for 177Lu-DOTA-octreotate (i.e. suspected high SSTR expression), only the cost of diagnosing the treated population was included, which is likely to underestimate the budget impact of 177Lu-DOTA-octreotate. To test this uncertainty, 4 scenarios were considered in which 25%, 50%, 75% and 100% of the incident NEN population incurs diagnostic test costs, the results of which are presented in Table 16.

Table 16: Impact of uncertainty in the size of the diagnostic testing population on net financial impact to the MBS

| Parameter | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 |
| --- | --- | --- | --- | --- | --- | --- |
| Base case: 3.5% of incident population incurs diagnostic test cost | $7,430,686 | $7,713,832 | $8,007,768 | $8,312,904 | $8,629,667 | $8,958,500 |
| Scenario 1: 25% of incident population incurs diagnostic test cost | $8,905,198 | $9,244,530 | $9,596,793 | $9,962,478 | $10,342,098 | $10,736,184 |
| Scenario 2: 50% of incident population incurs diagnostic test cost | $10,619,746 | $11,024,411 | $11,444,496 | $11,880,589 | $12,333,298 | $12,803,258 |
| Scenario 3: 65% of incident population incurs diagnostic test cost | $11,648,475 | $12,092,340 | $12,553,119 | $13,031,455 | $13,528,018 | $14,043,503 |
| Scenario 4 75% of incident population incurs diagnostic test cost | $12,334,295 | $12,804,293 | $13,292,200 | $13,798,699 | $14,324,498 | $14,870,333 |
| Scenario 5: 100% of incident population incurs diagnostic test cost | $14,048,843 | $14,584,174 | $15,139,904 | $15,716,809 | $16,315,698 | $16,937,407 |

Abbreviations: MBS = Medicare Benefits Schedule.

Table 17 shows the net financial impact to the MBS for a scenario in which the proportion of patients expected to receive 177Lu-DOTA-octreotate is doubled (i.e. approximately 400 patients expected to receive treatment in Year 1).

Table 17: Net financial impact of 177Lu-DOTA-octreotate to the MBS, scenario with twice the expected treated population; *and ESC indicative sensitivity analyses*

| Parameter | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 |
| --- | --- | --- | --- | --- | --- | --- |
| Estimated use and cost of the proposed health technology | | | | | | |
| Incidence of NENs | 5,642 | 5,857 | 6,080 | 6,312 | 6,552 | 6,802 |
| Number of people eligible for 177Lu-DOTA-octreotate | Unknown Assumed 7% to match applicant-advised treatment population of approximately 400 | | | | | |
| Number of people who receive 177Lu-DOTA-octreotate | 395 | 410 | 426 | 442 | 459 | 476 |
| Number of 177Lu-DOTA-octreotate recipients tested with 68Ga-DOTA-octreotate PET/CT (100%) | 395 | 410 | 426 | 442 | 459 | 476 |
| Number of 177Lu-DOTA-octreotate recipients tested with 18F-FDG PET/CT (30%) | 118 | 123 | 128 | 133 | 138 | 143 |
| Cost to the MBS; treatment drug cost | $14,381,299 | $14,929,298 | $15,498,178 | $16,088,736 | $16,701,797 | $17,338,219 |
| Cost to the MBS; diagnostic test cost | $480,074 | $498,367 | $517,357 | $537,071 | $557,536 | $578,781 |
| Change in use and cost of other health technologies | | | | | | |
| Change in use of comparator and other | N/A  177Lu-DOTA-octreotate proposed as an add-on therapy | | | | | |
| **Net financial impact to the MBS** | **$14,861,372** | **$15,427,665** | **$16,015,535** | **$16,625,807** | **$17,259,333** | **$17,917,000** |
| ***ESC additional sensitivity analyses: net financial impact to MBS*** | | | | | | |
| 1. *80% of incident population incurs diagnostic test cost* | *$12,677,204* | *$13,160,269* | *$13,661,741* | *$14,182,321* | *$14,722,738* | *$15,283,748* |
| 1. *Number of 177Lu-DOTA-octreotate = 4.0 (3.5 base case)* | *$8,401,325* | *$8,721,457* | *$9,053,788* | *$9,398,782* | *$9,756,923* | *$10,128,710* |
| 1. *#1 and uptake of 177Lu-DOTA-octreotate is doubled* | *$19,867,854* | *$20,624,918* | *$21,410,830* | *$22,226,689* | *$23,073,637* | *$23,952,857* |

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; MBS = Medicare Benefits Schedule; N/A = not applicable; NEN = neuroendocrine neoplasm; PET = positron emission tomography.

## 15. Other relevant information

Nil.

## 16. Key issues from ESC to MSAC

**Main issues for MSAC consideration**

**Clinical issues:**

* There is limited direct evidence for 177Lu-PRRT treatment therapy across different NENs, indicating a need for further RCT-based evidence. Whilst clinical trials are underway, results will not be available for some years to come.
* There is a lack of evidence for diagnostic accuracy, test reliability and change in clinical outcomes for the 68Ga-DOTA-octreotate PET/CT and FDG PET/CT, and the tests have not been studied with respect to these outcomes.
* Noninferiority of 177Lu-DOTA-octreotate and Lutathera® (177Lu-DOTATATE) is assumed based on a comparison of pharmaceutical forms only and is therefore a key area of uncertainty.
* Multiple assumptions in the production of the network meta-analysis (NMA) and transitivity issues that may bias the results of the NMA have resulted in significant uncertainty in the indirect estimates of comparative effectiveness. This has flow on effects to the reliability of the inputs used to model comparative effectiveness in the economic model.

