MSAC Application 1744

^{177}Lutetium(nca)-DOTA-octreotate treatment for advanced neuroendocrine neoplasms (NENs) with high somatostatin receptor (SSTR) expression

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for ^{177}Lutetium(nca)-DOTA-octreotate (applicant's proposed intervention) in patients with advanced neuroendocrine tumours NETs and other high somatostatin receptor (H-SSTR) expressing tumours: PICO Set 1

Component	Description
Population	**Overall population (test 1 and therapeutic intervention):** Patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine tumours (NETs) with documented disease progression or uncontrolled symptoms related to their NET and suspected high somatostatin receptor (H-SSTR) expression (***for Test 1***) **and** demonstrated H-SSTR (***for Therapeutic Intervention***), referred by a multidisciplinary team (MDT). **Test 2:** Population for **Test 1** who have (i) Grade 2 (G2; Ki-67 >10-20%) or Grade 3 (G3) well-differentiated (Ki-67> 20-55%) NET, or (ii) Grade 1 with disease progression in less than 6 months. **Therapeutic intervention**: Patients with demonstrated high concentration of somatostatin receptor expressions (H-SSTR) ***at all, or the majority of***, tumour sites. For the purposes of the Assessment Report, the majority of sites (where tumours should not be too small to accurately reflect SSTR-expression) of known disease should have a modified Krenning score ≥3 (greater than liver). However, it is still unresolved whether the modified Krenning score needs to be ≥3 in (i) all sites ≥2cm in size (ii) in the majority of sites ≥2 cm, or (iii) in the majority of all identified lesions. With respect to discordant disease from Tests 1 and 2, the applicant proposes that eligibility for the therapeutic intervention should be that patients have no more than three sites of discordance where the tumour is greater than or equal to 2 cm in size. In clinical practice, suitability for treatment, with consideration of discordant disease, should be at the discretion of an MDT. Proposed Exemplars: Pancreatic NETs and Midgut NETs.
Intervention	Test 1: Whole body ^{68}Gallium (^{68}Ga)-DOTA-octreotate positron emission tomography (PET)/computed tomography (CT) - ^{68}Ga-DOTA-octreotate PET/CT imaging to document adequate target tumour expression of somatostatin receptor (SSTR) to predict likely tumour response to the therapeutic intervention. **AND**

Component	Description
	Test 2: Whole body fluorodeoxyglucose (FDG) PET/CT – FDG PET/CT imaging. The FDG PET/CT scan assists in sequencing decisions for the therapeutic intervention (i.e., depending on whether SSTR and FDG results are dis-/concordant will influence the sequencing of the therapeutic intervention). Therapeutic Intervention: Peptide receptor radionuclide therapy (PRRT) with ^{177}Lutetium-DOTA-octreotate (^{177}Lu-DOTA-octreotate) treatment. Standard administered activity is 7.4 GBq (GigaBecquerel). An induction treatment course is four treatment cycles at six to 12 but typically eight-weekly intervals. Progression/consolidation cycles are proposed for individuals with documented progression or relapse of uncontrolled hormonal symptoms, where the individual has had a favourable response to the induction treatment course with no self-limiting side-effects, after repeat SSTR imaging with or without FDG PET/CT imaging. Usually, repeat ^{177}Lu-DOTA-octreotate treatment consists of two cycles.
Comparator/s	Tests 1 & 2: No comparators for ^{68}Ga-DOTA-octreotate PET/CT or FDG PET/CT imaging were nominated, nor are any apparent (i.e., no testing). Treatment/therapy: ^{177}Lu-DOTA-octreotate is proposed as an adjunct to current therapies; it is not proposed to substitute for current treatment. Nominated comparators for the purpose of the Assessment Report, and determined by the exemplars and where in the treatment pathway the intervention is used: • Long-acting somatostatin analogue (SSA) (unlabelled) - octreotide depot and lanreotide. • Target therapies – everolimus and sunitinib. • Chemotherapy. • Best supportive care (considered the most relevant comparator).
Reference standard	No reference standards for ^{68}Ga-DOTA-octreotate PET/CT imaging or FDG PET/CT were nominated. Immunohistochemistry (IHC) for SSTR-2 was considered to be a relevant reference standard for ^{68}Ga-DOTA-octreotate PET/CT imaging.
Clinical utility standard	Test 1: Octreoscan® is a valid clinical utility standard: results of studies based on Octreoscan® uptake (Krenning score) need to be translated to ^{68}Ga-DOTA-ocreotate uptake (modified Krenning score) for the Assessment Report. Test 2: A clinical utility standard for FDG PET/CT has not been nominated by the applicant.

Component	Description
Outcomes	• Efficacy/effectiveness (tests: intra-/inter-observer variability; change in management: 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; oncological and patient-relevant: quality of life, disease response (objective response rate, disease control rate, biomarkers relevant to patient outcomes, survival duration [overall and progression-free]). • Safety (treatment emergent adverse events). Long term for myelodysplasia. • Health care resources (cost of therapies, administration). • Cost-effectiveness (cost per additional quality adjusted life year [QALY]). • Total Australian Government health care costs.
Assessment questions	• What is the clinical utility of ^{68}Ga-DOTA-octreotate PET/CT for the selection of patients with progressive, advanced, metastatic or inoperable NETs 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 NETs with known H-SSTR expression for ^{177}Lu-DOTA-octreotate therapy? • What is the safety, effectiveness and cost effectiveness of ^{177}Lu-DOTA-octreotate versus alternative active and supportive care in patients with advanced NETs tumours as identified by ^{68}Ga-DOTA-octreotate PET/CT? • What is the safety, effectiveness and cost effectiveness of ^{177}Lu(no carrier added [nca])-DOTA-octreotate versus ^{177}Lu(carrier added [ca])-DOTA-octreotate in patients with advanced NETs or other H-SSTR tumours as identified by ^{68}Ga-DOTA-octreotate PET/CT?

Abbreviations: ca = carrier added; CT = computed tomography; FDG = Fluorodeoxyglucose; Ga = Gallium; G2 = grade 2; G3 = grade 3; H-SSTR = high somatostatin receptor; MDT = multidisciplinary team; nca = no carrier added; NET = neuroendocrine tumour; PET = positron emission tomography; SPECT = single photon emission computed tomography; SSTR-2 = somatostatin receptor subtype 2; VIP = vasoactive intestinal peptide

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of ^{177}Lutetium (no carrier added) Octreotate treatment, ^{177}Lu(nca) Octreotate (applicant proposed intervention), ^{177}Lu(nca)-DOTA-octreotate herein, for advanced neuroendocrine tumours (NETs) and other high somatostatin receptor (H-SSTR) expressing tumours was received from Applied Molecular Therapies (AMT) Pty Ltd by the Department of Health.

Although the application detailed a request for the use of ^{177}Lu(nca)-DOTA-octreotate, only for the treatment of NETs and other H-SSTR expressing tumours, the application acknowledged that a number of current MBS items would require amendment to allow for patient selection. Thus, the application is for a new MBS item for ^{68}Gallium (^{68}Ga)-octreotate positron emission tomography (PET)/computed tomography (CT) to identify patients with H-SSTR and [^{18}F]fluorodeoxyglucose (FDG) PET/CT – FDG PET/CT imaging) and one therapeutic intervention (Peptide receptor radionuclide therapy [PRRT] therapy with ^{177}Lu-DOTA-octreotate *(PASC preferred terminology for the proposed intervention)* with post-infusion single photon emission tomography (SPECT) for treatment assessment (i.e. co-dependent technology).

The clinical claim implied in the application is that the use of ^{177}Lu(nca)-DOTA-octreotate results in superior health outcomes compared to alternative active and supportive care strategies. The application also infers that the use of ^{177}Lu(nca)-DOTA-octreotate results in noninferior safety compared to alternative active and supportive care strategies. The applicant clarified that the safety claim was "a generally non-overlapping and noninferior safety profile compared to alternative active and supportive care strategies".

Although not specifying a clinical claim for the co-dependent technology, expanding to include the pre-requisite tests is presumed to not change the clinical claim for the therapy. The applicant expressed agreement with this claim.

Background

Following consideration of MSAC application 1744 – ^{177}Lutetium(nca)-DOTA-octreotate treatment for advanced neuroendocrine and other high somatostatin receptor expressing tumours *at the April 2023 meeting, PASC considered the outstanding issues would be best resolved through a re-consideration at the August 2023 PASC meeting*. Table 2 provides a summary of the outstanding matters from consideration of this PICO Confirmation at the April 2023 PASC, in addition to matters that may require re-consideration.

Table 2 Outstanding matters for consideration at April 2023 PASC

Outstanding matters for consideration at April 2023 PASC; or matters for re-consideration	Comment
'Patients with NET in whom neoadjuvant treatment may facilitate successful localised curative intent ablative therapies' and 'Patients with advanced malignancy characterised by high somatostatin receptor expression such as neuroblastoma, phaeochromocytoma and paraganglioma whose outcomes may be improved by ^{177}Lu-DOTA-octreotate treatment') should be removed from consideration.	The applicant considered that this PASC recommendation would deny a small number of patients with incurable malignancy the opportunity to receive highly beneficial disease modifying treatment, also noting that the treatment would only attract a Medicare benefit if there was a positive recommendation from an MDT.
Whether an MDT referral is required for ^{68}Ga-DOTA-octreotate PET/CT.	The current MBS Item 61647 for a ^{68}Ga-DOTA-octreotate PET/CT does not require referral by an MDT.

Outstanding matters for consideration at April 2023 PASC; or matters for re-consideration	Comment
Whether a Krenning score ≥3 needs to be reflected in all sites ≥2 cm, the majority of sites ≥2 cm or the majority of all identified lesions and if 'majority', how that should be defined.	The applicant suggested that the decision about the "majority" of sites expressing modified Krenning ≥3 or only those ≥2 cm be left to the judgement of the multidisciplinary team that is treating the patient as this is a complex decision especially in patients with discordant disease.
Referral to FDG PET/CT	Whether the decision to refer a patient for a FDG PET/CT should be determined by the MDT taking into consideration the patient's clinical history, prior treatments, symptom burden, and prognosis
Role of FDG PET/CT and its consideration in the Assessment Report.	Consider whether FDG PET/CT be excluded in the clinical management algorithm to determine eligibility for PRRT therapy. Or alternatively, the assessment report justifies the requirement of co-dependent investigations with FDG PET/CT including by estimating the patient outcomes and consequences for the subsequent provision of healthcare resource of not including this use.
Definition of discordance from FDG PET/CT to preclude eligibility for PRRT.	The applicant suggests that eligibility for PRRT should include that there are no more than three sites of discordance of tumours >2 cm in size or that it should be left to the discretion of the MDT.
Restriction to ^{177}Lu(nca)-DOTA-octreotate.	The applicant maintains that listing is sought for ^{177}Lu(nca)-DOTA-octreotate; however, based on PASC considerations, the intervention described in this updated PICO refers to the more generic ^{177}Lu-DOTA-octreotate.
Limit treatment to four cycles	Request that wording of descriptor may allow for five cycles for the rare patient with high tumour burden.
Availability of follow-up cycles after the induction cycle. PASC has indicated that evidence for this will need to be provided.	Does PASC propose that the same thresholds that apply to eligibility for induction treatment will also apply for any follow-up/consolidation therapy?
Whether treatment with ^{177}Lu-DOTA-octreotate therapy would occur after failure of the nominated comparator treatments, leaving only best supportive care as a relevant comparator	Not addressed.
An MBS item associated with a multidisciplinary team (MDT).	The applicant's clinical expert indicated that MBS Item 872 looked appropriate as an MDT Item.
MBS fee for the intervention, updated to incorporate (i) patient preparation, including amino acid infusion; (ii) radiopharmaceutical preparation and administration; (iii) immediate aftercare and (iv) post-infusion SPECT	Not addressed.

PICO criteria

Population

Neuroendocrine tumours (NETs), recently reclassified as neuroendocrine neoplasms (NENs, older references use NETs), are a heterogeneous group of tumours with variability in their disease course and outcome (Reccia 2023). Reccia (2023) also state that complex mechanisms involving spatial and temporal changes in tumour biology affect their treatment response and survival and treatment strategies are often based on information regarding tumour stage and grade. The hallmark of NENs is their expression of somatostatin receptors (SSTRs), as somatostatin inhibits cell growth and hormone secretion in normal and cancerous neuroendocrine cells (Reccia 2023).

