Medical Services Advisory Committee (MSAC) Public Summary Document

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

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

Date of MSAC consideration: **29 November 2024**
1-2 August 2024

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

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 ^{177}Lutetium (no carrier added)-DOTA-octreotate (^{177}Lu (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 ^{68}Gallium (Ga)-DOTA-octreotate SSTR-positron emission tomography (PET)/computed tomography (CT) (^{68}Ga-DOTA-octreotate PET/CT) to determine eligibility for ^{177}Lu (nca)-DOTA-octreotate treatment, as well as for monitoring the post-treatment effect of ^{177}Lu (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 ^{177}Lu-DOTA-octreotate.

Furthermore, the original application included the requirement for an additional test, ^{18}F-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 ^{177}Lu-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

November 2024 MSAC consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for ^{177}Lutetium Octreotate (^{177}Lu-DOTA-octreotate) therapy for the treatment of advanced neuroendocrine neoplasms (NENs) with high somatostatin receptor (H-SSTR) expression, including phaeochromocytomas and paragangliomas and whole body ^{68}Gallium (Ga)-DOTA-octreotate SSTR-positron emission tomography (PET)/computed tomography (CT) (^{68}Ga-DOTA-octreotate PET/CT) to identify patients eligible for ^{177}Lu-DOTA-octreotate and/or to monitor response to this treatment.

MSAC had previously deferred its advice and requested independent radiochemist advice on the extent of similarity of the chemical structure of ^{177}Lu-DOTA-octreotate and ^{177}Lu-DOTATATE because the clinical evidence presented in the assessment had been based on ^{177}Lu-DOTATATE and was premised on non-inferiority between ^{177}Lu-DOTA-octreotate and ^{177}Lu-DOTATATE.

MSAC accepted, based on advice from two independent radiochemists, that the chemical structures of ^{177}Lu-DOTA-octreotate and ^{177}Lu-DOTATATE were identical in terms of:

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

MSAC considered that, because the chemical structures of ^{177}Lu-DOTA-octreotate and ^{177}Lu-DOTATATE were identical (as outlined above), further comparative assessment of the biodistribution, efficacy and safety of ^{177}Lu-DOTA-octreotate and ^{177}Lu-DOTATATE was not required to demonstrate that the two products are non-inferior in terms of health outcomes and the evidence presented for ^{177}Lu-DOTATATE could be used to assess ^{177}Lu-DOTA-octreotate.

Therefore, MSAC considered ^{177}Lu-DOTA-octreotate was acceptably safe and effective compared with standard care and despite limitations in the economic evaluation, ^{177}Lu-DOTA-octreotate was acceptably cost-effective. MSAC noted that the net financial impact to the MBS from the funding of the treatment and expanding testing for its eligibility was acceptable. MSAC advised the treatment MBS item should refer to ^{177}Lutetium-DOTA-somatostatin receptor agonist treatment to align with the evidence base and testing item descriptor.

MSAC noted the patent related issues raised during the consultation process. MSAC referred to its Terms of Reference and concluded that patent related matters were not within its Terms of Reference and would require consideration by Government prior to any decision to list the MBS items as a result of this application.

Category T3 – Therapeutic Nuclear Medicine

MBS item XXXX

^{177}Lutetium-DOTA-somatostatin 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:

a) have high tumour somatostatin receptor expression demonstrated on whole body ^{68}Ga DOTA somatostatin agonist PET study; and

b) are considered suitable for ^{177}Lutetium-DOTA-somatostatin receptor agonist therapy by a formally convened neuroendocrine neoplasm multidisciplinary board.

The item fee is inclusive of necessary patient preparation such as:

a) patient preparation (including cost of amino acid infusion),

b) radiopharmaceutical preparation and administration,

c) immediate patient aftercare; and

d) 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: $10,000

Category 5 – Diagnostic Imaging Services

Group I4 – Nuclear Medicine Imaging, Subgroup 2 – PET

MBS item XXXX

Whole body ^{68}Ga-DOTA-octreotate or somatostatin receptor agonist PET study of patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine neoplasms (NENs) with

a) Localisation of functioning (hormonally active) NEN when conventional imaging negative or equivocal; or

b) Staging of histologically confirmed NEN considered surgically curable on conventional imaging, or

c) Evaluation of somatostatin analogue (SSA) avidity (SSTR-2 expression) of NEN under consideration for peptide receptor radionuclide therapy (PRRT); or

d) Evaluation of response to PRRT therapy; or

e) Evaluation of suspected recurrent/metastatic disease in known SSA-avid (H-SSTR) NEN

when referred by a specialist or consultant physician.

Fee: $953

Consumer summary - November 2024 MSAC consideration

This is an application from Applied Molecular Therapies requesting Medicare Benefits Schedule (MBS) listing of ^{177}Lutetium-DOTA-octreotate (^{177}Lu-DOTA-octreotate) for the treatment of advanced neuroendocrine neoplasms and other high somatostatin receptor expressing tumours. This application also requests a new MBS item for ^{68}Gallium[Ga]-DOTA-octreotate somatostatin receptor 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. Neuroendocrine cells are found throughout the body and form part of 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 cause significant problems and worsen the person's quality of life. High-grade tumours can affect organ function and lead to death.

Some neuroendocrine tumour cells have specific receptors 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 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 Lutetium treatment that a person needs depends on the grade or severity of their cancer.

MSAC had considered this application at its meeting in August 2024. Although the evidence had suggested that ^{177}Lu-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 ^{177}Lu-DOTA-octreotate was chemically identical to another product ^{177}Lu-DOTATATE. MSAC previously could not be sure that the products were chemically identical, so deferred its decision so that it could seek expert advice from radiochemists.

MSAC received the advice from two separate radiochemists, who both independently confirmed that the chemical structures of the two products were identical[1]. This meant that MSAC's previous conclusions for ^{177}Lu-DOTATATE were applicable to the ^{177}Lu-DOTA-octreotate product in this application. Therefore, MSAC supported public funding for this treatment for advanced neuroendocrine neoplasms. It also supported an MBS item for a PET/CT scan so that it could be used to assess a patient's suitability and response to the therapy, as well as checking whether their tumours have returned.

MSAC's advice to the Commonwealth Minister for Health and Aged Care – November 2024 MSAC consideration

MSAC supported public funding for ^{177}Lu-DOTA-octreotate treatment for advanced neuroendocrine neoplasms. MSAC also supported public funding for DOTATATE PET/CT to include assessment of suitability for ^{177}Lu-DOTA-octreotate therapy, therapy response and disease recurrence. MSAC had previously accepted the safety, effectiveness and cost-effectiveness of a similar treatment (^{177}Lu-DOTATATE), but it had not been sure if ^{177}Lu-DOTA-octreotate worked in the same way. After receiving expert advice that the two treatments were chemically identical, MSAC accepted that 177Lu-DOTA-octreotate is more effective and just as safe as other treatments and has good value for money.

[1] Specifically the chemical structure of ^{177}Lu-DOTA-octreotate and ^{177}Lu-DOTATATE were identical because the (i) targeting moiety (peptides), (ii) chelators binding ^{177}Lu-DOTATATE to the peptides and (iii) the linker which joins the chelator to the targeting part of the peptides were identical.

August 2024 MSAC consideration

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) ^{177}Lutetium Octreotate (^{177}Lu-DOTA-octreotate) treatment of advanced neuroendocrine neoplasms (NENs) with high somatostatin receptor (H-SSTR) expression and 2) whole body ^{68}Gallium (Ga)-DOTA-octreotate SSTR-positron emission tomography (PET)/computed tomography (CT) (^{68}Ga-DOTA-octreotate PET/CT) to identify those eligible for ^{177}Lu-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 ^{177}Lu-DOTA-octreotate and Lutathera® (^{177}Lu-DOTATATE). MSAC noted that the assessment assumed non-inferiority of ^{177}Lu-DOTA-octreotate and Lutathera® (^{177}Lu-DOTATATE), and therefore assumed that the randomised controlled trial (RCT) data presented for Lutathera® (^{177}Lu-DOTATATE) would be relevant to ^{177}Lu-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., ^{177}Lu-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 ^{177}Lu-DOTA-octreotate and Lutathera® (^{177}Lu-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 ^{177}Lu-DOTA-octreotate and Lutathera® (^{177}Lu-DOTATATE) be conducted in order to demonstrate that the two products are non-inferior 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 non-inferiority between ^{177}Lu-DOTA-octreotate and Lutathera® (^{177}Lu-DOTATATE) products was subsequently accepted. This was because MSAC concluded from the evidence presented that ^{177}Lu-DOTATATE, and thus ^{177}Lu-DOTA-octreotate if non-inferiority was subsequently accepted, was acceptably safe and effective compared with standard care and despite limitations in the economic evaluation, ^{177}Lu-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 - August 2024 MSAC consideration

This is an application from Applied Molecular Therapies requesting Medicare Benefits Schedule (MBS) listing of ^{177}Lutetium (no carrier added [nca])-DOTA-octreotate (^{177}Lu [nca]-DOTA-octreotate) for the treatment of advanced neuroendocrine neoplasms with high somatostatin receptor expression. This application also requests listing of a new MBS item for whole body ^{68}Gallium[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 ^{177}Lutetium(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.

^{177}Lu-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 ^{177}Lu-DOTATATE, not ^{177}Lu-DOTA-octreotate (the applicant's product). Although the evidence suggested that ^{177}Lu-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 ^{177}Lu-DOTA-octreotate was chemically similar to ^{177}Lu-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 ^{177}Lu-DOTATATE and ^{177}Lu-DOTA-octreotate are chemically similar and/or have the same effects on the body before it can be assumed that the evidence presented for ^{177}Lu-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. MSAC noted that additional evidence may need to be included for consideration if this advice established that the two products were not chemically identical.

MSAC's advice to the Commonwealth Minister for Health and Aged Care – August 2024 consideration

MSAC deferred its advice on MBS listing of ^{177}Lu (nca)-DOTA-octreotate treatment for advanced neuroendocrine neoplasms with high somatostatin receptor expression. The evidence presented was for another product, ^{177}Lu-DOTATATE. Although ^{177}Lu-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 ^{177}Lu-DOTATATE . Therefore, MSAC could not make a decision without

Consumer summary - August 2024 MSAC consideration
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

November 2024 MSAC consideration

MSAC noted that this was an application from Applied Molecular Therapies Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of ^{177}Lutetium (no carrier added)-DOTA-octreotate (^{177}Lu (nca)-DOTA-octreotate) for the treatment of advanced neuroendocrine neoplasms (NENs) with high somatostatin receptor (H-SSTR) expression. The application was also requesting a new MBS listing for ^{68}Gallium (Ga)-DOTA-octreotate SSTR-positron emission tomography (PET)/computed tomography (CT) — ^{68}Ga-DOTA-octreotate PET/CT — to determine eligibility for ^{177}Lu (nca)-DOTA-octreotate treatment, as well as for monitoring the post-treatment effect of ^{177}Lu (nca)-DOTA-octreotate. This treatment is a type of peptide receptor radionuclide therapy (PRRT).