**Economic issues:**

* The cost-effectiveness of 177Lu-DOTA-octreotate is highly sensitive to changes in plausible variation in the hazard ratios for overall survival and progression free survival versus all 6 comparators (including best supportive care), switching from the incremental cost-effectiveness ratio (ICER) being dominant, the ICER < ~$70,000 per QALY for most modelled scenarios, or dominated. The ICER is highly volatile against pharmaceutical comparators.
* Additional one-way sensitivity analyses should be undertaken incorporating the number of cycles and choice of parametric curves. Two-way analyses incorporating variation in treatment costs (number of cycles) and use of 68Ga-DOTA-octreotate PET/CT imaging for monitoring treatment response would also be informative. Subsequently, the assessment group produced an Addendum (see **Attachment**) which included the requested additional sensitivity analyses. The choice of parametric distribution for progression-free survival (PFS) and overall survival (OS) and scenarios using different estimated time on treatment for 177Lu-DOTA-octreotate had a moderate impact on the ICER. The scenario which assumed an additional 68Ga-DOTA-octreotate PET/CT scan as part of monitoring resulted in a small increase in the ICER.

**Financial issues:**

* There is insufficient evidence to support estimations of both pre-intervention tests resulting in high uncertainty in the financial estimates.
* Additional advice from the applicant on the extent of current use of 177Lu PRRT therapy, such as from Department of Veterans’ Affairs (DVA) claiming data may be informative.
* The uptake rate and number of cycles of 177Lu-DOTA-octreotate are uncertain and small changes will affect financial estimates. The financial estimates should be refined to better estimate the incident testing population based on published estimates, account for repeat 68Ga-DOTA-octreotate PET/CT imaging for monitoring treatment response and use the amended fee of $10,000 fee for 177Lu-PRRT. Subsequently, the assessment group produced an Addendum (see **Attachment**) which included the requested additional analyses. The financial impact under this ESC scenario (80% of eligible population tested; additional 68Ga-DOTA-octreotate PET study for treated patients) resulted in a much higher net cost of $82.93 million by 2029. However, these estimates were still considered uncertain due to the limitations in the clinical data and assumptions informing these estimates.

**ESC discussion**

ESC noted that this application is requesting Medicare Benefits Schedule (MBS) listing of 177Lutetium (no carrier added)-DOTA-octreotate (177Lu (nca)-DOTA-octreotate) for the treatment of advanced neuroendocrine neoplasms (NENs) with high somatostatin receptor (H-SSTR) expression. The application is also requesting a new MBS listing for 68Gallium (Ga)-DOTA-octreotate SSTR-positron emission tomography (PET)/computed tomography (CT) — 68Ga-DOTA-octreotate PET/CT — to determine eligibility for 177Lu (nca)-DOTA-octreotate treatment, as well as for monitoring the post-treatment effect (i.e. treatment response) of 177Lu (nca)-DOTA-octreotate. This treatment is a type of peptide receptor radionuclide therapy (PRRT). The applicant’s clinical claim implied that 177Lu(nca)-DOTA-octreotate results in superior health outcomes and non-inferior safety.

The 177Lu-DOTA-octreotate product is supplied as an extemporaneously manufactured medicine for individual patient use as prescribed by a medical practitioner. ESC noted that the 177Lu-DOTA-octreotate product is exempt from ARTG entry. ESC noted that the applicant’s proposed product is produced by a TGA-licensed manufacturer following Good Manufacturing Practice (GMP).

ESC noted that the application and ratified PICO confirmation was restricted to the ‘no carrier added’ product. Other similar medical isotopes are ‘carrier-added’ including a commercial product called Lutathera® which is not currently registered in Australia. ESC noted that the applicant advised that 177Lu(nca)-DOTA-octreotate is recommended in Europe and USA due to environmental considerations because the “ca” product contains 177mLu, with a half-life of 160 days, whereas nca 177Lu does not, which may have implications for radioactive waste storage and disposal. ESC noted in line with PASC considerations, the intervention described in the department contracted assessment report (DCAR) refers to the more generic 177Lu-DOTA-octreotate.

ESC noted and welcomed consultation input from eight (8) professional organisations, and one (1) consumer organisation. ESC noted the consumer feedback that there is a strong clinical need for this therapy because the condition is rare and often diagnosed late. ESC also noted that although this therapy is novel to the MBS, it has been successfully conducted in Australia for the past 10 years and is currently funded through the Department of Veterans' Affairs (DVA) on a case-by-case basis. ESC noted that access to PET services is limited based on the location of PET machines. ESC noted that all states and territories of Australia (except for the Northern Territory) can provide PRRT to patients with NENs, although these centres are limited. Most, if not all PRRT is administered in public hospitals. ESC also noted the clinical expert feedback that both no carrier added and carrier added treatment options are currently being used and that having both options subsidised would enable clinicians to manage radiopharmaceutical shortages.

ESC noted that the proposed population is patients with histologically confirmed, locally advanced or metastatic, inoperable NENs with documented disease progression or uncontrolled NEN-related symptoms despite standard therapy, who have suspected H-SSTR expression. ESC noted that NENs are highly heterogeneous cancers and that patients are managed by a multidisciplinary team due to the complexity and rarity of individual cases. ESC noted that due to complexities in patient management, the PICO proposed pancreatic NETs and midgut NETs as exemplars. ESC acknowledged the high clinical need of this population.

ESC noted that there were multiple comparators nominated in the ratified PICO, namely long-acting somatostatin analogues (SSA) comprising octreotide depot and lanreotide; targeted therapies – everolimus and sunitinib; chemotherapy and best supportive care (BSC). Adding to the assessment report’s complexity of multiple comparators, patients with advanced disease, due to their poor prognosis, are typically cycled through multiple treatments.177Lu-DOTA-octreotate is not intended to replace chemotherapy and is often administered concurrently to chemotherapy. Similarly, SSAs are not replaced by 177Lu-DOTA-octreotate but continued alongside it. ESC noted that consistent with PASC, the DCAR considered BSC the most relevant comparator as 177Lu-DOTA-octreotate is proposed as an add-on therapy rather than a replacement for comparator management strategies.