Neuroendocrine tumours (NETs) are defined as epithelial neoplasms with predominant neuroendocrine differentiation (Yang 2023). They comprise a broad range of tumours, the most common of which arise in the gastrointestinal tract, lungs and bronchi, thymus, and pancreas (Shah 2021). Most NETs appear to be sporadic, and the risk factors are poorly understood (Shah 2021). NETs may also arise from inherited genetic syndromes including multiple endocrine neoplasia types 1 (*MEN1*), 2 (*MEN2*), and 4 (*MEN4*), and succinate dehydrogenase mutations (Shah 2021). Additionally, Von Hippel Lindau disease (*VHL*) is associated with pancreatic neuroendocrine tumours, phaeochromocytoma and paraganglioma, as well as other benign and malignant neoplasms, especially clear cell carcinoma of the kidney (Flynn 2015). The application (p21) states that tumours with H-SSTR expression can also arise in a variety of different sites, including the thyroid (medullary thyroid cancer), the thymus, the skin (Merkel cell carcinoma), adrenal glands (phaeochromocytoma [PCC]) or autonomic nervous system (paraganglioma [PGL]) and may also demonstrate dysregulated production of physiologically active molecules, particularly catecholamines. Unlike gastro-entero-pancreatic (GEP)-NET, paraganglioma and phaeochromocytoma (PCC/PGL) have a significant heritable component accounting for up to 25% of all cases (Flynn 2015).

The application (pp21-22) notes that the natural history of the disease is highly variable and dependent on several key tumour characteristics including:

(i) The location of the primary tumour. The location of the primary tumour commonly defines the cell type of origin of the NET or H-SSTR tumour and together with the site of tumour origin can highly influence tumour behaviour and as a result, patient management and outcomes.

(ii) Whether the disease is local or metastatic. The application states (p21) that metastatic NETs present in approximately 50% of patients at first diagnosis and is the most likely cause of death in these patients.

(iii) The proliferative rate of the tumour. The rate of tumour cell replication is an important prognostic factor and is used to grade NETs (according to the Ki-67 labelling index). Based on World Health Organization (WHO) 2019, NETs which ae GEP-NENs are classified as grade 1 (G1), grade 2 (G2), or grade 3 (G3) according to proliferative rate (i.e., Ki-67 index and mitotic count) as shown in Table 3 (however note that there are separate WHO classifications for non-GEP NENs of epithelial origin[1] and of neuroectodermal origin[2]). Tumours classified as G3 can be divided into well-differentiated NETs (typically have Ki-67 of 21-55%) and poorly differentiated neuroendocrine carcinomas (NECs; typically have Ki-67 of >55%). The applicant also stated that cellular morphology and not Ki-67 is used to separate well-differentiated NET from NEC. Tumours of higher grade are associated with more rapid tumour growth and worse average overall survival duration, with patients with neuroendocrine carcinomas (NECs) experiencing the shortest overall survival (6-18 months; p21 of the application).

[1] Rindi G et al: Endocr Pathol 2022; 33:115-154. doi:10.1007/s12022-022-09708-2

[2] Mete O et al: Endocr Pathol 2022; 33:90-114. doi: 10.1007/s12022-022-09704-6

Table 3 Classification for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) [2]

Morphology	Grade	Mitotic count (2mm²)	Ki-67 Index (%)
Well-differentiated NETs	G1 (Low)	<2	<3
Well-differentiated NETs	G2 (Intermediate)	2-20	3-20
Well-differentiated NETs	G3 (High)	>20	>20
Poorly differentiated small cell type (SCNEC)	G3 (High)	>20	>20
Poorly differentiated, large-cell type (LCNEC)	High	>20	>20
MiNEN Well or poorly differentiated	Variable	Variable	Variable

Source: modified from Pavel 2020 and Reccia 2023.
Abbreviations: GEP-NETs = gastroenteropancreatic neuroendocrine tumours; G1 = grade 1; G2 = grade 2; G3 = grade 3; LCNEC = large-cell neuroendocrine carcinoma, MiNEN = mixed neuroendocrine-non neuroendocrine neoplasm; NECs = neuroendocrine carcinomas; NETs = neuroendocrine tumours; SCNEC = small-cell neuroendocrine carcinoma
NOTE: Along with the change in nomenclature the histology has changed in the last 15 years (G1-G3- NET+NE carcinoma) so some of the old survival curves may not be relevant.

(iv) The type and quantity of peptide hormone secretion. Patients who have excessive hormone secretion (i.e., considered to have 'functional' tumours) will experience adverse events that can be the primary factor in diminishing a patient's quality of life. For example, lower grade slow growing NETs may produce insulin (insulinomas) leading to hypoglycaemia that is difficult or impossible to control with associated morbidity and sometimes death. Peptide hormone secretion in NET patients with carcinoid tumours not infrequently develop endocardial fibrosis and life-threatening valvular dysfunction or mesenteric fibrosis with associated malabsorption syndromes. Carcinoid NET patients frequently have severe morbidity related to diarrhoea and malabsorption that is difficult to ameliorate with pharmacological and/or supportive treatments and the patient may be disabled by bronchospasm. Intractable diarrhoea is also a cause of a rare but serious morbidity in patients secreting vasoactive intestinal peptide (VIP). Diabetes, skin rash and steatorrhea can cause a rare but major morbidity in patients who secrete excessive somatostatin. Gastric ulceration can occur with gastrinoma, while skin necrosis (migratory necrolytic erythema) and diabetes is typical of glucagonoma. Patients with H-SSTR that secrete excess catecholamines may experience difficult to control hypertension or life-threatening hypertensive crises. Several other less common hormonal secretion syndromes are recognised.
(v) Response to treatments applied and associated adverse effects of treatment.

According to the European Society of Medical Oncology (ESMO) clinical practice guidelines for gastroenteropancreatic (GEP) NETs (Pavel 2020), " histological diagnosis is mandatory in all NET patients and can be carried out on resection specimens or core biopsies in advanced disease. The diagnosis of a NET is suspected on haematoxylin eosin (HE)-stained tissue by histomorphological growth pattern and cytology. The neuroendocrine phenotype is proven by the immunohistochemical detection of the neuroendocrine markers synaptophysin and/or chromogranin A (CgA)." Pavel (2020) also indicates that for grading NETs, immunohistochemistry (IHC) for Ki-67 (also known as Antigen KI-67 or MKI67 [Marker Of Proliferation Ki-67]) is mandatory, where NETs are classified based on morphology and proliferation into well-differentiated NETs (G1 to G3) and poorly-differentiated NECs (always G3). Other biomarkers are optional, for example, SSTR-2 staining when functional imaging is unavailable, and specific staining for peptide hormones such as gastrin, insulin, glucagon, and amines (serotonin) to confirm the source of a clinical symptomatology (Pavel 2020).

As noted above, the application is making a request for MBS listing of up to two pre-requisite PET/CT scans to determine eligibility for the therapeutic intervention and one post-treatment SPECT imaging.:

Test: Whole body ^{68}Gallium (^{68}Ga)-octreotate positron emission tomography (PET)/computed tomography (CT) - ^{68}Ga-DOTA-octreotate PET/CT. Of note, the MSAC and the literature have referred to this test as ^{68}Ga-Dotatate PET/CT or ^{68}Ga-DOTA-peptide PET/CT, however, *consistent with PASC's preferred term, this PICO confirmation will use ^{68}Ga-DOTA-octreotate PET/CT herein*: This test can be used for both measuring SSTR expression to assess eligibility for PRRT but also to assess the effect of ^{177}Lu-DOTA-octreotate treatment, usually three months after. This test is also required for consideration of follow-up treatment with PRRT.

Indicated for patients who have advanced NETs and suspected H-SSTR expression.

At its April 2023 meeting, PASC noted that the applicant was asked to clarify how patients with "other H-SSTR expressing tumours" who are proposed to be eligible for treatment with ^{177}Lu-DOTA-octreotate in the proposed item descriptor will be initially identified for testing with ^{68}Ga-DOTA-octreotate PET/CT to determine the presence of a H-SSTR expressing tumour. The applicant clarified that these patients will commonly have been identified by prior ^{68}Ga-DOTA-octreotate PET scans that have been undertaken for staging purposes. As with scans undertaken for staging purposes selecting patients for ^{68}Ga-DOTA-octreotate PET scans to assess suitability for ^{177}Lu-DOTA-octreotate therapy is based on probability estimates that H-SSTR expression will be found and is informed by clinical experience and published evidence. The applicant clarified that the "probability estimates" equate to pre-test probability.

At its April 2023 meeting, PASC noted that the applicant proposed some additional qualifying elements to the testing population, namely that it should be described as "Patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine tumours (NETs) with high somatostatin receptor (H-SSTR) expression and documented disease progression or uncontrolled symptoms related to their NET despite standard therapy, when referred by a multidisciplinary team (MDT)." PASC considered that the testing population should be amended as follows "Patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine tumours (NETs) with documented disease progression or uncontrolled symptoms related to their NET and suspected high somatostatin receptor (H-SSTR) expression and, when referred by a multidisciplinary team (MDT)."

In response to a question to the applicant about the use of current MBS item 872 in place of the proposed MDT item, the applicant's clinical expert responded that Item 872 looks appropriate. The current MBS Item 61647 for a ^{68}Ga-DOTA-octreotate PET/CT does not require referral by an MDT, or the use of Item 872.

Although the application specified both ^{68}Ga-DOTA-octreotate PET/CT or OctreoScan® single photon emission computed tomography (SPECT)/CT imaging (OctreoScan® SPECT/CT; also referred to as ^{111}In-penetreotide, ^{111}In-DTPA-octreotide, and OctreoScan® in the literature and are interchangeable, for consistency with the application, this imaging will be referred to as OctreoScan® SPECT/CT herein) to determine SSTR expression, in subsequent discussions with the applicant, it was suggested this be restricted to ^{68}Ga-DOTA-octreotate PET/CT on the basis that:

(i) ^{68}Ga-DOTA-octreotate PET/CT was associated with a lower radiation dose, has superior diagnostic accuracy (higher sensitivity) and is less expensive than OctreoScan® SPECT/CT (accepted by MSAC in its consideration of MSAC 1479R in April 2017), and
(ii) given the limited use of OctreoScan® SPECT/CT (MBS item 61369), for which there were nil uses in the 2021/2022 financial year.

On this basis, this PICO Confirmation will only consider ^{68}Ga-DOTA-octreotate PET/CT for assessment of SSTR expression. *At its April 2023 meeting, PASC agreed that consideration of only ^{68}Ga-DOTA-octreotate PET/CT for determination of SSTR expression for selection of patients was reasonable given MBS item number 61369 (^{111}In-octreotide SPECT) has not been claimed since 2019-2020.* The MSAC 1479R Public Summary Document (PSD; p1) noted that the CT component of PET/CT imaging is claimed separately under MBS item 61505.

The application states (p23) that suitability for the proposed intervention (^{177}Lu-DOTA-octreotate treatment) requires that patients demonstrate high concentration of somatostatin receptor expressions at all, or the majority of, tumour sites by imaging with suitable somatostatin targeting radiopharmaceuticals using the ^{68}Ga-DOTA-octreotate PET/CT imaging technique. The applicant stated that due to the physical phenomenon of partial-volume effects, SSTR-expression may be underestimated in lesions smaller than 1cm.

The application did not specify a threshold for SSTR expression. The application indicates no formal system of tumour grading for H-SSTR has been implemented. The Krenning score was developed using planar OctreoScan® imaging, which is a 4-point scale measuring tumour uptake of the radioactive tracer: 1=uptake less than liver, 2=uptake is approximately equal to liver, 3=uptake is greater than liver, and 4=uptake is greater than kidney and spleen (Majala 2019); patients were deemed SSTR-positive if they demonstrated a Krenning score ≥2 in the clinical studies cited by the application. The Krenning score was later extrapolated to both SPECT/CT and SSTR-PET/CT imaging using the 5-point scale modified Krenning score: 0=no uptake, 1=very low uptake, 2=uptake no more than the liver, 3=uptake greater than the liver, 4=uptake greater than the spleen (Park 2021); patients were considered SSTR-positive if they demonstrated a modified Krenning score ≥3 in the clinical studies cited by the application. Notably, OctreoScan® SPECT/CT imaging is less sensitive than ^{68}Ga-DOTA-octreotate/^{64}Cu-Dotatate PET/CT for determining SSTR status and is recommended if PET/CT imaging is unavailable (Pavel 2020; Hope 2023). As such, the modified Krenning score will generally be used to assess SSTR expression, to which the applicant highlighted that the intensity of uptake of ^{68}Ga-DOTA-octreotate PET/CT (i.e., a modified Krenning score ≥3), has been shown to correlate with strong staining on immunohistochemistry. The applicant further noted that since PET/CT is an intrinsically quantitative technique, standardised uptake value (SUV) results can be used to confirm the SUV_{mean} of liver and spleen and use of lesion SUV_{max} compared to these values can now provide robust evaluation of the modified Krenning score.