MSAC recalled that it considered this application at its meeting in August 2024. The evidence that had been considered in the Department-contracted assessment report (DCAR) was for ^{177}Lu-DOTATATE (with the commercial name Lutathera®), with the assumption being that it was non-inferior to ^{177}Lu-DOTA-octreotate. At the time, MSAC accepted that there was no basis in the presented clinic evidence to distinguish ^{177}Lu-DOTA-octreotate treatment that was non-carrier added ('nca') from ^{177}Lu-DOTA-octreotate treatment that was carrier added ('ca'). MSAC had also accepted that, although evidence for some NEN subtypes was weak, overall, the evidence showed that:

- ^{177}Lu-DOTATATE was a safe and clinically effective therapy
- in most plausible scenarios, ^{177}Lu-DOTATATE had an acceptable incremental cost-effectiveness ratio (ICER)
- better data to inform decisions in the near future were unlikely.

MSAC had also noted the high clinical need and strong consumer support for the treatment. Therefore, MSAC had considered supporting funding for ^{177}Lu-DOTA-octreotate. However, MSAC noted that no reliable data were presented in the DCAR 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. This meant that the relevance of the evidence presented in the DCAR was uncertain. MSAC had therefore requested that the Department seek expert assessment on the chemical forms of the 2 products.

MSAC noted that two independent radiochemists advised that the chemical structures of ^{177}Lu-DOTATATE and ^{177}Lu-DOTA-octreotate were identical. Specifically, advice from the radiochemists confirmed that:

- the targeting moiety of both products feature the same octreotate analogue
- both products feature the DOTA chelator for binding ^{177} Lutetium
- the metal chelator in both products is conjugated to the N-terminus of the octreotate peptide via the same chemical methodology and is, therefore, of the same chemical structure.

Based on this advice, the MSAC Executive had agreed that this application should be reconsidered by MSAC.

MSAC accepted that the chemical structures of ^{177}Lu-DOTA-octreotate and ^{177}Lu-DOTATATE were identical, based on the aforementioned advice from the independent radiochemists.

MSAC considered that, because the chemical structures of ^{177}Lu-DOTA-octreotate ^{177}Lu-DOTATATE were identical, further comparative assessment of the biodistribution, efficacy and safety of ^{177}Lu-DOTA-octreotate and ^{177}Lu-DOTATATE was not required to demonstrate that the two products are non-inferior in terms of health outcomes and the evidence presented for ^{177}Lu-DOTATATE could be used to assess ^{177}Lu-DOTA-octreotate. Therefore, MSAC considered ^{177}Lu-DOTA-octreotate was acceptably safe and effective compared with standard care for treating advanced NENs based on the evidence presented for ^{177}Lu-DOTATATE. MSAC further acknowledged that this treatment has been used in Australia for more than 10 years and. has proven safety and effectiveness in day-to-day clinical practice. MSAC also considered that, in most plausible scenarios, ^{177}Lu-DOTA-octreotate is cost-effective.

MSAC noted that the generic definition of the agent in the MBS item descriptor was broader than the evidence presented in the DCAR and accepted by MSAC. MSAC was concerned that, by making the item descriptor too generic, new products with different targeting moieties, chelators or linkers could be claimed under this MBS item without MSAC consideration. Therefore, MSAC advised that the MBS item descriptor should specify '^{177}Lutetium-DOTA-somatostatin receptor agonist' to align with the evidence base that had been considered by MSAC. This would also better align the item descriptor for ^{177}Lu-DOTA-somatostatin receptor agonist treatment with that for the ^{68}Ga-DOTA-octreotate PET/CT scan.

MSAC agreed that it was important that the MBS item descriptor include patient preparation and post-infusion single-photon emission computed tomography (SPECT). MSAC also advised that the MBS item descriptor or an Explanatory Note should specify that phaeochromocytoma and paraganglioma are eligible, to ensure that these conditions are included under the umbrella of NENs.

Regarding the number of treatment cycles, MSAC noted that ^{177}Lu-DOTA-octreotate will be administered based on the consensus of a NEN multidisciplinary team and determined by the grade of tumour and patient response. MSAC considered that some patients may not tolerate having 4 initial treatment cycles, while a small proportion may need retreatment (typically 1 or 2 additional cycles). Therefore, MSAC agreed with the Department that, at least initially, it is appropriate to have no restrictions on the number of therapy cycles. MSAC suggested that utilisation and out-of-pocket costs be reviewed after 24 months, and if any overuse is detected, this can be addressed through consultation with relevant stakeholders.

Regarding the fee, MSAC acknowledged that this would depend on the cost of ^{177}Lu-DOTA-octreotate, which was difficult to predict. However, MSAC considered a fee of $10,000 to be appropriate, based on equivalent items and the available knowledge of ^{177}Lu-DOTA-octreotate therapy at this time.

MSAC noted that an MBS item number exists for DOTATATE PET (MBS item 61647), but it only covers diagnosis and presurgical staging. MSAC recommended a new item number to include assessing:

- patients for treatment eligibility before receiving ^{177}Lu-DOTA-octreotate therapy
- patient response to ^{177}Lu-DOTA-octreotate therapy
- progression of recurrent or metastatic disease following ^{177}Lu-DOTA-octreotate therapy.

Regarding training and accreditation, MSAC noted that ^{177}Lu-DOTA-octreotate is a specialised therapy using unsealed longer-acting beta-emitters, so it does carry some risk to the patient, staff, carers, the community and the environment (waste disposal). MSAC also noted that, clinically, there is a small risk of carcinoid crisis during therapy. MSAC considered that these risks can be mitigated if therapy is undertaken by properly trained staff in appropriately licensed facilities with adequate resuscitation capacity. MSAC noted that the Department plans to consult on training and accreditation requirements before implementation. MSAC noted that the only expert group currently offering training and accreditation for use of this treatment is the Australasian Association of Nuclear Medicine Specialists.

MSAC noted that, assuming a ^{177}Lu-DOTA-octreotate fee of $10,000 and that 80% of patients diagnosed with NENs each year have ^{68}Ga-DOTA-octreotate PET assessment (estimated by ESC), the Department estimates that the 'upper limit' cost to the MBS will be $12.6 million in year 1 to $14.1 million in year 4, totalling $53.2 million over 4 years. MSAC considered that the assumption that 80% of the eligible population will have PET imaging was an overestimate. MSAC noted that around 50% of all NENs are diagnosed early at stage I and therefore these patients would be too early in the disease process to be eligible for ^{177}Lu-DOTA-octreotate therapy. Thus, the figures presented in the financial estimates for utilisation were an overestimate. MSAC also noted that the costs included ^{18}Fluorodeoxyglucose (FDG) PET/CT imaging for 30% of patients. However, FDG PET/CT is already covered by MBS item 61612 and 61614. This item can be used for patients with rare and uncommon cancers, such as NENs, so MSAC considered that the cost to the MBS will likely be much lower than estimated.

MSAC also noted that patients who undergo ^{177}Lu-DOTA-octreotate treatment (3.5 cycles) would also require at least one follow-up whole body ^{68}Ga-DOTA-octreotate PET study for treatment response and recurrence. MSAC recalled that this had been discussed at its August 2024 meeting, and it retained its previous conclusion that this was reasonable.

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 before and during any decision in relation to whether to list new MBS items as a result of this application.

August 2024 MSAC consideration

MSAC noted that this application from Applied Molecular Therapies Pty Ltd was requesting Medicare Benefits Schedule (MBS) listing of ^{177}Lutetium (no carrier added)-DOTA-octreotate (^{177}Lu (nca)-DOTA-octreotate) for the treatment of advanced neuroendocrine neoplasms (NENs) with high somatostatin receptor (H-SSTR) expression. The application was also requesting MBS listing of a new item for whole body ^{68}Gallium [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 ^{177}Lu-DOTA-ctreotate and ^{177}Lu-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 ^{177}Lu-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 ^{68}Ga-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 ^{177}Lu (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 ^{177}Lu (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 ^{68}Ga-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 ^{68}Ga-DOTA-octreotate PET/CT is more accurate, easier for the patient,

less expensive and has a lower radiation dose than the alternative, ^{111}Indium-octreotide single-photon emission CT (SPECT). Also, some trials, including CONTROL NETS (which was omitted from the Department Commissioned Assessment Report [DCAR]) have used ^{68}Ga-DOTA-octreotate PET/CT to assess suitability for therapy. Regarding change in clinical outcomes, MSAC noted that ^{177}Lu-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 ^{177}Lu (nca)-DOTA-octreotate, there is no difference in biodistribution between the "carrier added" and "no carrier added" versions of ^{177}Lu-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, ^{177}Lu-DOTATATE, and not to ^{177}Lu-DOTA-octreotate (the applicant's product) and therefore the relevance of this evidence was premised on the assumed non-inferiority between ^{177}Lu-DOTATATE, and ^{177}Lu-DOTA-octreotate. This was because the DCAR identified a lack of randomised controlled (RCT) data available for ^{177}Lutetium Octreotate (^{177}Lu-DOTA-octreotate). MSAC noted that the commercial therapeutic product, ^{177}Lu-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 ^{177}Lu-DOTATATE (Lutathera®) and ^{177}Lu-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 ^{177}Lu-DOTA-octreotate and ^{177}Lu-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 ^{177}Lu-DOTA-octreotate. In addition, MSAC noted the applicant tendered expert opinion from a biochemist that the structure of the peptides in ^{177}Lu-DOTATATE and ^{177}Lu-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., ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTATATE services at the Royal Brisbane and Women's Hospital

(RBWH)[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, ^{177}Lu- Octreotate [Lutate].