ESC noted that the department-contracted assessment report (DCAR) included the European Society of Medical Oncology guideline[[32]](#footnote-33) for treatment, which illustrates the complexity of treatment and that PRRT may be used in different lines of treatment. ESC also noted the amended clinical management algorithm suggested by PASC, which highlights the thresholds for eligibility for PRRT Patients with a modified Krenning score of ≥3 with slowly progressing grade 1 and grade 2 (Ki67 <10%) NENs are eligible for PRRT. Patients with tumours with a modified Krenning score of ≥3 who have a grade 2 NEN (Ki67 >10%), grade 3 NEN (Ki67 ≤ 55%) or rapidly progressing grade 1 NEN will require further assessment with FDG PET/CT. Patients in the latter group with disease that shows low FDG/SSRI discordance (≤3 lesions discordant) are eligible for PRRT. However, ESC noted that these thresholds are for the purposes of the assessment report and that in clinical practice, it has been proposed that a multidisciplinary team (MDT) will provide the guidance for individual patient management on a case-by-case basis. ESC noted that this case-by-case approach is consistent with clinical guidelines and that a nuclear medicine specialist would likely to be the main specialist guiding a MDT. ESC noted that the algorithm does not include repeat 68Ga-DOTA-octreotate PET/CT imaging for monitoring purposes but this should have been included.

ESC noted that a new MBS listing for 68Ga-DOTA-octreotate PET/CT was proposed in the DCAR, based on a revision of current MBS item 61647 which is an initial gallium study for diagnosis and for determining surgical therapy and includes the same fee. The new listing was proposed for imaging pre therapy through evaluation of somatostatin analogue (SSA) avidity of NEN and also to monitor response to PRRT therapy.

In addition, ESC noted that the application originally requested the amendment of existing MBS item 61612 for whole body FDG PET study to include assessing patient eligibility for 177Lu-DOTA-octreotate treatment. ESC noted that this item is used for initial staging of rare or uncommon cancers for a patient considered suitable for active therapy. PASC therefore considered that existing MBS item 61612 would not require amendment, as neuroendocrine neoplasms (NENs) are considered rare or uncommon cancers.

For the proposed MBS item for 177Lu-DOTA-octreotate treatment, ESC noted that a standard course of treatment consists of four cycles, but proposed that the number of cycles should be unrestricted to accommodate varying case-by-case needs of patients, taking into account that treatment cycles will be determined by the grade of tumour and patient response to treatment. ESC also noted that in some patients, an extra two consolidation cycles of 177Lu-DOTA-octreotate treatment may be instituted in patients where no progression is evident but re-treatment is likely to delay progression, for example in higher grade (G3) NENs with rising tumour marker levels. ESC noted the item referred to the more generic ‘177Lutetium-somatostatin agonist’ without specifying ‘carrier added’ or ‘no carrier added’ which ESC considered would provide the broadest access to patients. ESC also considered that an amended uniform fee of $10,000 for 177Lutetium-somastatin receptor agonist treatment was appropriate rather than fee differentiation between carrier added and non-carrier added products.

ESC noted that there was no available evidence presented in the DCAR to support the superior safety and effectiveness of the ‘no carrier added’ product compared to the ‘carrier added’ product in terms of health outcomes to justify restriction of the benefit to the ‘no carrier added’ product only.

ESC noted that when examining the evidence for clinical utility of 68Ga-DOTA-octreotate PET/CT or FDG PET-CT for the selection of patients with progressive, advanced, metastatic or inoperable NETs with suspected H-SSTR expression for 177Lu-DOTA-octreotate therapy, four studies were identified. However, there were a number of limitations: none of the studies looked at the population relevant to this application (advanced/inoperable NENs), the studies used different radionuclides and were not limited to Ga-DOTA-octreotate, there were no data on sensitivity and specificity using an appropriate reference standard (e.g. histology), there were no data on intra- or inter-observer variability, there were no quantitative data on the change in clinical outcomes and there were no safety data presented.

ESC noted that the pre-ESC response claimed that the DCAR should have included four additional studies of diagnostic performance. ESC noted that of the additional references provided in the pre-ESC response as further evidence, two were very small studies but there were two larger studies which supported good effectiveness outcomes.[[33]](#footnote-34) [[34]](#footnote-35) ESC noted the evidence examining the equivalence of 68Ga-DOTA-octreotatePET/CT to Octreoscan®. PASC noted that Octreoscan® is a valid clinical standard and the results of studies based on Octreoscan® (using the Krenning score) needed to be translated to 68Ga-DOTA-octreotate (using the modified Krenning score) for the DCAR. This was done by comparing the results of the NETTER-1 trial[[35]](#footnote-36) (which used Octreoscan® for the diagnosis of midgut NENs based on the Krenning score) and the results reported in the abstract by Sood et al.[[36]](#footnote-37) (which used 68Ga-DOTA-octreotate PET/CT to determine somatostatin receptor presence based on the modified Krenning score). The DCAR concluded that the two imaging techniques were concordant due to the progression free survival and the objective response rate being similar across both studies. However, ESC considered that the results of this naïve comparison comparing longitudinal health outcomes across different cohorts of patients based on their respective clinical utility standards used in the trials should be interpreted with caution due to the very low level of evidence presented.

ESC noted that the applicant only provided a comparison of the pharmaceutical forms to support the claim of similarity or noninferiority in efficacy between 177Lu-DOTA-octreotate and Lutathera® (177Lu-DOTATATE). The DCAR concluded that based on this information the pharmaceutical composition of the two radio-isotopes were similar although their excipients were different. ESC also noted consultation input received from Novartis, which has a patent for 177Lu-DOTATATE, stating that there is no evidence to support the therapeutic equivalence of 177Lu-DOTATATE and 177Lutetium(nca)octreotate.