In addition, the ENETS (Hicks 2017) has noted higher remission rates on peptide receptor radionuclide therapy (PRRT) were positively correlated with high tumour uptake of radioactive tracer during pre-therapy OctreoScan® SPECT/CT. The patients referred to in this study were required to demonstrate tumour uptake of ^{111}In-octreotide equal to or greater than liver uptake (i.e., Krenning score ≥2) during SPECT/CT imaging, which suggested that the intensity of uptake of burden of disease on diagnostic scans are predictors of radiation dose delivery to disease and hence may influence the likelihood of response. Moreover, Iravani (2022) highlighted that for lesions >2 cm, the modified Krenning scores of 3–4 is deemed adequate for considering PRRT. However, for lesions smaller than 2 cm, the PET/CT scoring might overestimate SSTR expression compared to the original Krenning score and relying on the modified Krenning in this context is cautioned.

In response to the post-PASC (April 2023 meeting) comments in the PICO Confirmation, the applicant noted that there may be a discrepancy in the estimate of SSTR expression between the original Krenning score method using planar imaging and the modified Krenning score. However, the modified Krenning score will give an estimate of SSTR expression that is closer to the truth due to the greater accuracy of PET especially

for smaller tumours at sites of higher background uptake such as the liver. The applicant's nominated clinical expert indicated that treatment of tumours with a modified Krenning score less than three with ^{177}Lu-DOTA-octreotate therapy did not lead to improved patient outcomes in their experience.

In further discussion with the applicant during the development of the PICO, it was suggested that restricting PRRT to patients with a modified Krenning score of ≥3 (uptake greater than liver) would be unlikely to exclude any patients who would benefit from treatment, and it would also represent the threshold that would be considered by an MDT. *At its April 2023 meeting, PASC considered a threshold of a modified Krenning score of ≥3 (uptake greater than liver) was reasonable and questioned whether it should specify restriction to all known sites of disease ≥2 cm. In August 2023, PASC reiterated that the H-SSTR expression defined as a modified Krenning score ≥3 is reasonable for defining eligibility to the intervention PRRT with ^{177}Lu-DOTA-octreotate. PASC also considered that the same eligibility thresholds for induction treatment will also apply for any-follow-up/consolidation therapy as the success of PRRT is contingent on sufficient SSTR expression.*

The applicant commented that this appears to be a reasonable approach noting that tumours considerably less than 2 cm in diameter may still exhibit modified Krenning score of ≥3.

At its April 2023 meeting, PASC considered that a "majority" of sites should be defined, in regard to the statement that "patients demonstrate high concentration of somatostatin receptor expressions at all, or the majority of, tumour sites" see above. PASC then questioned whether all known sites of disease ≥2 cm should have a Krenning score ≥3.

In August 2023, PASC discussed whether the eligibility thresholds for PRRT should include a modified Krenning score of ≥3 in all sites ≥2cm in size, the majority of sites ≥2 cm, or the majority of all identified lesions (regardless of size) and noted this remains unresolved. PASC noted that:

a) for the assessment report, a threshold definition is required (e.g., NETTER-1 & Erasmus MC studies required Krenning score >2 [Octreoscan®] for all lesions; and
b) although thresholds have been designated to define eligibility for PRRT (e.g., modified Krenning score, the number of "majority" lesions required, number of discordant sites on FDG PET/CT), these are for the purposes of the assessment and are not intended to constrain the considerations of the MDT.

In response to these questions, the applicant has indicated that a modified Krenning score ≥3 as the nominated threshold to define H-SSTR is acceptable. There was equivocation on the question of whether the definition of majority should be:

- All known sites of disease ≥2 cm; or
- A "majority" of all known sites of disease, with the definition of majority not defined.

Although it was acknowledged by the applicant that defining the "majority" as all known sites of disease ≥2 would ensure that the highest rate of positive patient outcomes is maximised, it may exclude patients in whom hormone symptoms predominate and for which ^{177}Lu-DOTA-octreotate would provide best symptom control even though the patient's prognosis will be determined by the presence of more aggressive, less differentiated metastatic sites that are unlikely to be the source of the excess hormone production. It was further suggested, that under certain circumstances, patients may be suitable for resection or stereotactic radiotherapy of limited sites of spatially discordant disease or benefit from control of severe hormone

related symptoms and metabolic derangements results from these even in the presence of significantly discordant disease. This is particularly true of metastatic insulinoma, glucagonoma and VIPoma, or ectopic ACTH-secreting tumours which can be medical emergencies (email response received 14 July).

It was suggested that the decision about the "majority" of sites expressing modified Krenning ≥3 or only those ≥2 cm be left to the judgement of the multidisciplinary team that is treating the patient as this is a complex decision especially in patients with discordant disease.

Additional Test: Whole body fluorodeoxyglucose (FDG) PET/CT –FDG PET/CT:

The application noted for some patients with G2 tumours and patients with G3 tumours ^{18}F-FDG PET/CT imaging may be required in addition to ^{68}Ga-DOTA-octreotate PET/CT to optimise therapeutic decision making, particularly to enhance detection of discordant sites of disease and/or better define individual patient prognosis with and without available tumourcidal/tumourostatic therapy. It is proposed that information provided by the FDG PET/CT, in addition to the results of the ^{68}Ga-DOTA-octreotate PET/CT, in these patients will help the MDT or clinical specialists (if using Item 872) to plan further treatment for maximal attainment of patient important outcomes.

NENs are reported to often show heterogenous expression of SSTR, which could lead to inferior outcomes following targeted treatment and subsequently influence relapse and progression of the disease. High-grade lesions and metastases can have a lower expression of SSTRs which may not be fully assessed on receptor-based imaging alone (Graf 2020; Ortega 2021; Shi 2022; Charoenpitakchai 2017; Cives 2015).

Tumour heterogeneity is a common phenomenon in GEP-NENs (gastroenteropancreatic NENs) and has a negative impact on treatment success and prognosis and it produces cell clones that do not express treatment targets (i.e., SSTR, mammalian target of rapamycin-mTOR-signalling pathway, Ki-67).

The following figures (Figure 1 and Figure 2) illustrate the complexity of these patients in assessing treatment pathways and prognosis.

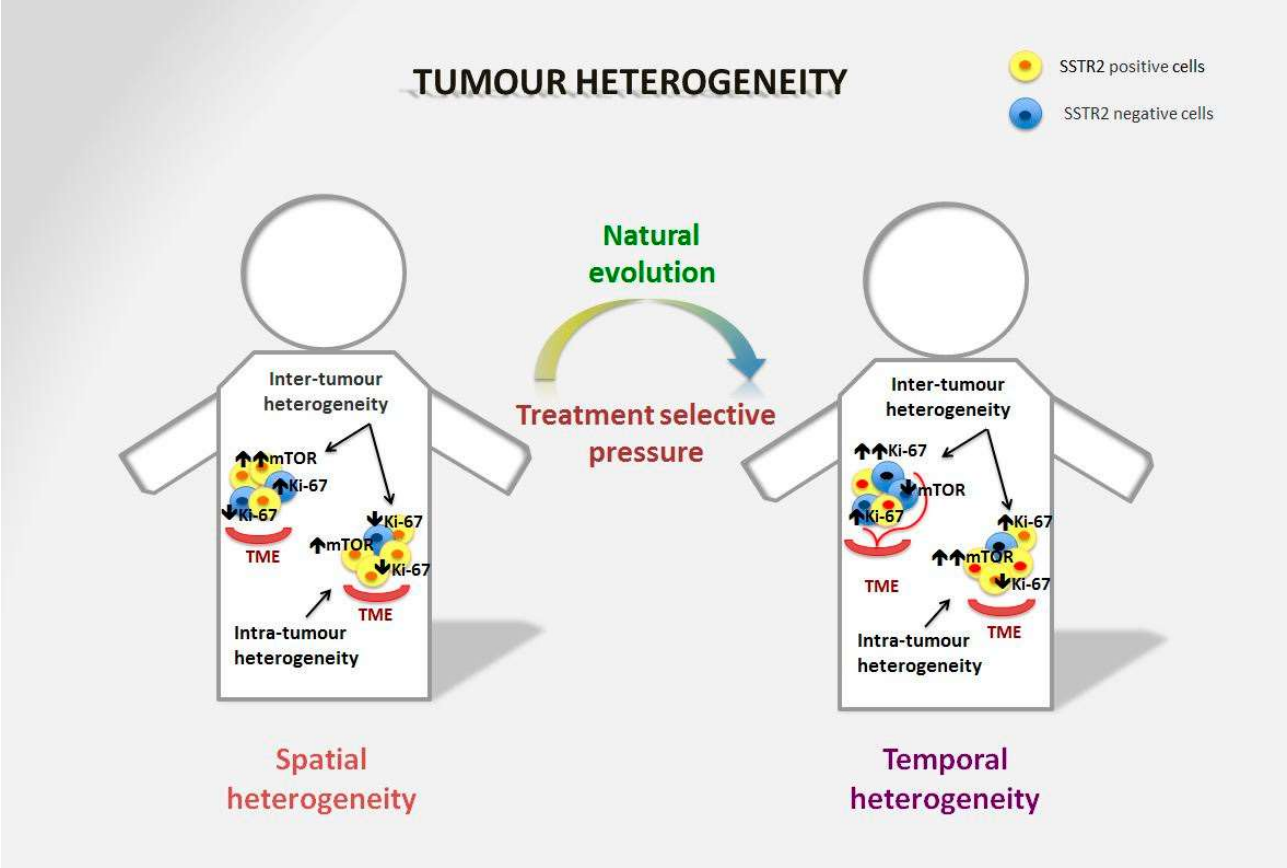

Figure 1 Spatial and temporal heterogeneity in NENs
Source Reccia 2023, Figure 1
TME=tumour microenvironment; mTOR=mammalian target of rapamycin
NENs generally express SSTR2 on the tumour surface and are well-differentiated tumours in the majority of cases. However, spatial heterogeneity within the primary tumour may lead to the presence of areas with lower expression of SSTR2 and/or a different Ki67 index. This heterogeneity is also frequent in metastatic sites and can differ significantly from the primary lesion. Temporal heterogeneity that can be linked to treatment selective pressure may lead to significant changes in tumour biology that affect prognosis and survival.

A recent review (Reccia 2023) suggests the addition of ^{18}F-FDG PET/CT in those particular cases (i.e., intermediate Ki-67 index, high grade lesions on biopsy, heterogenous or low uptake on somatostatin receptor imaging, clinically aggressive disease, poor response to PRRT) where high intra- and inter-tumour heterogeneity may not be revealed on only receptor-based imaging (Carideo 2019; Reccia 2023).

Dual imaging may give a better picture of intra-tumour heterogeneity in tumour biology (grading and SSTR expression) and guide biopsy and targeted therapeutic approach in NEN patients (Figure 2).