MSAC noted that a claim of non-inferiority needs to be accepted in order for the evidence for the Lutathera® product (^{177}Lu-DOTATATE; unspecified, used in the NETTER-1 trial), to be considered relevant for the applicant's product (^{177}Lu-DOTA-octreotate) or other ^{177}Lu 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 (^{177}Lu-DOTA-octreotate) was not assessed in the DCAR, including to inform the claim of non-inferiority of ^{177}Lu-DOTA-octreotate versus ^{177}Lu-DOTATATE. However, MSAC assessed the comparative safety and effectiveness of ^{177}Lu-DOTATATE and left for later consideration (as discussed below), the implications of this evidence for the clinical safety and effectiveness and cost effectiveness of ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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, ^{177}Lu-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

[2] Nalder M, Ladwa R, Raina A, Burge ME, Love A, Pattison DA et al. (2021). ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in patients with somatostatin-expressing neuroendocrine tumors: a real-world retrospective review of efficacy and safety from an Australian tertiary cancer Center [abstract]. *Journal of Clinical Oncology* 39(15_suppl):e16198.

- 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 ^{177}Lu-DOTA-octreotate is non-inferior to ^{177}Lu-DOTATATE, as well as acceptance of the results of the NMA. The economic evaluation used ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTATATE (OCCLURANDOM) showed that ^{177}Lu-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 ^{177}Lu-DOTA-octreotate (assuming non-inferiority between the applicant's product and ^{177}Lu-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 ^{68}Ga-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 ^{68}Ga-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 ^{177}Lu-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 ^{177}Lu-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 ^{68}Ga-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 ^{177}Lu-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 ^{177}Lu-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, ^{177}Lu-DOTATATE. Although MSAC considered that this product appeared to have superior clinical effectiveness and non-inferior safety, the assumed non-inferiority between ^{177}Lu-DOTATATE and the proposed product, ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate and Lutathera® (^{177}Lu-DOTATATE) be conducted in order to demonstrate that the two products are non-inferior in terms of health outcomes. MSAC noted that there was both available published observational studies

and Australian RCTs that used the applicant's product (^{177}Lu-DOTA-octreotate) rather than ^{177}Lu-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 (^{177}Lutetium-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate at its meeting in August 2023.

5. Prerequisites to implementation of any funding advice

^{177}Lu 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 ^{177}Lu-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.[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 ^{68}Ga-DOTA-peptide PET imaging (item 61647) (Table 1), would require revision or replacement to accommodate the ^{68}Ga-DOTA-

[3] Therapeutic Goods Administration *GMP information for manufacturers of compounded medicines and DAAs*, viewed 02/2024, <https://www.tga.gov.au/resources/resource/guidance/gmp-information-manufacturers-compounded-medicines-and-daas>.

octreotate PET/CT imaging proposed in this application. Specifically, the relevant radiopharmaceutical product should be a ^{68}Ga-DOTA-octreotate or SSTR agonist (excludes SSTR antagonists) and indications should be amended to include:

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

PASC also noted that a revised item for whole body ^{68}Ga-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 ^{68}Ga 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 ^{68}Ga DOTA-peptide PET

Category 5 – Diagnostic Imaging Services
MBS item 61647 Whole body ^{68}Ga 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 ^{68}Ga DOTA-peptide PET Study to determine SSTR expression

Category 5 – Diagnostic Imaging Services
MBS item [item number] Whole body ^{68}Ga-DOTA-octreotate or somatostatin receptor agonist PET study of patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine neoplasms (NENs) with a) Localisation of functioning (hormonally active) NEN when conventional imaging negative or equivocal; or b) Staging of histologically confirmed NEN considered surgically curable on conventional imaging, or c) Evaluation of somatostatin analogue (SSA) avidity (SSTR-2 expression) of NEN under consideration for peptide receptor radionuclide therapy (PRRT); or d) Evaluation of response to PRRT therapy; or e) 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 ^{177}Lu-DOTA-octreotate

Table 3 presents the item descriptor suggested by PASC for the proposed new MBS item for ^{177}Lu-DOTA-octreotate. It is proposed that the various service elements of ^{177}Lu-DOTA-octreotate treatment administration be bundled together into the per-cycle fee for ^{177}Lu-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 ^{177}Lu-DOTA-octreotate

Category T3-Therapeutic Nuclear Medicine
MBS item [item number] ^{177}Lutetium-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: a) have high tumour somatostatin receptor expression demonstrated on whole body ^{68}Ga DOTA somatostatin agonist PET study; and b) are considered suitable for ^{177}Lu-somatostatin agonist therapy by a formally convened neuroendocrine neoplasm multidisciplinary board. The item fee is inclusive of necessary patient preparation such as: a) patient preparation (including cost of amino acid infusion), b) radiopharmaceutical preparation and administration, c) immediate patient aftercare; and d) 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 ^{177}Lu-DOTA-octreotate

Service Element	Suggested Fee	Comments from applicant
GMP ^{177}Lu (nca)-DOTA-octreotate supply	$8,000.00	AMT cannot supply for a lower cost
GMP ^{177}Lu (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 ^{177}Lu 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 ^{177}Lu DOTA-octreotate fee bundled a number of essential service elements. Higher fee than suggested by AANMS for ^{177}Lu 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 ^{177}Lu 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 ^{177}Lu DOTA PSMA i&t therapy
Nuclear medicine technologist	$200.00	Derived directly from fee suggested by AANMS for ^{177}Lu 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 ^{177}Lu DOTA PSMA i&t therapy
Radiation safety officer/physicist	$75.00	Derived directly from fee suggested by AANMS for ^{177}Lu DOTA PSMA i&t therapy. Probable this function could be supplied without additional cost by the nuclear medicine technologist
Total GMP ^{177}Lu (nca)-DOTA-octreotate	$10,431.05	
Total GMP ^{177}Lu (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 ^{68}Ga-DOTA-octreotate PET/CT testing to assess eligibility for ^{177}Lu-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 ^{68}Ga-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 ^{177}Lu 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'.

^{177}Lu-DOTA-octreotate will be used in addition to existing therapies. ^{177}Lu-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 ^{177}Lu-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.[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 ^{177}Lu-DOTA-octreotate should not be viewed as a fixed line in any patient's therapy. The most appropriate line of therapy for ^{177}Lu-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.

[4] Pavel, M, Oberg, K, Falconi, M, Krenning, EP, Sundin, A, Perren, A, Berruti, A & clinicalguidelines@esmo.org, EGCEa 2020, 'Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up', *Ann Oncol*, vol. 31, no. 7, pp. 844-60.

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

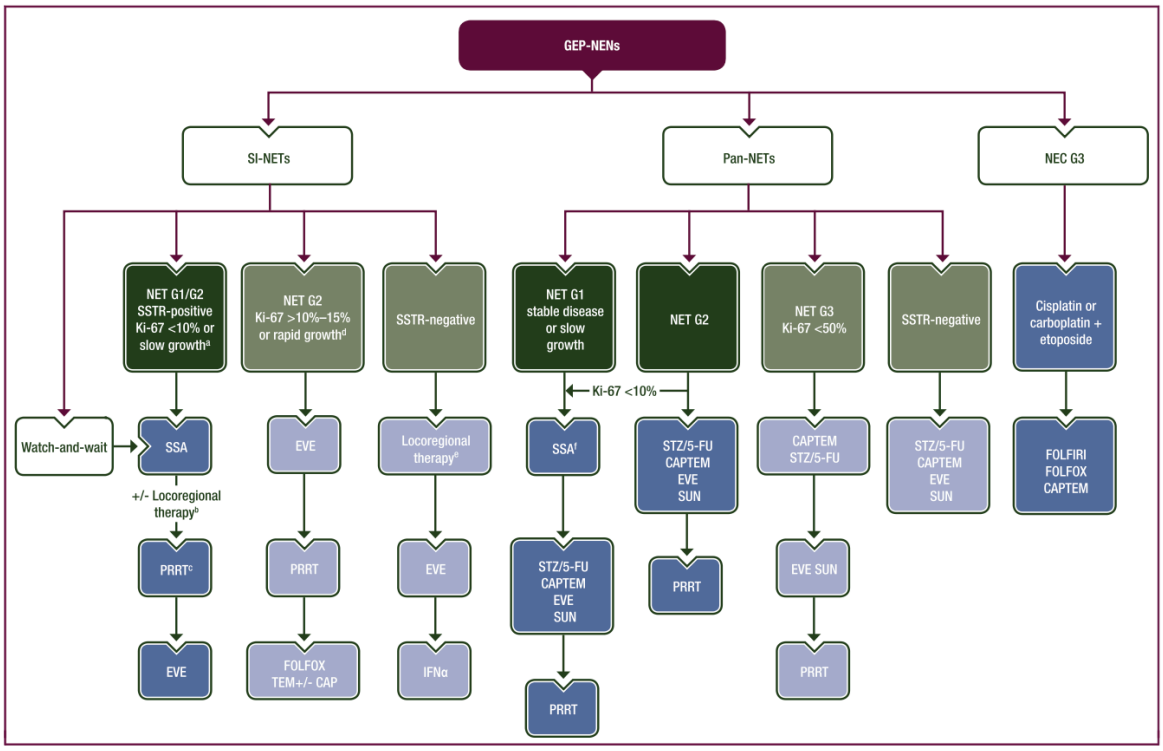


Figure 4. Systemic therapy in GEP-NENs.
The stratification factors are not predictive, but prognostic.
A watch-and-wait approach is recommended in asymptomatic low-grade tumour patients with absence of morphological progression. Locoregional therapy may be considered as an alternative approach to systemic therapies in SI- and Pan-NETs in liver disease only or predominant liver disease if extrahepatic lesions are stable. Locoregional therapy may also be considered early in NET G2 patients and advanced disease.
In Pan-NET G3 with moderate Ki-67, the treatment is similar to Pan-NET G2. The choice of ChT is mainly based on the tumour growth rate and Ki-67. STZ-based and TEM-based therapies provide similar ORRs, although a comparative study is not available.
STZ has been combined with doxorubicin in Pan-NETs and produced high ORRs, but its use is limited due to potential cardiotoxicity to maximal cumulative dose of 400 mg/m^2.
One author (EPK) indicates that in SSTR-positive Pan-NET G1/G2 (Ki-67 <10%) PRRT might be considered after first-line SSA or chemotherapy, equal to the choice of targeted drugs and that in SI NET G2 (Ki-67>10%) PRRT could be considered equal to everolimus.
Green arrows indicate progressive disease.
5-FU, 5-fluorouracil; CAP, capecitabine; CAPTEM, capecitabine and temozolomide; ChT, chemotherapy; EVE, everolimus; FOLFIRI, 5-fluorouracil/leucovorin/irinotecan; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; GEP-NEN, gastroenteropancreatic neuroendocrine neoplasm; IFN-α, interferon alpha; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; ORR, overall response rate; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RECIST, response evaluation criteria in solid tumours; SI, small intestinal; SI-NET, small intestinal neuroendocrine tumour; SSA, somatostatin analogue; SSTR, somatostatin receptor; STZ, streptozotocin; SUN, sunitinib; TEM, temozolomide.
[a] Slow tumour growth is defined as stable disease by RECIST criteria for >1 year.
[b] In liver-dominant disease.
[c] If PRRT is not available, everolimus can be used as second-line therapy.
[d] Rapid growth is defined as RECIST progression within a year or less.
[e] In liver-only disease or predominant liver disease.
[f] If SSTR-positive.