ESC noted the absence of safety and efficacy studies for the proposed treatment 177Lu-DOTA-octreotate. Therefore, the DCAR’s assessment of the safety and efficacy of the proposed treatment has been based on studies of 177Lu-DOTATATE based on a claim of noninferiority between 177Lu-DOTA-octreotate and 177Lu-DOTATATE, for which there is also a lack of evidence. As such, this is a significant area of uncertainty in the proposed analysis, as the evidence for the application’s clinical claims is based on indirect evidence (from 177Lu-DOTATATE). ESC noted the pre-ESC response which the applicant contended that, separate to Lutathera®, other 177 Lu therapeutic products should have been included in the assessment. In addition, the applicant contended that due to GMP, these two products are close biosimilars and highlighted that the European Medicines Agency (EMA) accepted the evidence using different formulations of the active substance in Erasmus Phase I/II study and NETTER-I trial.

ESC noted that the evidence base for 177Lu-DOTATATE (which as noted previously was used for assessment purposes to evaluate the safety and efficacy of 177Lu-DOTA-octreotate) comprised 14 RCTs of varying treatments for exemplar NENs. ESC noted the applicant’s concerns in its pre-ESC response that the systematic review was reliant on evidence from randomised controlled trials (RCT) to the virtual exclusion of highly relevant real-world evidence. ESC noted that the rejoinder provided by the assessment group responded that single-arm, non-randomised studies are of limited utility in assessing the cost-effectiveness of treatment. Consequently, the systematic literature review focused primarily on RCTs that provide the most robust and least biased estimates of the comparative efficacy between interventions by controlling for confounding variables, minimising biases, and ensuring consistency in treatment administration and outcome measurement.

For comparative safety, ESC noted that the rates of adverse events (AEs) and serious AEs (SAEs) were pooled from individual studies. ESC noted the pooled proportions of patients experiencing AEs was high across all studies but that the rates of serious AEs varied across treatments. The rates of SAEs for octreotide plus everolimus (59%) were more than double those for 177Lu-DOTATATE (26%). ESC considered that the frequency of serious AEs was no worse with PRRT treatment than other comparator treatments but there was no data on types of AEs reported in the DCAR. ESC noted that long-term side effects of PRRT can include myelodysplastic syndrome, which occurred in 2 (2%) of 111 patients in NETTER-1. Overall, ESC considered there was only limited evidence which demonstrated that 177Lu-DOTATATE (and thus 177Lu-DOTA-octreotate based on assumed noninferiority between the two products) treatment had noninferior safety compared with octreotide monotherapy, everolimus monotherapy, sunitinib, lanreotide and placebo/BSC; and superior safety compared to octreotide plus everolimus combination therapy.

Notwithstanding that the DCAR considered BSC the most relevant comparator, ESC noted that the comparators in this evidence base included all the listed comparators (SSA, targeted therapies, chemotherapies, BSC). ESC noted that of the comparators highlighted in the PICO, comparative evidence against 177Lu-DOTATATE was only found for two of these (octreotide and sunitinib) and the other 12 trials were of chemotherapies/targeted therapies vs. BSC. The most common outcomes studied in the RCTs were progression free survival (PFS) and overall survival (OS). To generate indirect estimates of the relative effects of 177Lu-DOTATATE against the other comparators, a network meta-analysis (NMA) was conducted.

ESC noted that there were numerous methodological issues associated with the individual studies (in addition to the uncertainty of assuming noninferiority between 177Lu-DOTA-octreotate and 177Lu-DOTATATE based solely on a comparison of their pharmaceutical forms):

* selection bias because patients were selected on the basis of Octreoscan results (rather than Gallium scans) and because of inadequate allocation concealment
* measurement bias because seven of the studies were open label which may have led to subjective interpretation of PFS and risk of favouring the intervention (this included NETTER-1)
* as already discussed above, the therapies in the trials were only for 177Lu-DOTATATE (meaning that for assessment purposes, non-inferiority between 177Lu-DOTATATE and 177Lu(nca)-DOTA-octreotate was assumed).

ESC also noted the following uncertainties related to the network meta-analysis (NMA):

* Only 1 or 2 trials were available to inform each pairwise connection in the network for the assessment of comparative efficacy which introduces statistical imprecision due to results being underpowered
* NMA relies on the key assumptions of similarity and transitivity and consistency of results
* The NENs discussed in the trials comprising the NMA had different origins (11/14 were pancreatic or GI; the sensitivity analyses excluded cancers originating in the lung)
* Not all the trials required SSTRs on target lesions
* The interventions being studied were used in different lines of treatment and in differing doses across trials but these were assumed to be similar for the purpose of the NMA
* There will be biases associated with the individual studies with the direction and magnitude of the bias unknown.

ESC noted that based on the NMA, 177Lu-DOTATATE was associated with statistically significant improvements in PFS over all examined comparators. ESC noted that when 177Lu-DOTATATE is compared against all 5 comparators on the outcome of OS only non-significant improvement was identified for four of these comparators (while sunitinib was superior to 177Lu-DOTATATE). While the DCAR interpreted this finding as indicating that 177Lu-DOTATATE was at least non-inferior to sunitinib (as the difference was non-significant), ESC considered that it may be more appropriate to interpret these results with caution, as there was no evidence of comparable effectiveness between 177Lu-DOTATATE and sunitinib, at least on OS. In addition, there was inconsistency between OS and PFS results across comparators (e.g. sunitinib was ranked as most likely to be best for OS compared with fourth best for PFS). ESC considered this may reflect the transitivity and potential biases associated with the indirect treatment comparisons.

While acknowledging the context of high clinical need and that current practice already includes both the proposed tests and the intervention, ESC considered that the indirect evidence from the NMA provided to support improvement in progression free survival (PFS) was weak, there was no evidence of change in overall survival and extensive assumptions were made at each step of the clinical assessment phase due to lack of evidence. 177Lu-DOTATATE ESC considered that there was a clear need for further RCT based evidence. However whilst clinical trials are underway, results will not be available for some years to come.