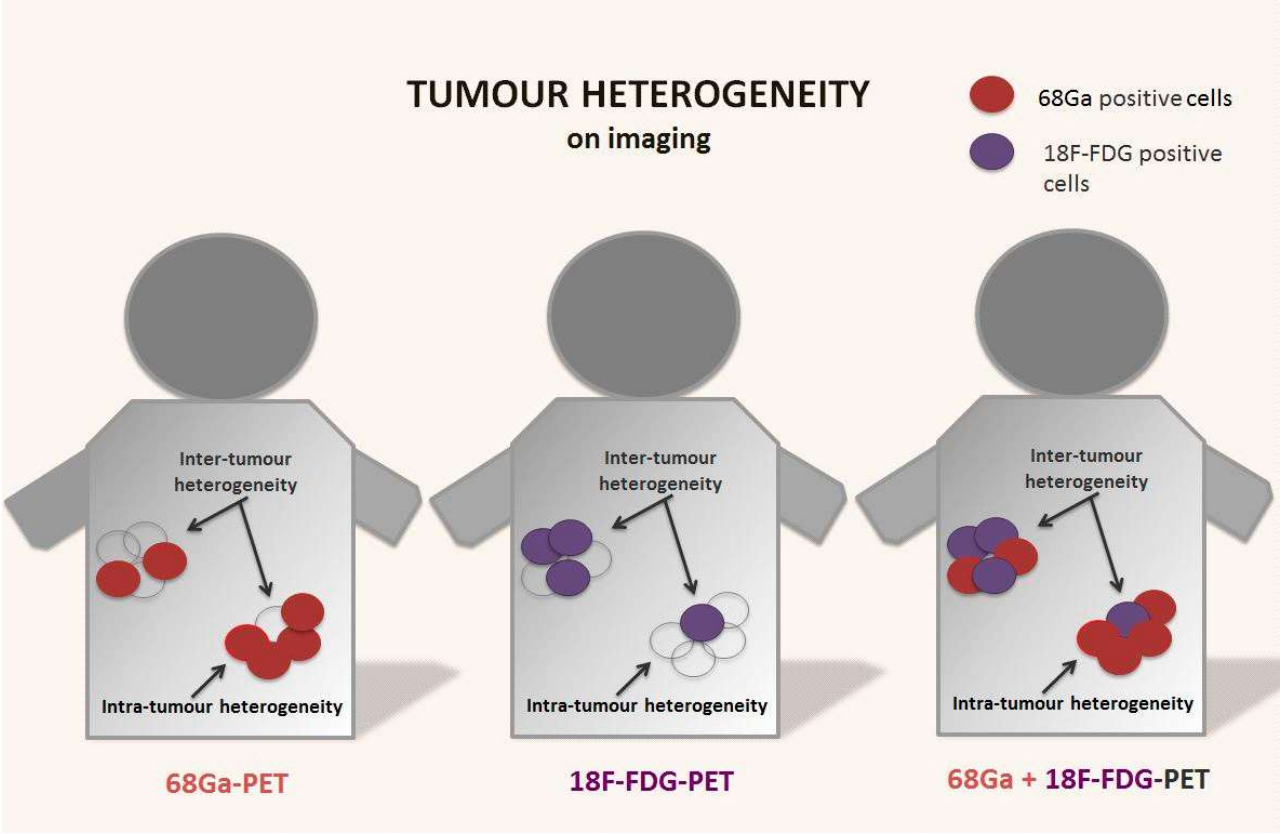

Figure 2 Tumour heterogeneity on receptor-based and functional imaging of NENs
Source: Reccia 2023, Figure 2
NENs are usually positive on somatostatin receptor-based imaging (i.e., ^{68}Ga-DOTA-peptides PET). However, the presence of tumour heterogeneity with areas that express lower, or no somatostatin receptors is common on baseline scans, and often after disease relapse or progression. These areas are often less differentiated and metabolically active. The use of ^{18}F-FDG-PET, especially in combination with receptor-based imaging, can potentially provide a better picture of metabolic spatial intra- and inter-tumour heterogeneity of the disease, especially in higher-grade tumours.

The application highlights (pp21-22) that tumour grade is reflected by metabolic imaging characteristics with a trend for decreasing somatostatin receptor imaging positivity and increasing FDG PET/CT positivity as tumour grade increases. The metabolic imaging phenotype of a patient provides important prognostic information as patients usually progress more rapidly when FDG positive tumour sites are present particularly when accompanied by low or absent tumour uptake on somatostatin receptor imaging. The prognostic relevance of tumours demonstrating low somatostatin receptor expression in part reflects the insensitivity of those tumour sites to somatostatin receptor antagonist treatment. Moreover, FDG-PET/CT intensity is also associated with a higher rate of tumour cell replication and degree of tumour differentiation. For some patients with G2 tumours and patients with G3 tumours FDG PET/CT imaging may be required in addition to optimise therapeutic decision making, particularly to enhance detection of discordant sites of disease and/or better define individual patient prognosis with and without available active tumoricidal/tumourostatic therapy.

A meta-analysis by Alevroudis (2021) reported that ^{18}F-FDG PET imaging in NET patients may be a useful prognostic tool for PRRT administration, where patients with FDG-PET positive tumours in the included studies demonstrated higher risk of progression and death following PRRT administration. However, the studies mainly included G1 or G2 NET patients (>80%) with G3 NETs only representing approximately 5% of patients. Consistently, the Society of Nuclear Medicine and Molecular Imaging (SNMMI, Hope 2023) have explained that ^{18}F-FDG PET provides complementary information to SSTR PET by assisting to identify lesions

that have lost SSTR expression. In G1/G2 NETs, ^{18}F-FDG positivity is not rare and is a stronger predictor of progression and prognosis than tumour grade. This is particularly useful in patients who are SSTR-PET-negative or have a well-differentiated G3 tumour.

The applicant identified the following patients for dual imaging:

> Indicated for patients, referred by an MDT, who have advanced NETs (some grade 2 and all grade 3), who have (i) tumours with Ki-67 greater than 10%;or (ii) progression in less than 6 months. For some patients in (i) and (ii) FDG PET/CT imaging may be required even if they test positive on H-SSTR to optimise therapeutic decision making (see paragraphs below for further details).

The application noted that MDT involvement would assist in determining which patients would be appropriately selected for FDG PET/CT imaging depending on the type of malignancy, tumour grade, disease stage, and clinical progress.

At its April 2023 meeting, PASC questioned the eligibility of patients, nominated by the applicant, with abnormal lesions on CT or MRI that do NOT meet the nominated threshold specified for H-SSTR on ^{68}Ga-DOTA-octreotate PET/CT being eligible for FDG PET/CT. PASC considered these patients were not relevant to the assessment due to the lack of sufficient H-SSTR expression for suitability for ^{177}Lu-DOTA-octreotate therapy. These patients have now been removed from the nominated population.

The applicant stated that "this appears to be a reasonable approach" in reference to removing patients who do not meet the nominated H-SSTR threshold for FDG scan. However, they have argued against the use of FDG PET/CT as an eligibility criterion (in the section under the Intervention: Test 2: FDG PET/CT).

In further discussions, the applicant's clinical expert explained that a patient with many H-SSTR metastases but only a few SSTR negative metastases that are positive on FDG PET/CT would indicate that FDG PET/CT has poor diagnostic accuracy for NET metastases. However, the utility of FDG PET/CT in such a scenario where a negative result can encourage use of PRRT but even limited sites of FDG-avid but non-SSTR-expressing disease can prevent futile treatment. The applicant further stated that sequencing PRRT after chemotherapy can be an effective strategy if FDG-discordant disease can be eradicated by chemotherapy.

The applicant was requested to further clarify the above as it is unclear how a negative result (on FDG PET/CT and/or SSTR-PET/CT) can optimise the clinical utility of PRRT, including in regard to obviating futile treatment. The applicant clarified that due to higher chemosensitivity of rapidly proliferating tumours, chemotherapy with regimens including capecitabine/temozolomide (CAPTEM) can depopulate these rapidly proliferating cells while leaving a higher proportion of lower-grade NET cells that can then be treated with PRRT. This can be confirmed by resolution of FDG-avid disease and an increase in modified-Krenning score or SUV_{max} on ^{68}Ga-DOTA-octreotate PET/CT. *In its consideration in April 2023, PASC noted the applicant's response stated the absence of SSTR receptors precludes delivery of high dose radiation to a tumour site. This meant that patients with high SSTR at all tumour sites regardless of FDG PET result can proceed to ^{177}Lu-DOTA-octreotate therapy with high probability that favourable patient relevant outcomes will be achieved.*

In response to further questions posed to the applicant, about whether the number of FDG/SSTR discordant sites representing the appropriate threshold for avoiding treatment with PRRT (a number of three discordant sites was raised) can be defined they responded that the purpose of suggesting PRRT treatment is managed under the auspices of an MDT team is that these are often value judgements. If the aim of treatment is

oncological control through stabilisation or regression of progressive disease, this goal cannot be achieved if there is even one site of spatial discordant FDG positive/SSTR negative disease but could be considered after control of this disease by either systemic or locoregional therapies. Treatment for hormonal control, may be indicated even in the presence of discordant disease. This is often as a bridge to systemic treatment of more aggressive disease elements by chemotherapy or targeted therapy.

The purpose of combining ^{68}Ga-DOTA-octreotate PET/CT followed by ^{18}F-FDG PET/CT is that less differentiated NENs often co-express SSTRs and glucose-transporters and the uptake of ^{18}F-FDG can show areas that are hypermetabolic. For these patients, the use of dual imaging can potentially provide a better picture of metabolic spatial intra- and inter-tumour heterogeneity of the disease, especially in higher-grade tumours. Higher uptake of ^{18}F-FDG seems to correlate more clearly with higher histological grades and poor overall survival. The purpose of using ^{18}F-FDG PET/CT after the ^{68}Ga-DOTA-octreotate PET/CT is not to change the SSTR threshold identified but, to identify the possible presence of less well-differentiated tumours that may be metabolically active but have lower or no somatostatin receptors. This information is used to assist the specialist in deciding whether the patient is suitable for PRRT therapy or whether another treatment may be indicated.

In further discussion with the applicant, it was considered that approximately 30% of patients would proceed to FDG PET/CT. The applicant cited a recent Australian study by Chan (2023) to support this estimation. The study examined the use of ^{68}Ga-DOTA-octreotate PET/CT and FDG PET/CT in patients with gastroenteropancreatic neuroendocrine neoplasms (NENs). Patients in the study received both types of scans. Chan (2023) reported that approximately 28% of patients had no FDG uptake, roughly equivalent to the proportion of G1 tumours in the study population but not necessarily the same patients. Only 12% of the cohort had exclusively FDG-avid disease. It should be noted that this study wasn't restricted to candidates for PRRT or patients who had been treated with PRRT. However, as a reasonable estimate, less than half of G2 NET and all G3 (51% and 15% of their cohort, respectively) would qualify for FDG PET/CT.

Therapeutic intervention ^{177}Lutetium Octreotate (^{177}Lu-DOTA-octreotate):

> Indicated for patients, referred by an MDT, who have advanced H-SSTR expressing NETs based on ^{68}Ga-DOTA-octreotate PET/CT imaging ± FDG PET/CT.

The application explains (pp22-23) that treatment with ^{177}Lu-DOTA-octreotate may be indicated for several patient groups who have been diagnosed with NET and/or other H-SSTR tumours who most commonly will have previously received one or more forms of local ablative or systemic therapy for their advanced disease. The application included:

- Patients with progressive metastatic disease that is, or has a high near-term probability of, diminishing the patient's quality and duration of life despite prior treatment with maintenance somatostatin antagonist medication, everolimus and/or sunitinib.
- Patients with high burden or high-grade metastatic disease that is, or has a high near-term probability of, diminishing the patient's quality and duration of life, particularly if they have failed first-line (1L) chemotherapy.
- Patients with NET who are experiencing reduced quality of life due to medically refractory excessive hormonal secretion, or the adverse effects of treatments specifically applied to modifying the effect of excessive hormone secretion, or pain that is refractory to other therapies.

- Patients with NET who require systemic therapy but cannot tolerate treatment with somatostatin antagonists, the targeted agents everolimus and sunitinib, or chemotherapy.
- Patients with NET in whom neoadjuvant treatment may facilitate successful localised curative intent ablative therapies.
- Patients with advanced malignancy characterised by high somatostatin receptor expression such as neuroblastoma, phaeochromocytoma and paraganglioma whose outcomes may be improved by ^{177}Lu-DOTA-octreotate treatment.

At its April 2023 meeting, PASC considered that of the six patient groups proposed in the application, the final two ('Patients with NET in whom neoadjuvant treatment may facilitate successful localised curative intent ablative therapies' and 'Patients with advanced malignancy characterised by high somatostatin receptor expression such as neuroblastoma, phaeochromocytoma and paraganglioma whose outcomes may be improved by ^{177}Lu-DOTA-octreotate treatment') should be removed from consideration.

The applicant considered that this PASC recommendation would deny a small number of patients with incurable malignancy the opportunity to receive highly beneficial disease modifying treatment, also noting that the treatment would only attract a Medicare benefit if there was a positive recommendation from an MDT.

At its August 2023 PASC meeting, PASC noted that the applicant requested that PASC reconsider its decision on whether or not to exclude 'Patients with NET in whom neoadjuvant treatment may facilitate successful localised curative intent ablative therapies' and 'Patients with advanced malignancy characterised by high somatostatin receptor expression such as neuroblastoma, phaeochromocytoma and paraganglioma whose outcomes may be improved by ^{177}Lu-DOTA-octreotate treatment' from the proposed population. PASC re-iterated that patients with non-NEN tumours with high somatostatin expression should not be included in the population. PASC considered that neuroblastoma, phaeochromocytoma and paraganglioma are considered NENs and therefore patients with these conditions are currently included in the eligible population. However, patients with advanced malignancy characterised by high somatostatin receptor expression that are not NENs (e.g., breast cancer, lymphoma, myeloma, renal cancer) should not be included in the eligible population.