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

[5] Pavel, M, Oberg, K, Falconi, M, Krenning, EP, Sundin, A, Perren, A, Berruti, A & clinicalguidelines@esmo.org, EGCEa 2020, 'Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up', *Ann Oncol*, vol. 31, no. 7, pp. 844-60.

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

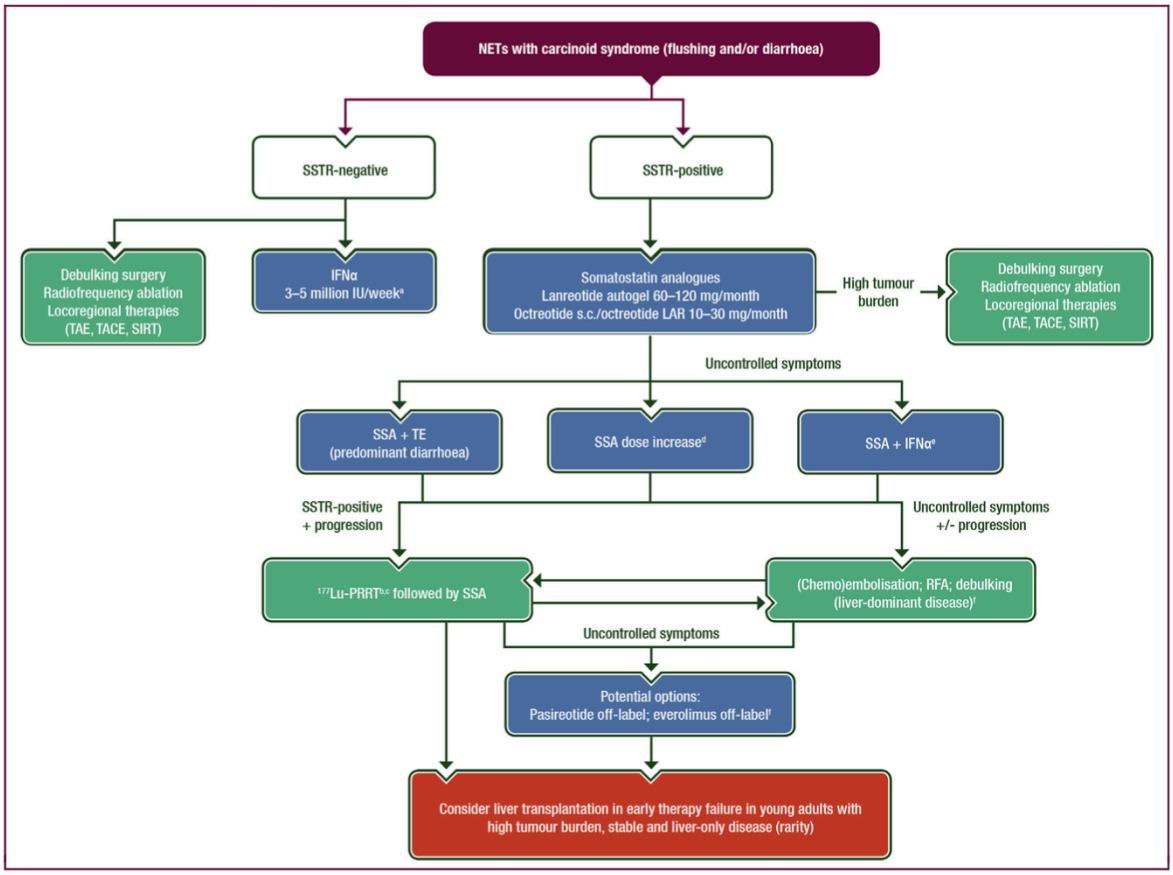


Figure 3. Therapeutic approach in NETs with carcinoid syndrome.
^{177}Lu, lutetium-177; IFN-α, interferon alpha; LAR, long-acting release; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; s.c., subcutaneous; SIRT, selective internal radiotherapy; SSA, somatostatin analogue; SSTR, somatostatin receptor; TACE, transarterial chemoembolisation; TAE, transarterial embolisation; TE, telotristat ethyl.
[a] SSAs can be tried in SSTR-negative patients, particularly if tumour burden is very low and/or lesion size is very small (potentially false-negative SSTR status).
[b] Long-acting SSAs should be interrupted at least 4 weeks before PRRT and should be continued 'not earlier than' 1 h after PRRT cycle(s).
[c] PRRT may be considered in patients without prior tumour progression but with high tumour burden and uncontrolled diarrhoea (off-label).
[d] Above labelled dosages [shortening of the injection interval of long-acting SSAs (lanreotide 120 mg; octreotide 30 mg) to every 3 or 2 weeks instead of every 4 weeks] (off-label) or short-acting octreotide s.c. as additional injections.
[e] IFN-α should be interrupted if PRRT is considered.
[f] TE can be continued with other treatments if patient has a benefit; it is not an option if patient has predominant flushing.

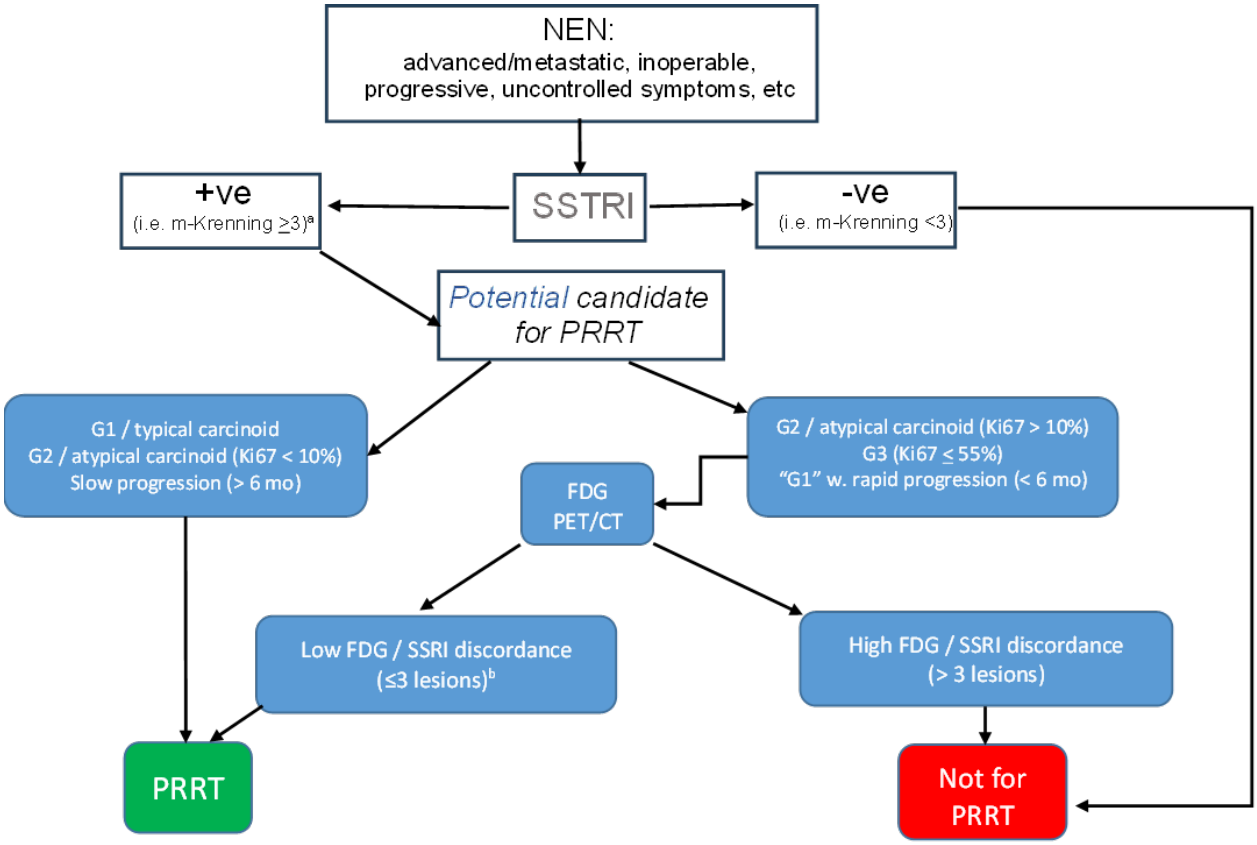
Source: Figure 3, p851 from ESMO guidelines[6]

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 ^{177}Lu-DOTA-octreotate will be made by an MDT.

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

[6] Pavel, M, Oberg, K, Falconi, M, Krenning, EP, Sundin, A, Perren, A, Berruti, A & clinicalguidelines@esmo.org, EGCEa 2020, 'Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up', *Ann Oncol*, vol. 31, no. 7, pp. 844-60.

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 sites of discordance where the tumour is ≥2 cm in size

Source: Developed by PASC

Alignment with PICO confirmation

This Department contracted assessment report (DCAR) of ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 (^{68}Ga-DOTA-octreotate PET/CT or FDG PET/CT) were nominated'. At its April 2023 meeting, PASC agreed that the relevant outcomes for ^{68}Ga-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 ^{68}Ga-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 ^{177}Lu-DOTA-octreotate treatment were also not retrieved from the studies identified; therefore, this information has not been addressed in this report.

8. Comparator

^{177}Lu-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 ^{177}Lu-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 consider PRRT as first-line treatment (versus alternative first-line treatments such as unlabelled SSA, targeted treatment [everolimus, sunitinib] or chemotherapy). Therefore, ^{177}Lu-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 ^{177}Lutetium 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 ^{177}Lu-DOTATATE drug product is protected by a granted patent.