In addition, ESC considered that due to the high uncertainty in the indirect NMA results that the direct evidence for comparative efficacy from the NETTER-1 and OCULRANDOM were likely most informative for decision making (see Direct evidence: 177Lu-DOTATATE trials in Section 9 of this document).

Overall, ESC considered that there was limited direct evidence to support the claim that177Lu-DOTATATE (and thus 177Lu-DOTA-octreotate based on assumed noninferiority between the two products) had superior effectiveness compared with nominated comparators. ESC also considered that the indirect evidence from NMA was also not convincing to support the superiority claim.

ESC noted that a cost-utility analysis was undertaken considering lifetime quality-adjusted life years (QALYs) and healthcare costs. ESC considered that the modelled economic valuation relied on the subsequent acceptance of the clinical evaluation which assumed that the efficacy and safety of 177Lu-DOTA-octreotate was noninferior to 177Lu-DOTATATE. The partitioned survival model considers the cost-effectiveness of 177Lu-DOTA-octreotate compared with all six comparator therapies independently, with the results expressed in terms of incremental cost per QALY gained. ESC considered this model to be reasonable.

ESC noted that while the DCAR’s economic model presented 177Lu-DOTA-octreotate as a first-line treatment against the six comparators, it is potentially more likely to be used as a second-line treatment in actual clinical practice. ESC also considered that PRRT treatment may also likely be used in combination with octreotide, everolimus, lanreotide and sunitinib, which was not modelled in the economic evaluation.

ESC noted that the validity of the model inputs and their appropriateness to an Australian setting were a potential issue insofar as there were no direct Australian RCTs and the background healthcare resource use was based on UK settings (in particular the heavy reliance on the UK NICE TA539).[[37]](#footnote-38) ESC considered that the model validity had been thoroughly undertaken.

ESC noted that the base case incremental cost-effectiveness ratio (ICER) range comparing  
177Lu-DOTA-octreotate versus all six identified comparators ranged from $18,643 to $31,792 per QALY gained, with 177Lu-DOTA-octreotate being dominated against sunitinib. ESC agreed with the DCAR that the ICER was highly uncertain as it was highly sensitive to changes in the comparative effectiveness of the intervention relative to the six comparators. ESC also noted the significant uncertainty introduced because the ICERs were derived based on a lifetime model even though the mean survival time followed in the NETTER-1 was under 5 years (see Figure 4). However, ESC noted that time horizon was not a driver of the ICER in the model.

ESC noted that the modelled average time on treatment for 177Lu-DOTA-octreotate was based on the weighted average number of administrations that patients received in the 177Lu-DOTATATE arm of the NETTER-1 trial (3.5 administrations converted to time based on dosing regimen in trial: 4 infusions at 1 infusion every 8 weeks; time on treatment = 6.5 months). ESC considered this was appropriate. Given the proposed MBS item for 177Lu PRRT therapy is unrestricted in terms of treatment cycles, ESC conducted further sensitivity analyses investigating the scenarios whereby patients modelled in the intervention arm received the full induction treatment course of 4 cycles over 8 months of 177Lu PRRT treatment (rather than the average 3.5 cycles over 6.5 months of PRRT treatment in base case); and also when all patients in the intervention arm received an additional two consolidation cycles of 177Lu PRRT therapy following progression of disease (see Table 14). ESC considered that this indicative sensitivity analyses demonstrated that the ICER was sensitive to the time on treatment and number of cycles of 177Lu-DOTA-octreotate treatment in the model. ESC further considered that the number of cycles of   
177Lu-PRRT as well as the choice of parametric curves should be tested further in sensitivity analyses. Two-way analyses incorporating variation in treatment costs (number of cycles) and use of 68Ga-DOTA-octreotate PET/CT imaging for monitoring treatment response would also be informative.

ESC noted that the pre-ESC response asserted that by failing to identify quality of life (QOL) as the main patient important outcome measure the DCAR had introduced significant potential for bias into the economic evaluation. However, ESC considered that the DCAR included a comprehensive assessment of AEs included in QALY measurement and healthcare resource use in the economic evaluation. ESC also noted and agreed with the rejoinder’s response that OS should be regarded as the most important patient relevant outcome and that health state utilities are adequately captured in the economic assessment.

ESC noted that diagnostic costs accounted for in the economic model only included diagnostic costs associated with patients already deemed eligible for treatment (i.e. it was assumed in the base case that 100% of people tested will qualify for treatment). Therefore, the model did not consider the screening-related costs or performance outcomes of testing all patients by PET/CT to select those eligible for 177Lu PRRT treatment. However, ESC considered that because most patients (intervention and comparator groups) would receive PET/CT testing regardless of treatment decision, the ICER was not substantially affected by this assumption. ESC also considered that the economic model excluded follow-up investigations and associated costs necessary to assess treatment response.

Following the ESC meeting, the assessment group produced an Addendum to address the ESC’s information request for the economic model. This resulted in additional sensitivity analyses conducted to explore the impact of choice of parametric distribution on the estimated cost-effectiveness of 177Lutetium (Lu)-DOTA-octreotate for the treatment of advanced NENs, as well as the mean number of treatment cycles influencing the total cost of treatment. The choice of parametric distribution for progression-free survival (PFS) and overall survival (OS) had a moderate impact on the estimated cost-effectiveness of 177Lu-DOTA-octreotate. Another scenario analysis was also conducted which assumed an additional 68Gallium (Ga)-DOTA-octreotate positron emission tomography (PET)/computed tomography (CT)—68Ga-DOTA-octreotate PET/CT— diagnostic test for patients treated with 177Lu-DOTA-octreotate was conducted as part of follow-up monitoring, in contrast with the model base case which assumes that additional monitoring costs will be equivalent between the intervention and comparators. This scenario resulted in a small increase in the ICER for treatment with 177Lu-DOTA-octreotate (see **Attachment**).