PASC further noted in August 2023 that with respect to the population of 'patients with NET in whom neoadjuvant treatment may facilitate successful localised curative intent ablative therapies':

a) this population is not included in any guidelines regarding treatment of patients with NEN;
b) data to support the effectiveness of the proposed intervention in this population is scarce, based only on case reports and inhomogeneous retrospective studies of limited numbers of patients;
c) the largest (retrospective) case series[3] was of 57 patients, in whom neoadjuvant PRRT rendered the neuroendocrine tumours of 15 patients resectable. The usual survival outcome measures such as progression free survival (PFS) and overall survival (OS) were not compared between those and the remaining 42 patients; and
d) the only relevant trial is NCT04385992 (NeoLuPsNET) which is a phase II trial of neoadjuvant PRRT with ^{177}Lu-DOTA-octreotate followed by surgery for resectable non-functioning pancreatic NET; (proposed N=30; primary endpoint rate of postoperative 90-day morbidity and mortality), due for completion June

[3] Parghane RV *et al: J Nucl Med* 2021; 62:1558-1563; DOI: 10.2967/jnumed.120.258772

2023. However, this trial population does not align with the proposed PICO population, which specifies that patients must have inoperable tumours.

On balance based on the above, PASC considered that patients with NET in whom neoadjuvant treatment may facilitate successful localised curative intent ablative therapies were not within the eligible population.

The application explains (p22) that although, as a group, NET, including those with H-SSTR are not rare, the incidence of different tumour types that comprise this category of malignancies is low. Accordingly, even experienced clinical cancer specialists may be asked to treat patients with a specific type of NET only rarely, and the development of high-quality evidence is difficult, particularly with respect to understanding the relative benefits and risks of new therapies compared with existing standards of care. To help address this, it is proposed that patients are managed by an experienced Multidisciplinary Team (MDT). With the highly heterogenous nature of NENs and the associated complexities in clinical management pathways, an experienced MDT would assist in delivering optimal outcomes for patients.

It has been consistently recommended in the literature that eligibility for PRRT be discussed by an MDT specialised in NET management (Ambrosini 2021; Becx 2022; Hicks 2017; Hope 2019). This is discussed in further detail below. Currently, NEN specialists are using MBS Items 871 & 872 for MDT meetings and the applicant noted that Item 872 was appropriate for this purpose.

The European Neuroendocrine Tumour Society (ENETS, Hicks 2017) eligibility for PRRT is as follows:

- Inoperable/metastatic well-differentiated (G1/G2) NETs.
- Well-differentiated G3 NET may be considered (may be suitable for patients with higher grade NETs who have failed a trial of chemotherapy).
- Sufficient tumour uptake on the diagnostic somatostatin receptor scintigraphy (SRS).
- Sufficient bone marrow reserves (grades 1–2 haematological toxicity usually accepted).
- Creatinine clearance >50 mL/min.
- Karnofsky Performance Score (KPS) greater than 50.
- Expected survival greater than three months.

International guidelines (including ESMO (Pavel 2020), National Comprehensive Cancer Network [NCCN, Shah 2021], ENETS (Hicks 2017), and North American Neuroendocrine Tumour Society [NANETS, Hope 2019b] are generally aligned with these eligibility criteria. Patients are required to demonstrate a tumour-positive SSTR status from PET/CT or somatostatin receptor scintigraphy (SRS) in combination with SPECT/CT imaging using a radioactive tracer (^{68}Gallium [Ga]-Dotatate, ^{68}Ga-Dotatoc, or ^{64}Copper [Cu]-Dotatate for PET/CT or ^{111}Indium [In]-octreotide for SRS SPECT/CT). The applicant noted that ^{64}Cu-Dotatate (DETECTNET) for PET/CT is not available in Australia but an alternative ^{64}Copper [Cu]-MecoSAR-octreotate (CuSARTATE) has been evaluated in a first-in-human study performed in Australia (Hicks 2019). The applicant stated that CuSARTATE is in phase II trials in North America and may become an alternative method for selection of patients for PRRT.

The line of therapy for PRRT appears to be variable depending on the characteristics of the NET, in particular the primary site, grade, and proliferation of the tumour (Figure 7). The ESMO (Pavel 2020) recommend PRRT as second-line (2L) therapy in the advanced or metastatic setting for patients with unresectable midgut NETs with disease progression on somatostatin analogues (SSAs) who fulfil the general requirements for PRRT,

and for pancreatic NETs, PRRT was recommended after failure of chemotherapy or targeted therapies, such as everolimus and sunitinib (i.e., second-line and beyond [2L+] setting). In addition, PRRT is also indicated as a third-line (3L) therapy after failing SSAs in unresectable NETs with carcinoid syndrome to control symptoms due to excess hormone secretion (Figure 8). The NANETS/SNMMI (Hope 2019b) described similar indications for PRRT for midgut NETs and also noted that the Food and Drug Administration (FDA) included pancreatic NETs in the indication for ^{177}Lu-Dotatate (Lutathera®) and considered it for the treatment of progressive pancreatic NETs. For lung NETs, evidence of effectiveness using PRRT is limited but its use may be considered in patients with SSTR-positive tumours if they progress on everolimus.

Consistently, expert consensus from Ambrosini (2021) recommended PRRT as a 2L treatment after non-radiolabelled SSAs for patients with unresectable or disseminated gastrointestinal NETs (G1, G2, and G3) with high SSTR expression and patients with moderate/high uptake (tumour uptake of radiolabelled tracer greater than normal liver i.e., modified Krenning score of ≥3) in all metastases. However, consensus was not reached for the use of PRRT as a 2L treatment after failing non-radiolabelled SSA in patients with disseminated pancreatic NETs; as a 1L or 2L treatment for patients with local but non-resectable primary disease (i.e., no metastases); in patients with G1 or G2 NETs with mismatch lesions (i.e., ^{18}F-FDG-positive but ^{68}Ga-SSA-negative imaging results); or the use of PRRT as a neoadjuvant treatment.

Meanwhile, ^{177}Lu-Dotatate (Lutathera®) has attained regulatory approval by the FDA in 2018 for SSTR-positive GEP-NETs, including foregut, midgut, and hindgut NETs in adults and by the European Medicines Agency (EMA) in 2017 for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), SSTR-positive GEP-NETs in adults (Hennrich & Kopka 2019). The applicant stated that ^{177}Lu(nca)-DOTA-octreotate appears to be a very close biosimilar to the Lutathera product apart from the buffering agent formulation used to ensure radiochemical stability. The applicant further stated ^{177}Lu-DOTA-octreotate has been used in Australia since 2005 without patent restriction.

Given the complexity in patient management due to the heterogeneity of tumour progression, symptoms, and response to different tumoricidal or tumourostatic treatments, the applicant considered that 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 NETs and other H-SSTR tumours. In further discussion, the applicant's clinical expert noted that while experienced MDTs will follow the best available evidence and guidelines for NET management and PRRT use, this may not necessarily always come from multicentre randomised controlled trials (RCTs) with overall survival (OS) as the primary endpoint given that the objective of treatment varies with the disease grade, hormonal status, and primary tumour origin, hence clinical experience and judgement can sometimes take priority.

The application (pp6-17) provided a summary of studies, including one RCT (NETTER-1; Strosberg 2017), three single-arm prospective cohort studies (PCS; Brabander 2017, Khan 2011, Marinova 2019), nine single-arm retrospective cohort studies (RCS; Bergsma 2016, Bodei 2015, Kong 2017, Kong 2016, Sitani 2020, Thang 2018, Vaughn 2018, Zhang 2016, Zidan 2022), one meta-analysis of 22 RCTs (Wang 2020), two clinical practice guidelines (Pavel 2020; Hicks 2017), and two expert opinion papers (Ambrosini 2021, Leyden 2020) to support the use of the proposed intervention, ^{177}Lu-DOTA-octreotate, in advanced NETs and H-SSTR malignancies.

The RCT investigated patients with advanced midgut NETs who had disease progression during first-line SSRT therapy (metastasised, or were locally advanced, that were inoperable, histologically confirmed and verified) (NETTER-1; Strosberg 2017), the majority of prospective and retrospective cohort studies investigated a wider range of NETs but were primarily midgut, pancreas, lung NETs, and NETs of unknown origin, one retrospective study included only patients with lung NETs (Zidan 2022), and one included only paediatric patients with neuroblastomas (Kong 2016).

Prevalence and incidence of NETs in Australia

According to the Australian Institute of Health and Welfare (AIHW 2022), the number of people living with NETs at the end of 2017 (diagnosed in the 5-year period between 2013 and 2017) was 11,656. The number of new NET cases diagnosed between 1982 and 2018 increased from 1,173 to 4,508, respectively and the age standardised incidence rate (ASIR) increased from 9 per 100,000 persons (14 for males and 5.3 for females) to 16 per 100,000 persons (17 for males and 14 for females) from 1982 to 2018.

In a study based on 8,106 patients with NETs from the Victorian Cancer Registry between 1982 and 2019 (Michael 2022), a total of 8,136 NETs were diagnosed, with G1 NETs comprising 60% of diagnoses and colorectal (26%), small intestine (17%), and lung (13%) being the most commonly reported primary tumour sites (Table 4).

Table 4 Summary of the number of NETs diagnoses in 1982–2019 by tumour grade/morphology and site (as per ICD-O-3)[4]

Primary tumour	G1 Well-diff (%)	G2 Moderately-diff (%)	G3 Poorly-diff (%)	Undifferentiated (%)	Unknown grade (%)	Total per site, N=8136 (%)
Stomach	248 (62)	30 (8)	82 (21)	9 (2)	30 (8)	399 (5)
Small intestine	1112 (82)	98 (7)	137 (10)	1 (0)	14 (1)	1362 (17)
Pancreas	289 (34)	97 (12)	268 (32)	8 (1)	176 (21)	838 (10)
Other UGI	37 (16)	1 (0)	64 (27)	38 (16)	93 (40)	233 (3)
Colorectal	1831 (85)	56 (3)	181 (8)	15 (1)	61 (3)	2144 (26)
Lung	964 (88)	131 (12)	NR	0 (0)	1 (0)	1096 (13)
Breast and Gynae	74 (29)	6 (2)	70 (27)	34 (13)	73 (28)	257 (3)
Prostate and male genital	5 (5)	1 (1)	26 (25)	19 (18)	53 (51)	104 (1)
Urinary tract	8 (4)	1 (0)	62 (30)	36 (18)	98 (48)	205 (3)
Other sites	31 (14)	12 (6)	74 (34)	28 (13)	73 (33)	218 (3)
Unknown site	251 (20)	28 (2)	418 (33)	130 (10)	453 (35)	1280 (16)
Total	4850 (60)	461 (6)	1382 (17)	318 (4)	1125 (14)	8136 (100)

Source: Table 1, p308 from Michael 2019
Abbreviations: diff = differentiated; G1 = grade 1; G2 = grade 2; Grade 3 = grade 3; ICD = International Classification of Diseases; N = total number of cases; NETs = neuroendocrine tumours; UGI = upper gastrointestinal

Michael (2022) also reported an increasing trend in NETs (Table 5). The total prevalence of NETs in 2020 was estimated to be 4,342, with the period specific prevalence in the decades of 1990-1999 and 2010-2019, increasing from 740 to 3,123, respectively. This increase was observed across all primary tumour sites, in particular small bowel, colorectal, and lung, especially for G1 NETs.

The ASIR for all NETs increased more than three-fold over the study period (3.1 per 100,000 persons in 1982-1989 to 9.7 per 100,000 persons in 2010-2019), with the greatest increases in terms of primary tumour site

being the pancreas (7.7-fold) and the stomach (4.6-fold). Based on tumour grade, the highest increase was observed in G2 (206-fold) and G3 (4.8-fold) NETs.