Novartis requested that the MSAC refrains from making a determination of non-inferiority based on assumed biosimilarity of the two products ^{177}Lu DOTA Octreotate and ^{177}Lu-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 ^{177}Lutetium (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 ^{177}Lu- DOTATATE and any ^{177}Lutetium(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 ^{177}Lu 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 ^{177}Lutetium(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 ^{177}Lutetium(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 ^{177}Lu-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 (^{177}Lu-DOTA-octreotate) and no randomised controlled trials (RCTs) were identified in the systematic literature review supporting this assessment. Instead, the applicant claimed that ^{177}Lu-DOTA-octreotate appears to be a very close biosimilar to the Lutathera® product (referred to as ^{177}Lu-DOTATATE). An evidence-based assessment of non-inferiority efficacy and safety between ^{177}Lu-DOTATATE and ^{177}Lu-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 ^{177}Lu-DOTATATE[7] and information provided by the applicant on ^{177}Lu-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 ^{177}Lu-DOTA-octreotate is equivalent to ^{177}Lu-DOTATATE. Therefore, the clinical claim for ^{177}Lu-DOTA-octreotate presented in this assessment report is based on the relative effectiveness and safety of ^{177}Lu-DOTATATE. As such, this assumption is a key area of uncertainty in the assessment report.

7 European Medicines Agency. Lutathera: EPAR - Product Information. 2024. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/lutathera

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

	^{177}Lu-DOTATATE (Lutathera®) (European Medicines Agency 2024)	^{177}Lu-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 (^{68}Ga-DOTA-octreotate PET/CT and FDG PET/CT) and for the therapeutic intervention (^{177}Lu-DOTATATE).

Investigative technologies

An additional systematic literature review investigated 2 research questions including:

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

Four systematic reviews/meta-analyses including Bauckneht et. al (2020),[8] Carideo et. al (2019),[9] Treglia et al (2012)[10] and Alevroudis et al (2021)[11] met the inclusion criteria to provide information on the diagnostic performance and clinical usefulness of ^{68}Ga-DOTA-octreotate PET/CT and FDG PET/CT in addition to ^{68}Ga-DOTA-octreotate PET/CT in selecting patients with

8 Bauckneht, M, Albano, D, Annunziata, S, Santo, G, Guglielmo, P, Frantellizzi, V, Branca, A, Ferrari, C, Vento, A, Mirabile, A, Nappi, AG, Evangelista, L, Alongi, P & Laudicella, R 2020, 'Somatostatin Receptor PET/CT Imaging for the Detection and Staging of Pancreatic NET: A Systematic Review and Meta-Analysis', Diagnostics, vol. 10, no. 8, p. 598.
9 Carideo, L, Prosperi, D, Panzuto, F, Magi, L, Pratesi, MS, Rinzivillo, M, Annibale, B & Signore, A 2019, 'Role of Combined [(68)Ga]Ga-DOTA-SST Analogues and [(18)F]FDG PET/CT in the Management of GEP-NENs: A Systematic Review', J Clin Med, vol. 8, no. 7.
10 Treglia, G, Castaldi, P, Rindi, G, Giordano, A & Rufini, V 2012, 'Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis', Endocrine, vol. 42, pp. 80-7.
11 Alevroudis, E, Spei, ME, Chatziioannou, SN, Tsoli, M, Wallin, G, Kaltsas, G & Daskalakis, K 2021, 'Clinical Utility of (18)F-FDG PET in Neuroendocrine Tumors Prior to Peptide Receptor Radionuclide Therapy: A Systematic Review and Meta-Analysis', Cancers (Basel), vol. 13, no. 8.

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.[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 ^{177}Lu-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 ^{177}Lu-DOTATATE (via network meta-analysis [NMA]). Following data extraction, 2 studies—van der Zwan (2018)[13] and Sood et al (2023)[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 ^{177}Lu-DOTATATE versus a relevant comparator. These were NETTER -1 and OCLURANDOM, comparing ^{177}Lu-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 ^{68}Ga-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).[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).

[12] Whiting, P, Savović, J, Higgins, JP, Caldwell, DM, Reeves, BC, Shea, B, Davies, P, Kleijnen, J & Churchill, R 2016, 'ROBIS: a new tool to assess risk of bias in systematic reviews was developed', Journal of clinical epidemiology, vol. 69, pp. 225-34.

13 van der Zwan, W, Wyld, D, Brabander, T, Teunissen, J, Kam, B, MacFarlane, D, Krenning, E, Kwekkeboom, D & De Herder, W 2018, 'A randomized controlled study comparing treatment of gastro-entero-pancreatic neuroendocrine tumors (GEPNET) with 177lu-dotatate alone and in combination with capecitabine', Neuroendocrinology, vol. 106, p. 261.

14 Sood, A, Satapathy, S & Chandekar, K 2023, 'Concomitant 177Lu-DOTATATE and low-dose capecitabine versus 177Lu-DOTATATE alone in patients with advanced well-differentiated gastroenteropancreatic neuroendocrine tumours - preliminary results of a randomized controlled trial', Clinical Nuclear Medicine, vol. 48, no. 5, pp. e261-e2.

15 Higgins, JP, Altman, DG, Gotzsche, PC, Juni, P, Moher, D, Oxman, AD, Savovic, J, Schulz, KF, Weeks, L, Sterne, JA, Cochrane Bias Methods, G & Cochrane Statistical Methods, G 2011, 'The Cochrane Collaboration's tool for assessing risk of bias in randomised trials', BMJ, vol. 343, p. d5928.

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[16]	^{177}Lu-DOTATATE	OCT	231	Multicentric, randomised, controlled trial	High	Midgut NET	PFS	Yes
OCLURANDOM[17]	^{177}Lu-DOTATATE	SUN	84	Multicentric, randomised, open-label study	High	pNET	PFS	No
Comparator therapies studies								
CLARINET[18]	LAN	PBO	204	Randomised, double-blind, placebo-controlled trial	Low	NEEPT	PFS	Yes
PROMID[19]	OCT	PBO	85	Randomised, double-blind, placebo-controlled trial	Low	Midgut NET	TTP	Yes
ECOG-ACRIN E2211[20]	TEM	CAPTEM	144	Open-label, multicentre randomised controlled trial	Low	pNET	PFS	No
TOPIC-NEC[21]	Etoposide + cisplatin	Irinotecan + cisplatin	170	Randomised, open-label, multicentre clinical trial	High	Gastro-hepato-pNET	OS	No
RADIANT-2[22]	OCT + EVO	OCT+ PBO	429	Multicentre, double-blind, randomised trial	High	NET with carcinoid syndrome	PFS	Yes

16 ClinicalTrials.gov 2022, A Study Comparing Treatment With 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours, https://classic.clinicaltrials.gov/show/NCT01578239.

17 Baudin, E, Walter, T, Beron, A, Smith, D, Hadoux, J, Moreau-Triby, C, Taieb, D, Ansquer, C, Dierickx, L, De Mestier, L, Deshayes, E, Quak, E, Dahan, L, Guimbaud, R, Touchefeu, Y, Haissaguerre, M, Vuillez, J, Courbon, F, Hindie, E, Do Cao, C, Lombard-Bohas, C, Attard, M & Foulon, S 2022, 'Results from OCLURANDOM: the first multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionuclide therapy with lutetium-177 octreotate (OCLU) in patients with unresectable progressive neuroendocrine pancreatic tumors', European Journal of Nuclear Medicine and Molecular Imaging, vol. 49, p. S52.

18 Caplin, ME, Pavel, M, Ćwikła, JB, Phan, AT, Raderer, M, Sedláčková, E, Cadiot, G, Wolin, EM, Capdevila, J & Wall, L 2014, 'Lanreotide in metastatic enteropancreatic neuroendocrine tumors', New England Journal of Medicine, vol. 371, no. 3, pp. 224-33.

19 Rinke, A, Muller, H-H, Schade-Brittinger, C, Klose, K-J, Barth, P, Wied, M, Mayer, C, Aminossadati, B, Pape, U-F & Blaker, M 2009, 'Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group', J Clin Oncol, vol. 27, no. 28, pp. 4656-63.

20 Kunz, PL, Catalano, PJ, Nimeiri, H, Fisher, GA, Longacre, TA, Suarez, CJ, Yao, JC, Kulke, MH, Hendifar, AE, Shanks, JC, Shah, MH, Zalupski, M, Schmulbach, EL, Reidy, DL, Strosberg, JR, O'Dwyer, PJ & Benson, AB 2018, 'A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211)', Journal of Clinical Oncology, vol. 36, no. 15.

21 Morizane, C, Machida, N, Honma, Y, Okusaka, T, Boku, N, Kato, K, Nomura, S, Hiraoka, N, Sekine, S, Taniguchi, H, Okano, N, Yamaguchi, K, Sato, T, Ikeda, M, Mizuno, N, Ozaka, M, Kataoka, T, Ueno, M, Kitagawa, Y, Terashima, M & Furuse, J 2022, 'Effectiveness of Etoposide and Cisplatin vs Irinotecan and Cisplatin Therapy for Patients with Advanced Neuroendocrine Carcinoma of the Digestive System: The TOPIC-NEC Phase 3 Randomized Clinical Trial', *JAMA Oncology*, vol. 8, no. 10, pp. 1447-55.

22 Pavel, ME, Hainsworth, JD, Baudin, E, Peeters, M, Horsch, D, Winkler, RE, Klimovsky, J, Lebwohl, D, Jehl, V, Wolin, EM, Oberg, K, Van Cutsem, E & Yao, JC 2011, 'Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): A randomised, placebo-controlled, phase 3 study', *The Lancet*, vol. 378, no. 9808, pp. 2005-12.