ESC noted that the DCAR estimated a net cost to the MBS of approximately $8.96 million by 2029 based on an assumption of a constant 3.5% of the incident population with NENs undergoing the proposed imaging scan and treatment. ESC noted that the DCAR’s sensitivity analysis assuming 75% of the incident population undertook the proposed imaging and a doubling of the population undergoing treatment estimated a net cost of $17.9 million by 2029.

ESC noted that the department has received advice from the applicant that approximately 65% of patients diagnosed with a NENs (i.e. those with suspected high SSTR expression) would receive a whole-body 68Ga-DOTA-octreotate PET study, of these 30% would also undergo a FDG PET and based on this be potentially eligible for 177Lu-DOTA-octreotate. However, ESC noted that published estimates indicated that the estimate of those with suspected high SSTR expression and thus eligible for 68Ga-DOTA-octreotate PET/CT testing could be as high as 80% in well differentiated NETs[[38]](#footnote-39) and >80% in endocrine tumours of gastroenteropancreatic-NETs[[39]](#footnote-40) . ESC conducted additional sensitivity analysis assuming 80% of the incident population undertook the proposed imaging and a doubling of the population undergoing treatment (as uptake of 177Lu-DOTA-octreotate also based on assumption) estimated a net cost of $23.95 million by 2029 (see Table 17).

Due to the high uncertainty in the financial estimates which heavily relied on assumption, ESC advised that the assessment group investigate whether the financial estimates could be refined to better estimate the incident testing population based on published estimates[[40]](#footnote-41). In addition, ESC queried whether repeat 68Ga-DOTA-octreotate PET/CT imaging for monitoring treatment response (permissible in the proposed MBS item) was adequately captured in the financial analysis. ESC also considered that the financial analysis use the amended fee of $10,000 fee for 177Lutetium-somastatin receptor agonist treatment in the proposed item for PRRT therapy.

Following the ESC meeting, the assessment group produced an Addendum to address the ESC’s information request for the financial model. This resulted in an additional sensitivity analysis which updated the financial impact of 177Lu-DOTA-octreotate using the amended MBS fee of $10,000 for each treatment cycle (rebate=$9,901.30 for each treatment cycle after consideration of the greatest permissible gap). The assessment group also conducted additional scenario analyses: where an additional diagnostic test is assumed to be conducted as part of monitoring; and also an additional scenario exploring the impact of 80% of the eligible incident population receiving diagnostic testing was assessed based on published estimates which indicated that the estimate of those with suspected high SSTR expression and thus eligible for 68Ga-DOTA-octreotate PET/CT testing could be as high as 80% in well differentiated NENs7. Sensitivity analyses were also conducted for each additional scenario (see **Attachment**). The financial impact under the ESC scenario (80% of eligible population tested; additional 68Ga-DOTA-octreotate PET study for treated patients) resulted in a higher net cost of $82.93 million by 2029.

In addition, ESC queried whether the applicant could provide additional advice on extent of current use of 177Lu PRRT therapy, such as from DVA claiming data. ESC noted that patients also may be currently paying out-of-pocket for 177Lu PRRT therapy.

ESC also noted that insofar as there were evidence gaps deserving of future areas of research, evidence on patient outcomes and significant adverse events should already be available from major hospitals with a nuclear medicine facility.

## 17. Applicant comments on MSAC’s Public Summary Document

## 18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](http://msac.gov.au/internet/msac/publishing.nsf/Content/Home-1)

# Attachment

### Addendum

## 1. Additional cost-effectiveness sensitivity analysis

Additional sensitivity analysis has been conducted to explore the impact of choice of parametric distribution on the estimated cost-effectiveness of 177Lutetium (Lu)-DOTA-octreotate for the treatment of advanced neuroendocrine neoplasms (NENs), as well as the mean number of treatment cycles influencing the total cost of treatment. The results of these one- and 2-way sensitivity analyses are presented in Table 1.

The choice of parametric distribution for progression-free survival (PFS) and overall survival (OS) had a moderate impact on the estimated cost-effectiveness of 177Lu-DOTA-octreotate. Incremental cost-effectiveness ratios (ICER) in comparison with placebo ranged between $31,576 per quality-adjusted life year (QALY) and $44,210/QALY for the lognormal and Gompertz distributions, respectively. This trend was consistent across considered comparators.

Scenarios using different estimated time on treatment for 177Lu-DOTA-octreotate also resulted in moderate changes in the estimated ICER, with an assumed additional 0.5 cycles of treatment increasing the estimated ICER in comparison with placebo from $31,792/QALY in the base case to $35,114/QALY. Similarly, assuming 0.5 fewer cycles of treatment resulted in a reduction in the estimated ICER in comparison with placebo to $28,378/QALY. This trend was repeated across all comparators, and regardless of the choice of parametric distribution. Sunitinib was a dominant treatment option in comparison with 177Lu-DOTA-octreotate in all scenarios.

Another scenario considering an assumed additional 68Gallium (Ga)-DOTA-octreotate positron emission tomography (PET)/computed tomography (CT)—68Ga-DOTA-octreotate PET/CT— diagnostic test for patients treated with 177Lu-DOTA-octreotate as part of follow-up monitoring was also considered, in contrast with the model base case which assumes that additional monitoring costs will be equivalent between the intervention and comparators. This scenario resulted in a small increase in the ICER for treatment with 177Lu-DOTA-octreotate.