Table 5 Number of new diagnoses and ASIR of NETs in Victoria in 1982-1989, 1990-1999 and 2010–2019 by NET groups[4]

	1982-1989		1990-1999		2010-2019		Change
Primary tumour	**n**	**ASIR (95%CI)**	**n**	**ASIR (95%CI)**	**n**	**ASIR (95%CI)**	**%***
All NETs	629	3.1 (2.9, 3.3)	1283	4.4 (4.1, 4.6)	4392	9.7 (9.4, 10)	220
Stomach	15	0.1 (0.1, 0.1)	50	0.2 (0.1, 0.2)	231	0.5 (0.4, 0.5)	250
Small intestine	67	0.3 (0.2, 0.4)	178	0.6 (0.5, 0.6)	770	1.6 (1.5, 1.7)	267
Pancreas	43	0.2 (0.2, 0.3)	77	0.3 (0.2, 0.3)	592	1.3 (1.2, 1.4)	433
Other UGI	28	0.1 (0.1, 0.2)	35	0.1 (0.1, 0.2)	99	0.2 (0.1, 0.2)	200
Colorectal	229	1.2 (1.1, 1.4)	366	1.4 (1.3, 1.6)	1253	3.3 (3.1, 3.5)	236
Lung	79	0.4 (0.3, 0.5)	185	0.7 (0.6, 0.8)	570	1.3 (1.2, 1.4)	286
Breast	31	0.1 (0.1, 0.2)	43	0.1 (0.1, 0.2)	118	0.3 (0.2, 0.3)	300
Prostate and male genital	3	0.1 (0, 0.2)	16	0.1 (0, 0.1)	52	0.1 (0.1, 0.1)	100
Urinary tract	10	0.1 (0, 0.1)	16	0.1 (0.1, 0.1)	112	0.2 (0.2, 0.2)	200
Other sites	25	0.1 (0.1, 0.2)	49	0.1 (0.1, 0.2)	86	0.2 (0.1, 0.2)	200
Unknown site	99	0.5 (0.4, 0.6)	268	0.8 (0.7, 0.9)	509	0.9 (0.8, 1)	112
Primary tumour site and grade as per ICD-O-3							
Colorectal G1	222	1.2 (1, 1.3)	324	1.3 (1.2, 1.4)	1044	2.9 (2.7, 3.1)	223
Lung G1	78	0.4 (0.3, 0.5)	184	0.7 (0.6, 0.8)	467	1 (0.9, 1.1)	143
Pancreas G1	4	0 (0, 0.1)	8	0.1 (0, 0.1)	259	0.6 (0.5, 0.6)	600
Small intestine G1	60	0.3 (0.2, 0.3)	169	0.5 (0.5, 0.6)	570	1.2 (1.1, 1.3)	240
Stomach G1	9	0.1 (0, 0.1)	36	0.1 (0.1, 0.2)	141	0.3 (0.2, 0.3)	300
Other sites G1	7	0.1 (0, 0.1)	11	0.1 (0, 0.1)	9	0 (0, 0.1)	0
Overall tumour grade as per pathology report							
G1	436	2.2 (2, 2.4)	803	2.9 (2.7, 3.1)	2634	6.2 (6, 6.5)	214
G2	1	0 (0, 0.2)	2	0 (0, 0.1)	413	0.9 (0.8, 1)	NR
G3	27	0.2 (0.1, 0.3)	157	0.5 (0.4, 0.6)	761	1.5 (1.4, 1.6)	300
G4	16	0.3 (0.2, 0.5)	150	0.4 (0.4, 0.5)	37	0.1 (0, 0.1)	25
Grade unknown	149	0.7 (0.6, 0.8)	171	0.5 (0.5, 0.6)	547	1 (0.9, 1.1)	200

Source: modified from Table 2, p310-14 from Michael 2019

Abbreviations: ASIR = age-standardised incidence rate; CI = confidence interval; G1 = grade 1; G2 = grade 2; Grade 3 = grade 3; G4 = grade 4; ICD = International Classification of Diseases; n = number; NETs = neuroendocrine tumours.

* Percentage change is between the complete decades of 1990-1999 and 2010-2019 (as reported in Michael 2022

Intervention

The proposed intervention is for ^{177}Lu(nca)-DOTA-octreotate. Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor for the treatment of non-resectable or metastatic neuroendocrine tumours (NETS) expressing somatostatin subtype 2 receptors when coupled with a suitable carrier molecule. The quantity of ^{177}Lu labelled PRRT that is subsequently administered will depend on the carrier molecule to be radiolabelled and its intended use (AusPAR TGA Product Information). Octreotate is the higher affinity analogue of octreotide, a somatostatin analogue, that binds with high affinity to the SSTR2 and SSTR5

subtype and with low affinity to the SSTR3 subtypes. This analogue does not bind to the SSTR1 and SSTR4 subtypes.

The ^{177}Lu(nca) product that will be supplied by the applicant, is produced by a TGA licenced manufacturer following Good Manufacturing Practice (GMP).

Consistent with the applicant's advice, the TGA Guidance on GMP information for manufacturers of compounded medicines and dose administration aids (DAAs)[4] a person with a TGA issued manufacturing licence manufacture can supply a medicine that has been extemporaneously compounded for a particular person for therapeutic application to that person.

The application (p19) notes non-GMP quality radiopharmaceuticals that are, or have been, used in Australia for this treatment indication include ^{177}Lu(carrier added [ca] and nca) Octreotide, ^{90}Yttrium Octreotate and Octreotide, and ^{111}Indium DTPA-Octreotate and Octreotide. In addition, Novartis sponsors a GMP quality ^{177}Lu(ca and nca) Octreotate (Lutathera®) radiopharmaceutical product for use in a similar treatment indication in the European Union (EU) and the United States (US). It is unknown whether the company intends to sponsor supply of their product to Australia. Lutathera® is also referred to as ^{177}Lu-DOTATATE, ^{177}Lu-Oxodothreotide, ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate, or ^{177}Lu-DOTA-D-Phe-Tyr^{3}-octreotate,[1] and its various nomenclature has been used in the studies cited in the application, with some studies using ^{177}Lu Octreotate, ^{177}Lu-DOTA-octreotate and Lutate. The applicant further explained that apart from use of different excipients for prevention of radiolysis, Lutathera® appears to be a very close biosimilar to the product proposed in this application.

The carrier added route uses stable lutetium as the material to irradiate with neutrons. To enhance the yield, and to prevent the creation of unwanted other radionuclides, the lutetium is enriched in ^{176}Lu. The first advantage of this route is that the nuclear reaction occurs with high probability, so that only one milligram of enriched lutetium is needed to produce approximately 50 patient doses. The other advantage is that the radiochemical processing after irradiation is limited to producing lutetium chloride, which is relatively simple. This route also has some drawbacks. At the end of irradiation only about 30% of the lutetium is useful radioactive ^{177}Lu. Since the ^{177}Lu decays while the rest of the lutetium is stable, the fraction of useful lutetium is smaller by the time it reaches the patient. The other drawback of this route is that the irradiation not only produces ^{177}Lu but also some ^{177m}Lu, which is an unwanted beta emitter with a long half-life of 160 days that comes with additional challenges for example related to waste management (Vogel 2021), see Figure 3.

Radionuclides have maximum theoretical specific activity values referred to as 'carrier-free' when all the atoms contain one isotope of the element. The no carrier added route to produce ^{177}Lu uses ytterbium (Yb) as the material to irradiate with neutrons. Similarly, to enhance the yield, and to prevent the creation of unwanted other radionuclides, the ytterbium is enriched in ^{176}Yb to a level above 99%. The irradiation created ^{177}Yb, which has a half-life of under 2 hours, decaying to ^{177}Lu. One advantage of this route is that once the produced lutetium is separated from the ytterbium, the product consists of useful lutetium only with a high specific activity. The other advantage is that the decay of ^{176}Yb to ^{177}Lu does not co-produce the undesired ^{177m}Lu. There are however also downsides to this route. Firstly, the nuclear reaction occurs with a

[4] https://www.tga.gov.au/resources/resource/guidance/gmp-information-manufacturers-compounded-medicines-and-daas

low probability, so that a gram of enriched ytterbium is needed to produce the same amount of activity that is reached with only a milligram of lutetium. Secondly, the lutetium needs to be separated chemically from the ytterbium, which is a challenging process: only 1 in roughly 5000 atoms in the irradiated material is a ^{177}Lu atom, so the chemical separation process needs to have a high separation efficiency. Currently, the only production of enriched ^{176}Yb comes from low-throughput facilities (calutrons) in Russia (Meeting isotope needs and capturing opportunities for the future 2015) accessed 20 July 2023, which is a problem for the future of carrier-free ^{177}Lu production. (Vogel 2021).

For the direct production of ^{177}Lu, the co-production of ^{177m}Lu with a half-life of 160.1 days has emerged as one factor that may be an impediment restricting its utility in some countries. The ^{177m}Lu content in the final product depends not only on the irradiation time, but also on the time elapsed after the end of the irradiation (EOI). The presence of ^{177m}Lu raises concerns for laboratory waste and wastewater. The application noted that the use of ^{177}Lu-DOTA-octreotate biosimilars (ca and nca) have been used at several sites throughout Australia for several decades. It was noted by the applicant (email 14 July) that waste management is more difficult with "carrier added" ^{177}Lu and this is a whole of government issue in essence (assume this might mean that Environmental Protection Agency might be involved).

It was noted by the applicant that the studies cited in the application did not involve the proposed intervention, ^{177}Lu(nca)-DOTA-octreotate. The cited studies investigated ^{177}Lu-DOTATATE (also referred to as ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate, ^{177}Lu-DOTA-octreotate , ^{177}Lu-octreotate, and Lutate in these studies) as the intervention, with two studies also investigating ^{90}Y-DOTATATE[25] and ^{90}Y-DOTATATE/-DOTATOC[26]. In further discussions with the applicant, it was noted by the applicant's clinical expert that carrier added ^{177}Lu-DOTATATE would have been most commonly used in these studies.

At its meeting in April 2023, PASC questioned the limitation of ^{177}Lu-DOTA-octreotate therapy to the "no carrier added" (nca) product, noting that the clinical evidence was silent on whether the "nca" or "carrier added" product was used. The applicant reiterated that the proposal was for ^{177}Lu(nca)-DOTA-octreotate specifically and there was potential for use of ^{177}Lu(ca)-DOTA-octreotate (carrier added) if the descriptor was left more 'generic' (as ^{177}Lu-DOTA-octreotate is prepared in Australian hospitals currently and may be either the "nca" or the "ca" product, depending on the source of ^{177}Lu).

The long-term supply of medical isotopes is becoming an emerging issue. ^{177}Lu has been identified as an example of a medical isotope that may be at risk for future shortages [Meeting isotope needs and capturing opportunities for the future-2015 accessed 20 July]. The increasing demand for ^{177}Lu is explained by its application in several current and new radionuclide therapies, notably radiolabelled somatostatin analogues for neuroendocrine tumours and prostate-specific membrane antigen (PSMA) ligands for prostate cancer. In combination with the challenges related to production, this leads to concerns that the availability of ^{177}Lu as a medical isotope may not be sufficient in the long term (Vogel 2021). Insufficient and slow supply remains a daunting problem for patients and treating physicians. It was reported that 5% of patients died while waiting for treatment, as this can be delayed by two months or longer. Novartis has experienced production and delivery problems at its sites, and it remains a significant problem due to operational issues (Ravi 2023; Czernin 2023).

In Australia, the source of ^{177}Lu(nca) is usually local but the backup source is overseas and supply issues have occurred. Lutetium (^{177}Lu) chloride is registered by the TGA, sponsored by Australian Nuclear Science and

Technology Organisation (ARTG 352151, September 2022). Its approved therapeutic use is as a radiopharmaceutical precursor, and it is not intended for direct use in patients. The registered use is: "For the treatment of non resectable or metastatic neuroendocrine tumours (NETS) expressing somatostatin subtype 2 receptors when coupled with a suitable carrier molecule" (AusPar: Lutetium (^{177}Lu) chloride).

The applicant agreed that the clinical advantages of "nca" ^{177}Lu compared to the "ca" ^{177}Lu is imputed from cogent theory and has not been established by robust evidence. However, one study has been identified (the search was not exhaustive) that compared the absorbed doses in organs and tumour lesions of [^{177}Lu]Lu-labelled DOTA-TATE carrier added (direct route) and [^{177}Lu]Lu-labelled DOTA-TATE no carrier added (indirect route) using post administration whole-body scintigraphy (5 time points,0.5, 2, 12, 24, and 72 hours post void) and one SPECT scan at 24 hours post void. The study found no statistically significant difference in the dosimetry data of patients treated with nca and ca [^{177}Lu]-labelled with DOTA-TATE (Kamaldeep 2022). This study may be of sufficient quality to determine the noninferiority of ^{177}Lu(nca) to ^{177}Lu(ca). The applicant has stated that the cost of manufacture of using "ca" ^{177}Lu as a starting material is substantially lower than "nca" ^{177}Lu.