Study	Intervention	Comparator	Number of patients	Design/ duration	Risk of bias	Patient population	Outcome(s)	Used in economic evaluation
ECOG-ACRIN EA2142[23]	CAPTEM	Etoposide + cisplatin / carboplatin	67	Multicentre, randomised controlled trial	Low	GEP-NET	PFS	No
REMINET[24]	LAN	PBO	53	Multicentre, randomised, controlled trial	Low	Duodeno-pNET	PFS	Yes
RADIANT-3[25]	EVO + BSC	PBO + BSC	410	International, multicentre, quadruple masking, parallel study	Low	pNET	PFS	Yes
RADIANT-4[26]	EVO + BSC	PBO + BSC	302	International, multicentre, double-blind, phase 3 study	Low	GI and lung NET	ORR	Yes
NET-01[27]	CAP + streptozocin	CAP + streptozocin + cisplatin	86	Randomised controlled trial	Unclear	GEP-NET	PFS	No
SPINET[28]	LAN + BSC	PBO + BSC	77	Prospective, multicentre, randomised, double-blind (participant, investigator), parallel study	Low	BP-NET	PFS	Yes
NCT00428597[29]	SUN	PBO	171	Multinational, randomised, double-blind, placebo-controlled trial	Unclear	pNET	PFS	
Indirect treatment comparisons								

[23] Eads, JR, Catalano, PJ, Fisher, GA, Rubin, D, Iagaru, A, Klimstra, DS, Konda, B, Kwong, MS, Chan, JA, De Jesus-Acosta, A, Halfdanarson, TR, Shaib, WL, Soares, HP, Hong, SC, Wong, TZ & O'Dwyer, PJ 2022, 'Randomized phase II study of platinum and etoposide (EP) versus temozolomide and capecitabine (CAPTEM) in patients (pts) with advanced G3 non-small cell gastroenteropancreatic neuroendocrine neoplasms (GEPNENs): ECOG-ACRIN EA2142', *Journal of Clinical Oncology*, vol. 40, no. 16.

[24] Lepage, C, Phelip, JM, Lievre, A, Le Malicot, K, Tougeron, D, Dahan, L, Toumpanakis, C, Di Fiore, F, Bohas, CL & Borbath, I 'Lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours (NETs): an international double-blind, placebo-controlled randomized phase II trial', in vol. 31, pp. S774-S.

[25] Yao, JC, Shah, MH, Ito, T, Bohas, CL, Wolin, EM, Van Cutsem, E, Hobday, TJ, Okusaka, T, Capdevila, J & De Vries, EGE 2011, 'Everolimus for advanced pancreatic neuroendocrine tumors', *New England Journal of Medicine*, vol. 364, no. 6, pp. 514-23.

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Study	Intervention	Comparator	Number of patients	Design/ duration	Risk of bias	Patient population	Outcome(s)	Used in economic evaluation
NMA	^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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
^{177}Lu-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 ^{68}Ga-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 ^{177}Lu-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 ^{68}Ga-DOTA-ocreotate uptake, the results of the NETTER-1 trial[30] were compared to those published in the abstract by Sood et al. 2023[31], where ^{68}Ga-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTATATE + capecitabine group and 67.3% (95% CI 47.3 to 87.3) in the ^{177}Lu-DOTATATE-only group. After a median follow-up of 23.6 months, ORR in the ^{177}Lu-DOTATATE + capecitabine group was 21.4% and 11% in the ^{177}Lu-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.

[30] Strosberg, J, El-Haddad, G, Wolin, et al. N-T 2017, 'Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors', N Engl J Med, vol. 376, no. 2, pp. 125-35.

31 Sood A, Aggarwal P, Satapathy S, et al. PP047 Concomitant 177Lu-DOTATATE and low dose capecitabine versus 177Lu-DOTATATE alone in patients with advanced well-differentiated gastroenteropancreatic neuroendocrine tumours–a randomized controlled trial. ESMO Open 2023;8(1)

Table 8 Summary of outcomes for patients treated with ^{177}Lu-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: ^{177}Lu-DOTATATE	Positive OctreoScan® imaging; uptake ≥normal liver uptake	No	Primary analysis: 14	^{177}Lu-DOTATATE: 18%	Median: NR PFS at month 20: 65.2% (95% CI: 50.0 to 76.8)	Median: NR
Sood et al (2023)	Intervention: ^{177}Lu-DOTATATE plus CAP. Comparator: ^{177}Lu-DOTATATE	SRS positive; ^{68}Ga DOTANOC	Yes, ^{18}F-FDG PET/CT	23.6 [95% CI: 21.1, 26.0]	^{177}Lu-DOTATATE + CAP: 21.4% ^{177}Lu-DOTATATE: 11%	Median: NR for either group PFS at 24 months: ^{177}Lu-DOTATATE + CAP: 96.4% [95% CI: 89.4, 100] ^{177}Lu-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: ^{177}Lu-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.

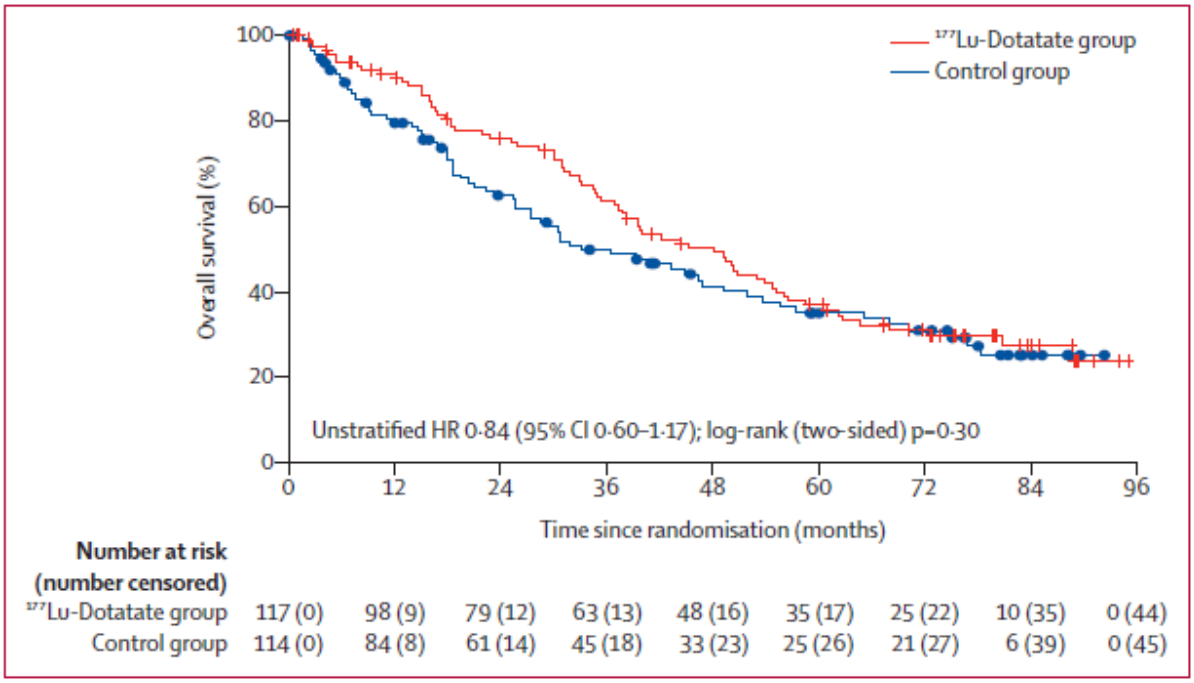
Table 9 Assessment of risk of bias of individual studies- direct RCTs: NETTER-1 and OCLURANDOM

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 ^{177}Lu-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

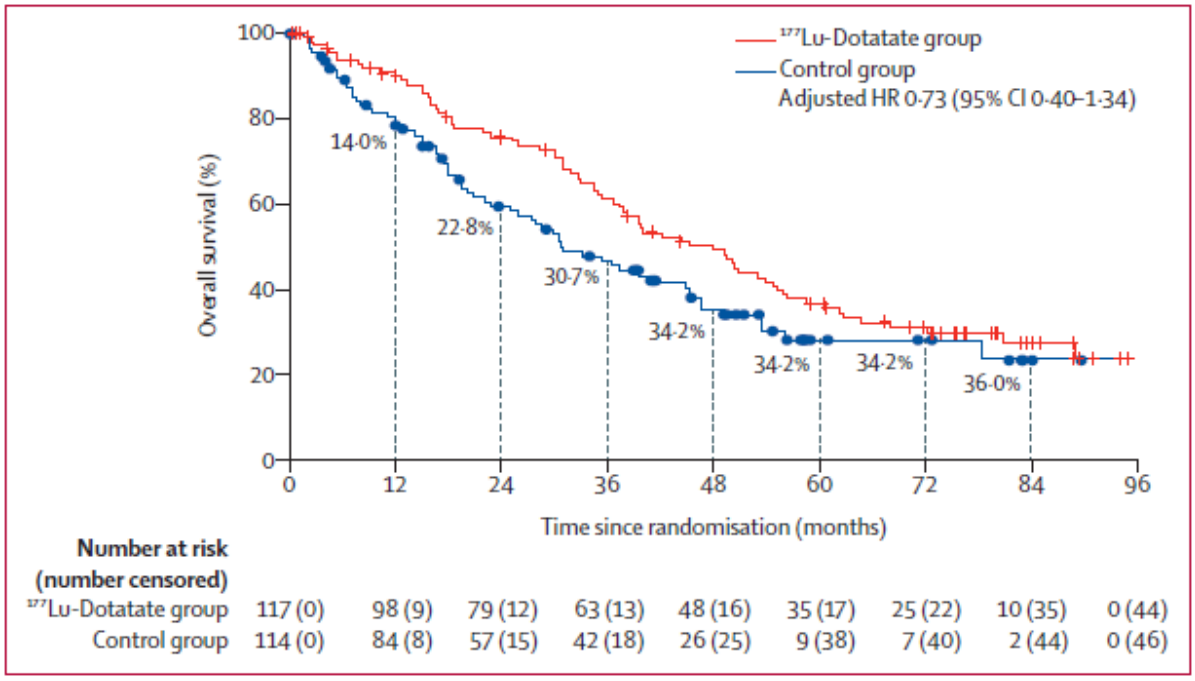


Source: Compiled by department from Figure 2, p1757 of Strosberg 2021
Abbreviations: HR = hazard ratio
Note Kaplan-Meier analysis of overall survival in intention-to-treat population. Crosses and circles represent patients who are censored

The authors of NETTER-1 noted that during long-term follow-up, 14 (12%) of 117 patients in the ^{177}Lu Dotatate group received further treatment with PRRT. Among these 14 patients, eight were treated further with additional cycles of ^{177}LuDotatate (the other six patients received ^{17}LuDotatoc or ^{90}YDotatoc). 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 ^{177}LuDotatate (the other five patients received ^{177}LuDotanoc, ^{90}YDotanoc, ^{90}YDotatoc, or ^{90}YDotatate). 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 ^{177}Lu 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.