Table 1: Additional sensitivity analysis exploring the impact of choice of parametric distribution and assumed treatment duration on the ICER (cost per QALY)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **PBO** | **OCT** | **LAN** | **EVO** | **SUN** | **OCT + EVO** |
| **Base case** | | **$31,792** | **$27,676** | **$22,621** | **$29,439** | **Lutetium dominated** | **$18,643** |
| Treatment cycles | 0.5 additional treatment cycles (4.02) | $35,114 | $33,691 | $28,178 | $33,592 | Lutetium dominated | $22,949 |
| 0.5 fewer treatment cycle (3.02) | $28,378 | $21,494 | $16,909 | $25,169 | Lutetium dominated | $14,218 |
| Choice of parametric distribution - OS & PFS Base case number of treatment cycles (3.52) | Weibull | $36,986 | $44,886 | $38,517 | $35,727 | Lutetium dominated | $21,506 |
| Loglogistic | $33,100 | $32,029 | $26,626 | $31,739 | Lutetium dominated | $19,537 |
| Lognormal | $31,576 | $27,582 | $22,558 | $29,968 | Lutetium dominated | $18,561 |
| Gompertz | $44,210 | $48,934 | $34,225 | $41,898 | Lutetium dominated | $23,440 |
| Exponential | $32,217 | $30,472 | $24,312 | $29,897 | Lutetium dominated | $17,892 |
| Gamma | $36,325 | $42,877 | $36,495 | $34,961 | Lutetium dominated | $21,156 |
| Choice of parametric distribution - OS & PFS Assumed 0.5 additional treatment cycles (4.02) | Weibull | $40,897 | $52,262 | $45,510 | $40,589 | Lutetium dominated | $26,433 |
| Loglogistic | $36,582 | $38,451 | $32,588 | $36,103 | Lutetium dominated | $24,035 |
| Lognormal | $34,866 | $33,566 | $28,089 | $34,087 | Lutetium dominated | $22,827 |
| Gompertz | $49,055 | $58,852 | $43,311 | $48,189 | Lutetium dominated | $29,904 |
| Exponential | $35,558 | $36,498 | $29,944 | $34,040 | Lutetium dominated | $22,153 |
| Gamma | $40,158 | $50,065 | $43,296 | $39,725 | Lutetium dominated | $25,994 |
| Choice of parametric distribution - OS & PFS Assumed 0.5 fewer treatment cycles (3.02) | Weibull | $32,983 | $37,334 | $31,357 | $30,750 | Lutetium dominated | $16,462 |
| Loglogistic | $29,530 | $25,444 | $20,514 | $27,265 | Lutetium dominated | $14,926 |
| Lognormal | $28,195 | $21,432 | $16,874 | $25,735 | Lutetium dominated | $14,176 |
| Gompertz | $39,258 | $38,797 | $24,938 | $35,469 | Lutetium dominated | $16,833 |
| Exponential | $28,796 | $24,303 | $18,547 | $25,656 | Lutetium dominated | $13,531 |
| Gamma | $32,397 | $35,513 | $29,527 | $30,080 | Lutetium dominated | $16,199 |
| Assumed one additional 68Ga-DOTA-octreotate PET/CT for patients treated with 177Lu-DOTA-octreotate | | $32,496 | $28,950 | $23,798 | $30,318 | Lutetium dominated | $19,555 |

Abbreviations: CT = computed tomography; EVO = everolimus; ICER = incremental cost-effectiveness ratio; LAN = lanreotide, OCT = octreotide; OCT+EVO = octreotide plus everolimus combination therapy; OS = overall survival; PBO = placebo; PET = positron emission tomography; PFS = progression-free survival; QALY = quality-adjusted life year; SUN =sunitinib.

## 2. Additional financial impact sensitivity analysis

The estimated financial impact of 177Lu-DOTA-octreotate has been updated using the amended MBS fee of $10,000 for each treatment cycle (Table 2). All scenarios presented in the addendum were undertaken using the updated MBS fee (rebate=$9,901.30 for each treatment cycle after consideration of the greatest permissible gap).

Table 2: Financial impact with updated MBS fee

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **2024 (year 1)** | **2025 (year 2)** | **2026 (year 3)** | **2027 (year 4)** | **2028 (year 5)** | **2029 (year 6)** |
| **Estimated use and cost of the proposed health technology** | | | | | | |
| Incidence of NENs | 5,642 | 5,857 | 6,080 | 6,312 | 6,552 | 6,802 |
| Number of people eligible for 177Lu-DOTA-octreotate | Unknown Assumed 3.5% to match applicant advised treatment population of approximately 200 | | | | | |
| Number of people who receive 177Lu-DOTA-octreotate | 197 | 205 | 213 | 221 | 229 | 238 |
| Of which, diagnosed with 68Ga-DOTA-octreotate PET/CT (100%) | 197 | 205 | 213 | 221 | 229 | 238 |
| Of which, diagnosed with 18FDG PET/CT (30%) | 59 | 61 | 64 | 66 | 69 | 71 |
| Cost to the MBS; treatment drug cost | $6,890,666 | $7,153,235 | $7,425,809 | $7,708,769 | $8,002,512 | $8,307,447 |
| Cost to the MBS; diagnostic test cost | $240,037 | $249,183 | $258,679 | $268,535 | $278,768 | $289,390 |
| **Change in use and cost of other health technologies** | | | | | | |
| Change in use of comparator and other. | N/A 177Lu-DOTA-octreotate is proposed as an add-on therapy | | | | | |
| **Net financial impact to the MBS** | **$7,130,703** | **$7,402,418** | **$7,684,487** | **$7,977,305** | **$8,281,280** | **$8,596,838** |

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; MBS = Medicare Benefits Schedule; N/A = not applicable; NEN = neuroendocrine neoplasm; PET = positron emission tomography.

A scenario where an additional diagnostic test is conducted as part of monitoring was conducted (Table 3). In this scenario, the estimated net financial impact of 177Lu-DOTA-octreotate to the Medicare Benefits Schedule (MBS) is estimated to be $7,315,347 in Year 1, increasing to $8,819,446 in Year 6. This corresponds to a total net financial impact over 6 years of $48.3 million, in comparison with $49.1 million in the original Department contracted assessment report (DCAR).