In response to the claim by the applicant that ^{177}Lu(nca)-DOTA octreotate appears to be a very close biosimilar to the Lutathera®[5] product (also referred to as ^{177}Lu-DOTATATE), at its August 2023 meeting, PASC noted that:

a) *MSAC may wish to consider whether this claim should be justified. PASC also advised a comparison against Lutathera® with particular attention to the pharmaceutical form (e.g. concentration, vehicle, excipients, incompatibilities, shelf-life, etc) may be necessary. The applicant stated that they would be able to provide this comparative information.*
b) *PASC noted the applicant's advice regarding the patent question raised by a commercial organisation.*
c) *In addressing the question of whether the item descriptor should be restricted to ^{177}Lu(nca), PASC noted that it may be difficult to demonstrate superiority (or noninferiority) of ^{177}Lu(nca)-DOTA-octreotate versus ^{177}Lu(ca)-DOTA-octreotate in terms of health outcomes. PASC further considered that there is no available evidence of the superior safety and effectiveness of the 'nca' product compared to the 'ca' product to justify restriction of the benefit to the 'nca' product and that the proportion of ^{177m}Lu in the clinical 'ca' product' is <0.1% and poses no significant additional radiation risk to the patient (Gleisner 2015). PASC also noted that with respect to the storage and disposal of ^{177m}Lu, the amount of ^{177m}Lu activity produced is small and theranostic nuclear medicine departments have established facilities to store and dispose of considerably higher activities of β-emitters.*

PASC also considered in August 2023, that based on the above considerations, the assessment report should further investigate the evidence to support the claim of noninferiority between the proposed product: ^{177}Lu(nca)-DOTA-octreotate, or ^{177}Lu(ca)-DOTA-octreotate, vs. the Lutathera® product (^{177}Lu-DOTATATE; unspecified, used in the NETTER-1 trial), or any other ^{177}Lu therapeutic product used in the clinical studies to support comparative safety and effectiveness of PRRT therapy with ^{177}Lu-DOTA-octreotate in the proposed population. However, PASC noted an evidence-based assessment of noninferiority between products in scope of the suggested MBS item for therapy may be difficult due to the current lack of available evidence.

[5] Lutathera®is also referred to as ^{177}Lu-DOTATATE in the Novartis submission

The applicant provided a comparison of the costs of the ^{177}Lu-DOTA-octreotate (nca) infusion and that for ^{177}Lu-DOTA-octreotate (ca), these are discussed later in this document.

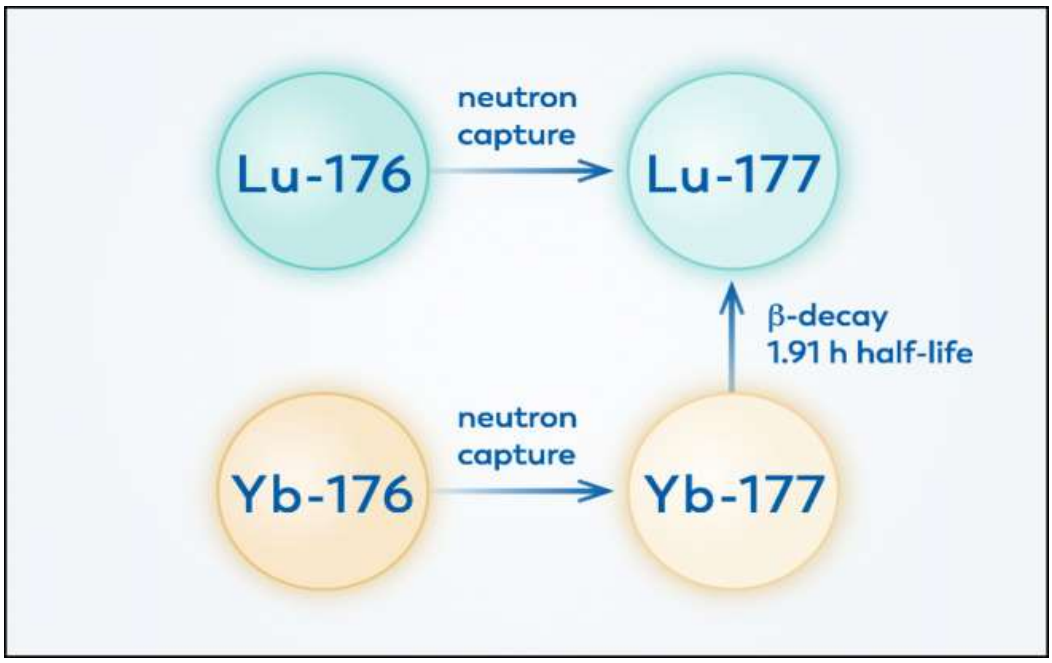

Figure 3 Production of carrier added versus no carrier added ^{177}Lu

Source: Vogel 2021, Figure 1
Abbreviations: Lu= lutetium; Yb = ytterbium
Illustration of possible production routes for ^{177}Lu. Neutron irradiation of ^{176}Lu yields carrier-added ^{177}Lu, while neutron irradiation of ^{176}Yb indirectly leads to no carrier added ^{177}Lu via subsequent decay. There is no feasible production route possible without neutron irradiation[6]

The application notes (p23) that referrals for the proposed intervention ^{177}Lu-DOTA-octreotate will come from an MDT experienced in managing patients with NETs with the procedure undertaken by an appropriately licensed theranostic specialist. The application is for two tests (^{68}Ga-DOTA-octreotate SSTR-PET/CT in all patients and ^{18}F-FDG PET/CT in some patients) and one therapeutic intervention (i.e., co-dependent technology).

Test 1: ^{68}Ga-DOTA-octreotate SSTR-PET/CT

PET imaging measures the biodistribution of an intravenously injected biological tracer labelled with a positron-emitting radionuclide, detecting, and quantifying biological processes occurring within the body (Scott 2001).

The MSAC 1632 Public Summary Document (PSD; July 2021) stated (p5) that the [MSAC 1632] Ratified PICO noted that PET imaging is now almost always combined with CT, with scans collected using a single, hybrid PET/CT scanner ([MSAC 1632] PICO Confirmation, p14). There are several hybrid PET/CT devices listed on the Australian Register of Therapeutic Goods (ARTG) (ARTG numbers: 343270, 324191, 296394, 292543, 271560, 144218 and 118077).

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Whole body ^{68}Gallium (Ga)-octreotate somatostatin receptor (SSTR)-positron emission tomography (PET)/computerised tomography (CT), ^{68}Ga-DOTA-octreotate SSTR-PET/CT herein, was considered by MSAC in 2017 for the diagnosis of GEP-NETs (MSAC 1479R, April 2017).

The current application proposes the use of ^{68}Ga-DOTA-octreotate PET/CT imaging to determine its uptake from somatostatin receptors on NET target sites and assess SSTR status and eligibility for ^{177}Lu-DOTA-octreotate treatment. The application is therefore requesting that the item descriptor for Whole body ^{68}Ga DOTA peptide PET (MBS item 61647/61505) be expanded to include patients with NETs and suspected H-SSTR tumours other than GEP-NETs as referred by an MDT to assess eligibility for ^{177}Lu-DOTA-octreotate treatment. No proposed wording was provided in the application, however the applicant subsequently provided some wording, see Proposal for public funding. The Department suggested a new item descriptor, rather than amending the current item descriptor, would be more suitable. This new item descriptor is provided at Table 13

In its consideration at the April 2023 meeting, PASC nominated the modified Krenning score ≥3 as the threshold for eligibility for accessing PRRT therapy and the Applicant has accepted this. In terms of the wider application of this threshold as a proposed criterion in the relevant MBS item, it would be helpful to know what information is routinely provided on a ^{68}Ga-DOTA-octreotate PET/CT report.

In August 2023, PASC considered that an MDT referral is not specifically required to request a ^{68}Ga-DOTA-octreotate PET/CT as an unknown proportion of patients will already have undergone SSTR expression assessment before review by the MDT. However, the current MBS item 61647 would require an amendment or a new item to include the eligible population for the proposed new therapeutic PRRT item.

The use of ^{68}Ga-DOTA-octreotate PET/CT is also required approximately three months after the treatment cycle to assess treatment outcomes.

PASC considered that data derived from evidence relating to SSTR expression determination by ^{111}In-pentetreotide (OctreoScan®) SPECT/CT would need to be translated to ^{68}Ga-DOTA-octreotate at the April 2023 meeting.

Test 2: FDG PET/CT

As noted by the applicant and outlined in Figure 9, a proportion of the patients eligible for and who have received a ^{68}Ga-DOTA-octreotate PET/CT revealing H-SSTR may also require a FDG PET/CT for the purposes of revealing whether high intra- and inter-tumour heterogeneity that may not be revealed on only receptor based imaging is present.

The Applicant nominated FDG PET/CT, imaging that may be required to optimise therapeutic decision making in the following patients:

(i) Some patients with G2 tumours and all patients with G3 tumours (tumours with Ki-67 >10%); or
(ii) Progression in less than 6 months.

As above, in its consideration at the April 2023 meeting, PASC questioned the use of FDG PET/CT (i.e. test 2) for patients with lesions on CT or MRI without adequate SSTR expression on ^{68}Ga-DOTA-octreotate PET/CT. PASC also stated that the use of FDG PET/CT as a selection criterion for (or against) eligibility for ^{177}Lu-DOTA-octreotate treatment required justification. Although the applicant has accepted the reason for removing

this population, they have also stated that FDG PET is no longer indicated to assess suitability for ^{177}Lu-DOTA-octreotate treatment (email July 14th 2023). *From the April 2023 PASC, and written in the draft PICO confirmation, PASC noted that "absence of SSTR receptors precludes delivery of high dose radiation to a tumour site. This meant that patients with high SSTR at all tumour sites regardless of FDG PET result can proceed to ^{177}Lu-DOTA-octreotate therapy with high probability that favourable patient relevant outcomes will be achieved"*.

The applicant stated that the question of use of FDG PET/CT as an eligibility criteria has been addressed previously. More patients with a higher probability of harbouring tumours that do not have modified Krenning score SSTR expression ≥3 who are unlikely to derive benefit from the treatment will be identified. Some patients who are unsuitable for treatment can be identified through correlation with diagnostic CT or MRI. However, the incremental sensitivity of FDG PET for detecting tumours means that reliance on CT or MRI alone will result in some patients with FDG positive/SSTR negative tumours being judged as suitable for treatment when they are not.

It is not a necessary condition for patients in groups (i) and (ii) to have tumours that are below the nominated threshold for H-SSTR (detected via ^{68}Ga-DOTA-octreotate PET/CT) before proceeding to Test 2.

The applicant is not in favour of the FDG PET/CT being used as an eligibility for ^{177}Lu-DOTA-octreotate, as noted in the literature, the purpose of the FDG PET is to identify inter-and intra-tumour heterogeneity, and it is recognised that pre-treatment ^{68}Ga-DOTA-octreotate PET/CT does not always correlate with a response to PRRT, as target lesion heterogeneity may affect the response (Iravani 2022). It is reported that a single standard fixed diagnostic algorithm is not optimal for this highly heterogenous group of tumours and that individualised strategies can lead to improved outcomes, better selection of candidates for specific treatment and evaluation in the post-treatment setting. For this reason, the application nominated an MDT, to determine these individualised strategies.

The application noted (p23) that MDT involvement would also assist in determining which patients would be appropriately selected for FDG PET/CT imaging depending on the type of malignancy, tumour grade, disease stage, and clinical progress*. As noted already, the current MBS Item 872 is considered suitable for the purposes of MDT involvement.*

The application originally proposed the descriptor for MBS item 61598 (Whole body FDG PET study performed for the staging of biopsy proven newly diagnosed or recurrent head and neck cancer) be amended to include eligibility for ^{177}Lu-DOTA-octreotate treatment. However, it was noted by the applicant following discussions that amendment to MBS item 61612 would be more appropriate. No proposed wording was provided in the application, however the item descriptor may not need amending as the eligible patient population for this item includes individuals diagnosed with rare or uncommon cancers, where these cancers are defined as having less than 12 cases per 100,000 persons per year (see Table 14 under Proposal for public funding).

At the April 2023 PASC, PASC agreed that the current MBS item descriptor for FDG PET/CT imaging would likely not require amendment. The current wording of this item (Item 61612) places limits in relation to the rarity of the cancer but does not place limits due to tumour grade or time from diagnosis.

In its consideration in August 2023, PASC noted that a proportion of patients will have ^{68}Ga-DOTA-octreotate PET/CT followed by FDG PET/CT. The purpose of this is to identify any intra-lesional and inter-lesional

heterogeneity to optimise therapeutic decision making, particularly to identify discordant (i.e., FDG-positive, SSRI-negative) sites of disease which may not respond to PRRT.

PASC also noted (August 2023) that with respect to whether the FDG PET/CT(after ^{68}Ga-DOTA-octreotae) is required to be included in the clinical management algorithm (see Figure 9*) to determine eligibility for PRRT therapy, PASC noted the following:*

a) *The purpose of FDG PET/CT is not to select patients for PRRT, but to identify patients who may not be suitable for PRRT.*
b) *The "discordance threshold" (FDG [+]/SSRI [-]) of ≥3 lesions to exclude or reconsider PRRT is based on expert opinion rather than evidence.*
c) *An estimate of FDG PET/CT frequency of use is required for the assessment report to assist in determining outcome impact, economic evaluation and financial consequences.*
d) *PASC considered the current MBS items 61612 (FDG PET for initial staging of rare and uncommon cancers) & proposed draft item 61614 (FDG PET for restaging & response assessment of rare & uncommon cancers) should be applicable for the proposed populations. Neither of these items require a referral from an MDT.*

Therapeutic intervention: ^{177}Lu-DOTA-octreotate

Mechanism of action

^{177}Lu-DOTA-octreotate involves intravenous administration of beta radiation-emitting radiopharmaceutical targeting SSTR on tumour cells. Somatostatin receptors are G-protein couple receptors with five subtypes of which subtype 2 (SSTR-2) is the most commonly expressed in NETs and targeted by the intervention (Becx 2022, Bidakhvidi 2021). After binding to the SSTR-2 receptor, ^{177}Lu-DOTA-octreotate is internalised into the tumour cell where the irradiation induces DNA damage, such as single strand breaks and DNA double strand breaks, of which the latter are the major contributors to tumour cell death induction (Becx 2022).