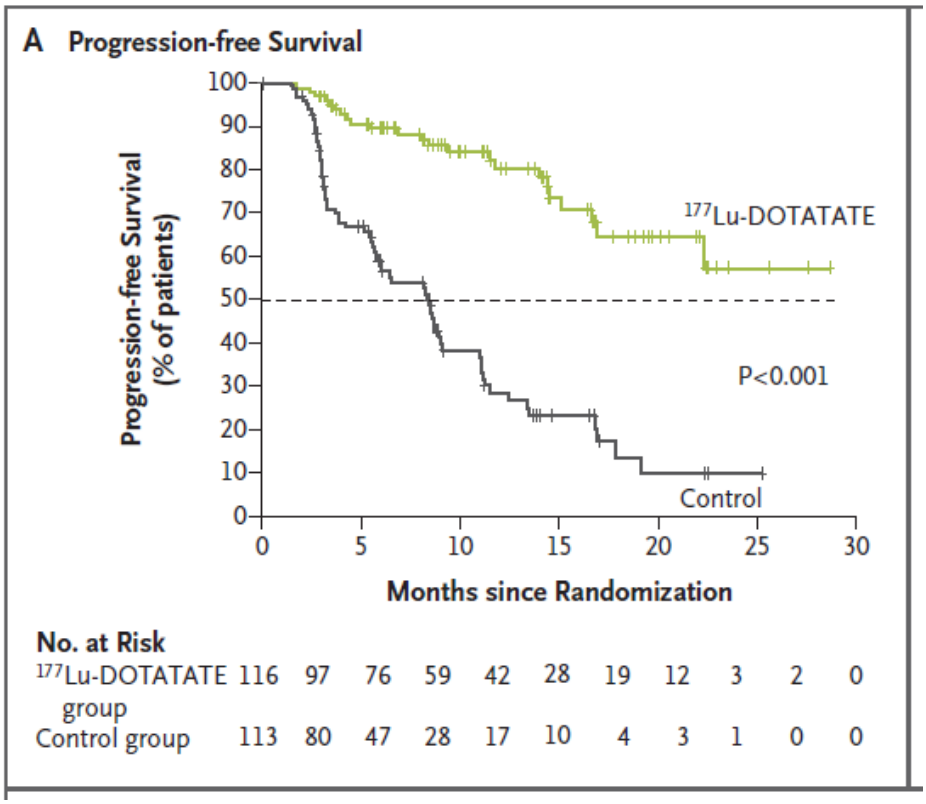
Figure 5 Rank -preserving structured failure time analysis of overall survival accounting for crossover to any PRRT in control group during long-term follow-up – NETTER 1



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 ^{177}Lu-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 ^{177}Lu-DOTATATE over octreotide. Treatment with ^{177}Lu-DOTATATE was also associated with more favourable PFS outcomes than sunitinib. In OCLURANDOM, median PFS was longer in patients treated with ^{177}Lu-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, ^{177}Lu-DOTATATE was associated with statistically significant improvements in PFS over all examined comparators. For OS, ^{177}Lu-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 (^{177}Lu-DOTATATE reference)

Comparator	PFS; HR (95% CrI)	OS; HR (95% CrI)
^{177}Lu-DOTATATE	1.00	1.00
Octreotide + Everolimus	3.8 (95% CrI: 2.1, 6.3)	1.5 (95% CrI: 0.9, 2.3)
Octreotide	4.9 (95% CrI: 3.0, 5.6)	1.2 (95% CrI: 0.9, 1.7)
Everolimus	5.9 (95% CrI: 2.6, 11.5)	1.5 (95% CrI: 0.4, 3.7)
Sunitinib	6.5 (95% CrI: 2.5, 13.8)	0.7 (95% CrI: 0.2, 2.2)
Lanreotide	8.6 (95% CrI: 3.5, 17.8)	NE
Placebo/BSC	14.9 (95% CrI: 6.8, 28.6)	1.7 (95% CrI: 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 ^{68}Ga-DOTA-octreotate PET/CT, they should be considered as an accurate imaging prognostic tool in patients with NENs. The use of dual imaging (^{68}Ga-DOTA-peptides and ^{18}F-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 ^{68}Ga-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 ^{68}Ga-DOTA-ocreotate—appeared consistent. In addition, the decision regarding eligibility for ^{177}Lu-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 ^{177}Lu-DOTATATE against its comparators, the following conclusions are made:

- Use of ^{177}Lu-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 non-inferior effectiveness compared with sunitinib.
- Use of ^{177}Lu-DOTA-octreotate is estimated to result in non-inferior 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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate treatment

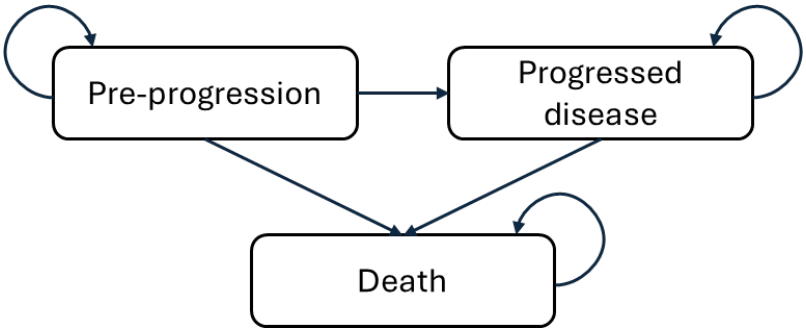
Component	Description
Perspective	Healthcare system perspective
Population	Patients referred by an MDT, with histologically confirmed, locally advanced or metastatic, inoperable NENs with documented disease progression or uncontrolled NEN-related symptoms despite standard therapy who have demonstrated H-SSTR.
Prior testing	The economic model considers 2 diagnostic tests: • ^{68}Ga-DOTA-octreotate SSTR-PET/CT • ^{18}F-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	^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTATATE and ^{177}Lu-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 ^{177}Lu-DOTA-octreotate is equivalent to ^{177}Lu-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 ^{177}Lu-DOTATATE plus long-acting octreotide.

An indirect treatment comparison was conducted to assess the comparative effectiveness of ^{177}Lu-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 ^{177}Lu-DOTATATE for treating unresectable or metastatic NETs was used for this analysis.[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 ^{177}Lu-DOTA-octreotate compared with current care (Table 11). As stated previously, ^{177}Lu-DOTA-octreotate therapy would most likely be offered after the failure of any nominated comparator treatments. The cost-effectiveness of ^{177}Lu-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 ^{177}Lu-DOTA-octreotate versus comparators

Treatment	Total costs	Incremental Costs	Total LYs	Incremental LYs	Total QALYs	Incremental QALYs	ICER (cost per QALY)
^{177}Lu-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, ^{177}Lu-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. ^{177}Lu-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, ^{177}Lu-DOTA-octreotate cannot be considered cost-effective versus sunitinib.

These cost-effectiveness results directly align to the results of the NMA, which showed that ^{177}Lu-DOTATATE is associated with statistically significant improvements in PFS and comparable OS, with nominally favourable outcomes observed for ^{177}Lu-DOTATATE versus octreotide + everolimus

[32] NICE 2018, National Institute for Health and Care Excellence. Multiple Technology Appraisal. Lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours [ID1224]: Committee Papers.

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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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

Scenario	Base case value	ICER result	Lower value	ICER result	Higher value	ICER result
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						
^{68}Ga-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 years[a]	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 ^{177}Lu PRRT treatment						

Scenario	Base case value	ICER result	Lower value	ICER result	Higher value	ICER result
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

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 ^{177}Lu-DOTA-octreotate should not be viewed as a 'fixed' line in any patient's therapy. The most appropriate line of therapy for ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate has been adopted.

To estimate the number of patients eligible for treatment with ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate	Unknown Assumed 3.5% to match applicant advised treatment population of approximately 200					
Number of people who receive ^{177}Lu-DOTA-octreotate	197	205	213	221	229	238
Number of ^{177}Lu-DOTA-octreotate recipients tested with ^{68}Ga-DOTA-octreotate PET/CT (100%)*	197	205	213	221	229	238
Number of ^{177}Lu-DOTA-octreotate recipients tested with ^{18}F-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate, so all patients receiving ^{177}Lu-DOTA-octreotate treatment incur the cost of ^{68}Ga-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate is doubled (i.e. approximately 400 patients expected to receive treatment in Year 1).

Table 17: Net financial impact of ^{177}Lu-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 ^{177}Lu-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*
2. 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*
3. #1 and uptake of ^{177}Lu-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 ^{177}Lu-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 ^{68}Ga-DOTA-octreotate PET/CT and FDG PET/CT, and the tests have not been studied with respect to these outcomes.
- Non-inferiority of ^{177}Lu-DOTA-octreotate and Lutathera® (^{177}Lu-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 ^{177}Lu-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 ^{68}Ga-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 ^{177}Lu-DOTA-octreotate had a moderate impact on the ICER. The scenario which assumed an additional ^{68}Ga-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 ^{177}Lu PRRT therapy, such as from Department of Veterans' Affairs (DVA) claiming data may be informative.
- The uptake rate and number of cycles of ^{177}Lu-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 ^{177}Lu-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 ^{68}Ga-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 ^{177}Lutetium (no carrier added)-DOTA-octreotate (^{177}Lu (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 ^{68}Gallium (Ga)-DOTA-octreotate SSTR-positron emission tomography (PET)/computed tomography (CT) — ^{68}Ga-DOTA-octreotate PET/CT — to determine eligibility for ^{177}Lu (nca)-DOTA-octreotate treatment, as well as for monitoring the post-treatment effect (i.e. treatment response) of ^{177}Lu (nca)-DOTA-octreotate. This treatment is a type of peptide receptor radionuclide therapy (PRRT). The applicant's clinical claim implied that ^{177}Lu(nca)-DOTA-octreotate results in superior health outcomes and non-inferior safety.

The ^{177}Lu-DOTA-octreotate product is supplied as an extemporaneously manufactured medicine for individual patient use as prescribed by a medical practitioner. ESC noted that the ^{177}Lu-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 ^{177}Lu(nca)-DOTA-octreotate is recommended in Europe and USA due to environmental considerations because the "ca" product contains ^{177m}Lu, with a half-life of 160 days, whereas nca ^{177}Lu 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 ^{177}Lu-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.^{177}Lu-DOTA-octreotate is not intended to replace chemotherapy and is often administered concurrently to chemotherapy. Similarly, SSAs are not replaced by ^{177}Lu-DOTA-octreotate but continued alongside it. ESC noted that consistent with PASC, the DCAR considered BSC the most relevant

comparator as ^{177}Lu-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[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 ^{68}Ga-DOTA-octreotate PET/CT imaging for monitoring purposes but this should have been included.