Additional sensitivity analyses were also conducted to explore the impact of assumptions around the duration of treatment with 177Lu-DOTA-octreotate (Table 3). Consistent with cost-effectiveness estimates, assuming increased duration of treatment results in increased net financial impact, and a reduced treatment duration results in reduced net financial impact. Scenarios including additional costs of diagnostic testing as part of monitoring resulted in 6-year net budget impacts of $54.7 and $41.8 million for an assumed additional 0.5 cycles of treatment and 0.5 fewer cycles of treatment, respectively.

An additional scenario exploring the impact of 80% of the eligible incident population receiving diagnostic testing was assessed based on published estimates indicating that the estimate of those with suspected high SSTR expression and thus eligible for 68Ga-DOTA-octreotate PET/CT testing could be as high as 80% in well differentiated NENs[[41]](#footnote-42). It is noted that this scenario assumes that none of these patients would receive 68Ga-DOTA-octreotate PET/CT testing in the absence of 177Lu-DOTA-octreotate.

In this scenario the 6-year budget impact increased to $81.7 million, with 44.3% of the net budget impact being attributable to increased diagnostic testing. Combined with an additional diagnostic test assumed as part of monitoring, the 6-year net budget impact increased to $82.9 million. The latter scenario (80% of eligible population tested; additional 68Ga-DOTA-octreotate PET study for treated patients) captures the Evaluation Sub-Committee (ESC)-defined scenario (Table 4).

Table 3: Financial impact sensitivity analysis varying treatment duration and additional costs of monitoring

|  | **Net financial impact to the MBS** | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **2024 (year 1)** | **2025 (year 2)** | **2026 (year 3)** | **2027 (year 4)** | **2028 (year 5)** | **2029 (year 6)** |
| **Base case with revised MBS item cost** | **$7,130,703** | **$7,402,418** | **$7,684,487** | **$7,977,305** | **$8,281,280** | **$8,596,838** |
| Additional diagnostic test (68Ga-DOTA-octreotate PET/CT) as part of monitoring | $7,315,347 | $7,594,098 | $7,883,471 | $8,183,870 | $8,495,717 | $8,819,446 |
| 0.5 additional treatment cycles (4.02) | $8,108,305 | $8,417,271 | $8,738,011 | $9,070,973 | $9,416,622 | $9,775,443 |
| 0.5 fewer treatment cycle (3.02) | $6,153,102 | $6,387,566 | $6,630,964 | $6,883,636 | $7,145,937 | $7,418,233 |
| 0.5 additional treatment cycles (4.02) + additional diagnostic test | $8,292,948 | $8,608,951 | $8,936,995 | $9,277,539 | $9,631,059 | $9,998,051 |
| 0.5 fewer treatment cycle (3.02) + additional diagnostic test | $6,337,745 | $6,579,245 | $6,829,947 | $7,090,202 | $7,360,374 | $7,640,841 |
| 80% of incident population receive initial diagnostic testing | $12,377,221 | $12,848,855 | $13,338,460 | $13,846,722 | $14,374,351 | $14,922,086 |
| 80% of incident population receive diagnostic testing + additional diagnostic test as part of monitoring for patients who receive 177Lu-DOTA-octreotate | $12,561,865 | $13,040,535 | $13,537,444 | $14,053,288 | $14,588,788 | $15,144,694 |
| 80% of incident population receive initial diagnostic testing + 0.5 additional treatment cycles (4.02) | $13,354,823 | $13,863,708 | $14,391,984 | $14,940,391 | $15,509,694 | $16,100,690 |
| 80% of incident population receive initial diagnostic testing + 0.5 fewer treatment cycles (3.02) | $11,399,620 | $11,834,002 | $12,284,937 | $12,753,054 | $13,239,009 | $13,743,481 |

Abbreviations: CT = computed tomography; MBS = Medicare Benefits Schedule; PET = positron emission tomography.

Table 4: Financial impact under ESC-defined scenario (80% of eligible population tested; additional 68Ga-DOTA-octreotate PET study for treated patients)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **2024 (year 1)** | **2025 (year 2)** | **2026 (year 3)** | **2027 (year 4)** | **2028 (year 5)** | **2029 (year 6)** |
| **Estimated use and cost of the proposed health technology** | | | | | | |
| Incidence of NENs | 5,642 | 5,857 | 6,080 | 6,312 | 6,552 | 6,802 |
| Number of people eligible for 177Lu-DOTA-octreotate | Unknown Assumed 3.5% to match applicant advised treatment population of approximately 200 | | | | | |
| Incident NEN patients who undergo 68Ga-DOTA-octreotate PET/CT (80% of incident population) | 4,514 | 4,686 | 4,864 | 5,049 | 5,242 | 5,442 |
| Of which, diagnosed with 18FDG PET/CT (30%) | 1,354 | 1,406 | 1,459 | 1,515 | 1,573 | 1,632 |
| Number of people who receive 177Lu-DOTA-octreotate | 197 | 205 | 213 | 221 | 229 | 238 |
| Additional 68Ga-DOTA-octreotate PET study for monitoring | 197 | 205 | 213 | 221 | 229 | 238 |
| Cost to the MBS; treatment drug cost | $6,890,666 | $7,153,235 | $7,425,809 | $7,708,769 | $8,002,512 | $8,307,447 |
| Cost to the MBS; diagnostic test cost | $5,671,199 | $5,887,300 | $6,111,635 | $6,344,519 | $6,586,276 | $6,837,246 |
| **Change in use and cost of other health technologies** | | | | | | |
| Change in use of comparator and other. | N/A 177Lu-DOTA-octreotate is proposed as an add-on therapy | | | | | |
| **Net financial impact to the MBS** | **$12,561,865** | **$13,040,535** | **$13,537,444** | **$14,053,288** | **$14,588,788** | **$15,144,694** |

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; MBS = Medicare Benefits Schedule; N/A = not applicable; NEN = neuroendocrine neoplasm; PET = positron emission tomography.

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