ESC noted that a new MBS listing for ^{68}Ga-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 '^{177}Lutetium-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 ^{177}Lutetium-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 ^{68}Ga-DOTA-octreotate PET/CT or FDG PET-CT for the selection of patients with progressive, advanced, metastatic or inoperable

[33] Pavel, M, Oberg, K, Falconi, M, Krenning, EP, Sundin, A, Perren, A, Berruti, A & clinicalguidelines@esmo.org, EGCEa 2020, 'Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up', Ann Oncol, vol. 31, no. 7, pp. 844-60.

NETs with suspected H-SSTR expression for ^{177}Lu-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.[34] [35] ESC noted the evidence examining the equivalence of ^{68}Ga-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 ^{68}Ga-DOTA-octreotate (using the modified Krenning score) for the DCAR. This was done by comparing the results of the NETTER-1 trial[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.[37] (which used ^{68}Ga-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 non-inferiority in efficacy between ^{177}Lu-DOTA-octreotate and Lutathera® (^{177}Lu-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 ^{177}Lu-DOTATATE, stating that there is no evidence to support the therapeutic equivalence of ^{177}Lu-DOTATATE and ^{177}Lutetium(nca)octreotate.

ESC noted the absence of safety and efficacy studies for the proposed treatment ^{177}Lu-DOTA-octreotate. Therefore, the DCAR's assessment of the safety and efficacy of the proposed treatment has been based on studies of ^{177}Lu-DOTATATE based on a claim of non-inferiority between ^{177}Lu-DOTA-octreotate and ^{177}Lu-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 ^{177}Lu-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

[34] Zhang J, Liu Q, Singh A, Schuchardt C, Kulkarni HR, Baum RP. Prognostic Value of 18F-FDG PET/CT in a Large Cohort of Patients with Advanced Metastatic Neuroendocrine Neoplasms Treated with Peptide Receptor Radionuclide Therapy. J Nucl Med. 2020 Nov;61(11):1560-1569. doi: 10.2967/jnumed.119.241414. Epub 2020 Mar 13. PMID: 32169914.

[35] Sitani K, Parghane RV, Talole S, Basu S. Long-term outcome of indigenous 177Lu-DOTATATE PRRT in patients with Metastatic Advanced Neuroendocrine Tumours: a single institutional observation in a large tertiary care setting. Br J Radiol. 2021 Jan 1;94(1117):20201041. doi: 10.1259/bjr.20201041. Epub 2020 Oct 29. PMID: 33095671; PMCID: PMC7774689.

[36] Strosberg, J., El-Haddad, G., Wolin, E., Hendifar, A., Yao, J., Chasen, B., Mittra, E., Kunz, P. L., Kulke, M. H., Jacene, H., Bushnell, D., O'Dorisio, T. M., Baum, R. P., Kulkarni, H. R., Caplin, M., Lebtahi, R., Hobday, T., Delpassand, E., Van Cutsem, E., … Krenning, E. (2017). Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *The New England Journal of Medicine*, *376*(2), 125–135.

[37] Sood, A., Aggarwal, P., Satapathy, S., Chandekar, K. R., Das, C. K., Kumar, A., Gupta, R., & Mittal, B. R. (2023). PP047 Concomitant 177Lu-DOTATATE and low dose capecitabine versus 177Lu-DOTATATE alone in patients with advanced well-differentiated gastroenteropancreatic neuroendocrine tumours – a randomized controlled trial. *ESMO Open*, *8*(1), 102138.

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 ^{177}Lu-DOTATATE (which as noted previously was used for assessment purposes to evaluate the safety and efficacy of ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTATATE (and thus ^{177}Lu-DOTA-octreotate based on assumed non-inferiority between the two products) treatment had non-inferior 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 ^{177}Lu-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 ^{177}Lu-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 non-inferiority between ^{177}Lu-DOTA-octreotate and ^{177}Lu-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 ^{177}Lu-DOTATATE (meaning that for assessment purposes, non-inferiority between ^{177}Lu-DOTATATE and ^{177}Lu(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, ^{177}Lu-DOTATATE was associated with statistically significant improvements in PFS over all examined comparators. ESC noted that when ^{177}Lu-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 ^{177}Lu-DOTATATE). While the DCAR interpreted this finding as indicating that ^{177}Lu-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 ^{177}Lu-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. ^{177}Lu-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: ^{177}Lu-DOTATATE trials in Section 9 of this document).

Overall, ESC considered that there was limited direct evidence to support the claim that^{177}Lu-DOTATATE (and thus ^{177}Lu-DOTA-octreotate based on assumed non-inferiority 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 ^{177}Lu-DOTA-octreotate was non-inferior to ^{177}Lu-DOTATATE. The partitioned survival model considers the cost-effectiveness of ^{177}Lu-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 ^{177}Lu-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).[38] ESC considered that the model validity had been thoroughly undertaken.

ESC noted that the base case incremental cost-effectiveness ratio (ICER) range comparing ^{177}Lu-DOTA-octreotate versus all six identified comparators ranged from $18,643 to $31,792 per QALY gained, with ^{177}Lu-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 ^{177}Lu-DOTA-octreotate was based on the weighted average number of administrations that patients received in the ^{177}Lu-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 ^{177}Lu 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 ^{177}Lu 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 ^{177}Lu 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 ^{177}Lu-DOTA-octreotate treatment in the model. ESC further considered that the number of cycles of ^{177}Lu-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 ^{68}Ga-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 ^{177}Lu 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.

[38] https://www.nice.org.uk/guidance/ta539

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 ^{177}Lutetium (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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate. However, ESC noted that published estimates indicated that the estimate of those with suspected high SSTR expression and thus eligible for ^{68}Ga-DOTA-octreotate PET/CT testing could be as high as 80% in well differentiated NETs[39] and >80% in endocrine tumours of gastroenteropancreatic-NETs[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 ^{177}Lu-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[41]. In addition, ESC queried whether repeat ^{68}Ga-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 ^{177}Lutetium-somastatin receptor agonist treatment in the proposed item for PRRT therapy.

[39] Zhang JY, Kunz PL. Making Sense of a Complex Disease: A Practical Approach to Managing Neuroendocrine Tumors. JCO Oncol Pract. 2022 Apr;18(4):258-264. doi: 10.1200/OP.21.00240. Epub 2021 Oct 15. PMID: 34652954.

[40] Oberg K, Kvols L, Caplin M, Delle Fave G, de Herder W, Rindi G, Ruszniewski P, Woltering EA, Wiedenmann B. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol. 2004 Jun;15(6):966-73. doi: 10.1093/annonc/mdh216. PMID: 15151956.

[41] Popa, O., Taban, S. M., Pantea, S., Plopeanu, A. D., Barna, R. A., Cornianu, M., Pascu, A., Dema, A. C."The new WHO classification of gastrointestinal neuroendocrine tumors and immunohistochemical expression of somatostatin receptor 2 and 5". Experimental and Therapeutic Medicine 22.4 (2021): 1179.

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 ^{177}Lu-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 ^{68}Ga-DOTA-octreotate PET/CT testing could be as high as 80% in well differentiated NENs[7]. Sensitivity analyses were also conducted for each additional scenario (see **Attachment**). The financial impact under the ESC scenario (80% of eligible population tested; additional ^{68}Ga-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 ^{177}Lu PRRT therapy, such as from DVA claiming data. ESC noted that patients also may be currently paying out-of-pocket for ^{177}Lu 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

The applicant had no comment.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website

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 ^{177}Lutetium (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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-DOTA-octreotate in all scenarios.

Another scenario considering an assumed additional ^{68}Gallium (Ga)-DOTA-octreotate positron emission tomography (PET)/computed tomography (CT)—^{68}Ga-DOTA-octreotate PET/CT—diagnostic test for patients treated with ^{177}Lu-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 ^{177}Lu-DOTA-octreotate.

Table 18: 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 ^{68}Ga-DOTA-octreotate PET/CT for patients treated with ^{177}Lu-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 ^{177}Lu-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 19: 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 ^{177}Lu-DOTA-octreotate	Unknown Assumed 3.5% to match applicant advised treatment population of approximately 200					
Number of people who receive ^{177}Lu-DOTA-octreotate	197	205	213	221	229	238
Of which, diagnosed with ^{68}Ga-DOTA-octreotate PET/CT (100%)	197	205	213	221	229	238
Of which, diagnosed with ^{18}FDG 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 ^{177}Lu-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 ^{177}Lu-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 ^{177}Lu-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 ^{68}Ga-DOTA-octreotate PET/CT testing could be as high as 80% in well differentiated NENs[42]. It is noted that this scenario assumes that none of these patients would receive ^{68}Ga-DOTA-octreotate PET/CT testing in the absence of ^{177}Lu-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 ^{68}Ga-DOTA-octreotate PET study for treated patients) captures the Evaluation Sub-Committee (ESC)-defined scenario (Table 4).

Table 20: 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 (^{68}Ga-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 ^{177}Lu-DOTA-octreotate	$12,561,865	$13,040,535	$13,537,444	$14,053,288	$14,588,788	$15,144,694

[42] Zhang JY, Kunz PL. Making Sense of a Complex Disease: A Practical Approach to Managing Neuroendocrine Tumors. JCO Oncol Pract. 2022 Apr;18(4):258-264. doi: 10.1200/OP.21.00240. Epub 2021 Oct 15. PMID: 34652954.

Parameter	Net financial impact to the MBS					
	2024 (year 1)	2025 (year 2)	2026 (year 3)	2027 (year 4)	2028 (year 5)	2029 (year 6)
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 21: Financial impact under ESC-defined scenario (80% of eligible population tested; additional ^{68}Ga-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 ^{177}Lu-DOTA-octreotate	Unknown Assumed 3.5% to match applicant advised treatment population of approximately 200					
Incident NEN patients who undergo ^{68}Ga-DOTA-octreotate PET/CT (80% of incident population)	4,514	4,686	4,864	5,049	5,242	5,442
Of which, diagnosed with ^{18}FDG PET/CT (30%)	1,354	1,406	1,459	1,515	1,573	1,632
Number of people who receive ^{177}Lu-DOTA-octreotate	197	205	213	221	229	238
Additional ^{68}Ga-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 ^{177}Lu-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.