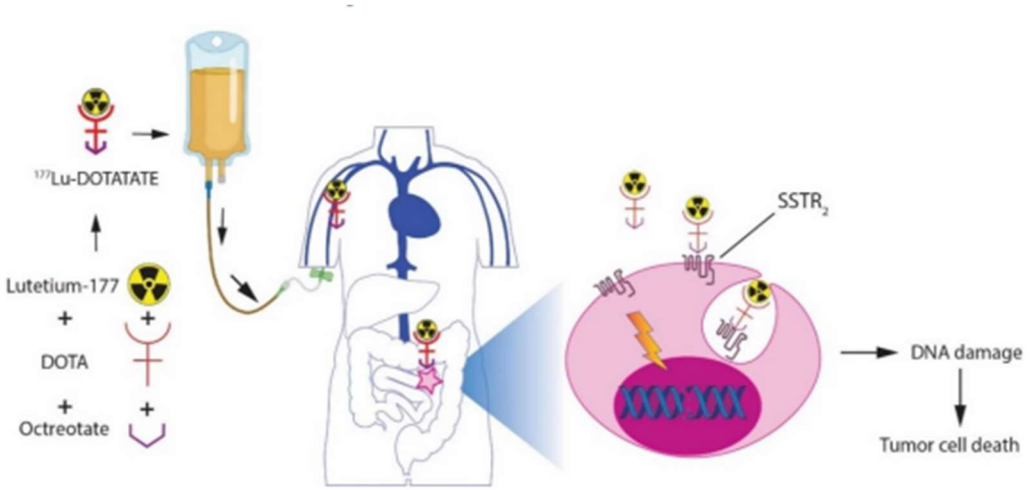

Figure 4 Mechanism of action of ^{177}Lu-DOTA-octreotate [6]

Source: Figure 1, p5792 from Becx 2022
Abbreviations: DNA = Deoxyribonucleic acid; $SSTR_2$ = somatostatin receptor 2

Pre-treatment

The application states (p24-5) that the theranostic specialist who supervises ^{177}Lu-DOTA-octreotate therapy will often be a member, or regular attendee, of the MDT (treating specialist) that has referred the patient for treatment in which case suitability of that patient will already be known to the specialist and pre-treatment consultation could be limited to:

- Explaining the risks and benefits of ^{177}Lu-DOTA-octreotate treatment to that patient.
- Describing the preparation for the treatment including adjustments to regular medications.
- Describing the performance of the procedure on the treatment day.
- Describing the follow-up procedures.
- Ensure data required for monitoring of ^{177}Lu-DOTA-octreotate treatment effects is current.
- Obtain formal patient consent for ^{177}Lu-DOTA-octreotate treatment.

The MBS item fee for pre-treatment specialist consultation is $167.75 (MBS item 110, see Table 10 (under Proposal for public funding). No amendment was proposed for this item.

The applicant was requested to provide details on the qualifications of a theranostic specialist (e.g. what college(s) the specialist must be a member of and what specific training/qualifications they require). The applicant responded that the specialist should have completed advanced training in Nuclear Medicine and Molecular imaging. In addition, relevant experience in theranostics is necessary to ensure that the specialist has an appropriate level of training and skill to supervise ^{177}Lu-DOTA-octreotate treatment. The applicant considered that the draft Australasian Association of Nuclear Medicine Specialists (AANMS) guidelines offer an acceptable position on the qualifications that are necessary to undertake ^{177}Lu-DOTA-octreotate treatment in conjunction with appropriate MDT (specialist) evaluation and guidance. The applicant additionally stated that access to multidisciplinary medical expertise in the management of infrequent but

severe acute reactions to ^{177}Lu-DOTA-octreotate treatment including carcinoid crisis and catecholamine crisis or delayed hypoglycaemia is required by either the practitioner or directly available within the team.

During treatment

^{177}Lu-DOTA-octreotate administration is mostly conducted as an outpatient procedure on a same day basis over a period of four to six hours. In some patients where there is a significant risk that treatment will trigger excess hormone release with life threatening consequences treatment should be undertaken as an inpatient. In the rare case where the patient is initially treated as an outpatient and experiences severe complications (e.g., neuroendocrine hormonal crisis or severe emesis) then this may result in an overnight hospital stay (Hope 2019a).

The administration facility will be suitably equipped and staffed to undertake the delivery of the ^{177}Lu-DOTA-octreotate radiopharmaceutical. Preferably such facilities would meet the standards specified in the appended document AANMS Position Statement on Practice of Theranostics in Australia -Version 1, dated February 2021 (AANMS Theranostics Position Paper). The application notes (pp26-27) that attendance of a credentialled theranostic specialist should be available for consultation during the procedure and proposes that the service should only be delivered by a trained and credentialled theranostic specialist. Moreover, a nuclear medicine technologist and a registered nurse are generally required to conduct the therapeutic administration and evaluate the patient's suitability for release from the facility. The application proposed amendments to MBS item 13950 for administration (see Table 11 under Proposal for Public Funding).

The application has stated that this treatment can be given in inpatient or outpatient settings (both private and public), but the outpatient setting is the most likely.

The TGA Australian Public Assessment Report (AusPar) (Lutetium (^{177}Lu) chloride) based on the study by Abuqbeitah (2018), which examined the blood clearance and occupational exposure following ^{177}Lu-DOTATATE compared to ^{177}Lu-prostate specific membrane antigen radionuclide therapy, reported that both treatment modalities are reasonably reliable for outpatient treatment, since the mean dose rate (2.1 µSv/(h GBq) is below the dose rate that allows release of the patient from the hospital (20 µSv/h) after 6 hours at a distance of 1 metre.

At a suitable facility the patient would have two intravenous cannulas inserted with appropriate process to ensure that extravasation of the radiopharmaceutical will not occur. It was noted in the application (p36) that a 'non-admitted patient facility cost' was required for administration, however, no corresponding item was provided despite noting that alteration of the item descriptor was required. The applicant has since indicated this could be included in the per cycle fee for ^{177}Lu-DOTA-octreotate treatment.

Premedication with antiemetics, usually selective 5-HT3 serotonin-receptor antagonist is routinely given. At some sites dexamethasone may also be administered as a premedication as specified by the supervising theranostic specialist.

Administration of an amino acid infusion is required to reduce uptake of the product in the kidneys immediately prior to ^{177}Lu-DOTA-octreotate administration. An amino acid infusion composed of 25gm arginine and 25gm lysine per litre is begun by an infusion pump through one intravenous cannula 30 minutes before ^{177}Lu-DOTA-octreotate administration to reduce kidney uptake of the radiopharmaceutical and continued for three to four hours after infusion of ^{177}Lu-DOTA-octreotate, which is undertaken using a

separate infusion pump and the second cannula. This is aligned with NANETS Procedure Standards for PRRT with ^{177}Lu-Dotatate (Hope 2019a). The compounded arginine/lysine amino acid solution is less emetogenic and can generally be infused over a short period, however, due to licensing requirements and compounding regulations, compounded arginine/lysine formulations may not be available at many institutions. In further discussions, the applicant explained that formulations are currently made by compounding pharmacies that add these amino acids to sterile normal saline. GMP production would be preferred, and it is likely that a current supplier of parenteral nutrition products or pharmaceutical company, would provide infusions meeting these specifications given globally increasing demand. The applicant has at this moment not provided information about supply of sterile suitable verified amino acid infusions outside of those currently made at hospital pharmacies.

No MBS item fee is associated with amino acid infusion, nor are the amino acids PBS-listed. As this is an essential component for treatment, the applicant has proposed that the cost for amino acid infusion may be incorporated into the per cycle fee for ^{177}Lu-DOTA-octreotate treatment.

The patient is monitored for vital signs and adverse reactions during the infusions of ^{177}Lu-DOTA-octreotate and amino acid solution and for at least three hours following these infusions. Occasionally treatment emergent symptoms require additional medication or slowing the rate of the infusions.

At the completion of the ^{177}Lu-DOTA-octreotate administration the NET patient is asked to void urine and has external dose rate counting to ensure safe discharge into the community. All patients are discharged with instructions to attend for a post treatment consultation the following day with the supervising theranostic specialist where patient progress is considered, and medication and monitoring requirements are confirmed and adjusted where necessary. The applicant has stated that individual patients are not required to take special precautions in relation to, for example, toileting. However, they have added that storing urine in which between 70-80% of the administered activity is excreted in the first 24-hours for 4-10 half-lives is obviously impractical.

Post-treatment

For quality assurance purposes after each ^{177}Lu-DOTA-octreotate treatment, single time point SPECT/CT imaging is recommended for tumour site uptake verification with formal radiation dosimetry estimation after the initial treatment (requiring several SPECT/CT imaging sessions several days apart) for optimal patient evaluation being recommended for research purposes, see discussion under Proposal for public funding. Usually, this imaging occurs the day after the infusion.

Treatment cycles and follow-up

The application stated (p26) that ^{177}Lu-DOTA-octreotate treatment after MDT referral will commonly be undertaken by an induction treatment course of four to five cycles at six to 12 but typically eight-weekly intervals and a post treatment review three months later. In patients with a high disease burden at diagnosis and a favourable but incomplete response to four cycles of treatment, a further cycle of treatment (i.e., five cycles total) may be considered worthwhile.

For routine clinical practice, when H-SSTR has been confirmed by an obligatory pre-treatment PET scanning, a single time point post ^{177}Lu-DOTA-octreotate treatment SPECT/CT scan is ideally performed to identify "super-responders" after two treatment cycles. These patients have a high degree of tumour site response

early following treatment commencement and are unlikely to benefit further from proceeding to complete a full "induction course" as the treatment target has already been largely ablated. Patients with lower grade (G1) NETs are commonly administered the full induction course due to lower sensitivity to ^{177}Lu-DOTA-octreotate and cycles may be separated by up to 12 weeks (p25).

Older patients, and particularly strong treatment responders, may also receive abbreviated treatment schedules and the interval between ^{177}Lu-DOTA-octreotate administrations may be adjusted to allow for haematological recovery if toxicity occurs.

It was highlighted in further discussions with the applicant that no fixed number of cycles is recommended, where two to six cycles are common in the initial treatment regimen depending on the individual NET characteristics. For example, patients who are hyper responders, with higher grade NETs, small volume disease and/or adverse reactions to treatment, will typically receive less cycles, whereas patients with bulky disease and/or lower grade NETs (particularly G1) that are slow to respond and are less radiosensitive, are likely to receive more cycles of ^{177}Lu-DOTA-octreotate. Moreover, for patients with functional but non-progressive G1 or G2 NETs, treatment can be ceased once hormonal control is achieved. Given the variability in cycles, the proportion of patients who will receive expected cycles of ^{177}Lu-DOTA-octreotate may be relevant to estimate overall costs in the economic and financial assessments for this treatment.

Consistently, Bidakhvidi (2021) has recommended ^{177}Lu-Dotatate be administered at 7.4 GBq every four to six weeks for four cycles (see Figure 5), while acknowledging there to be intra- and interindividual variability in the radiation absorbed in metastases. Similarly, in the NETTER-1 trial (Strosberg 2017), the patients in the ^{177}Lu-Dotatate arm were administered 7.4 GBq (200 mCi) of ^{177}Lu-Dotatate intravenously over a period of 30 minutes. Four infusions every eight weeks (cumulative radioactivity, 29.6 GBq [800 mCi]) were planned, unless unacceptable toxic effects occurred, centrally confirmed disease progression (according to RECIST) was present on imaging, the patient was unable or unwilling to adhere to trial procedures, the patient withdrew consent, or the patient died. A total of 77% of patients received the complete four cycles, 6% received three cycles, 12% received two cycles, 5% received one cycle, and 1% did not receive any cycles of the intervention. The applicant's clinical expert opined that there is a theoretical basis for tailoring the treatment schedule to the grade of tumour with shorter intervals between cycles for G3 (e.g. 4 weeks) than for G1 (e.g. 8-12 weeks) NET based on the time-frame for NET cells to come into cycle.

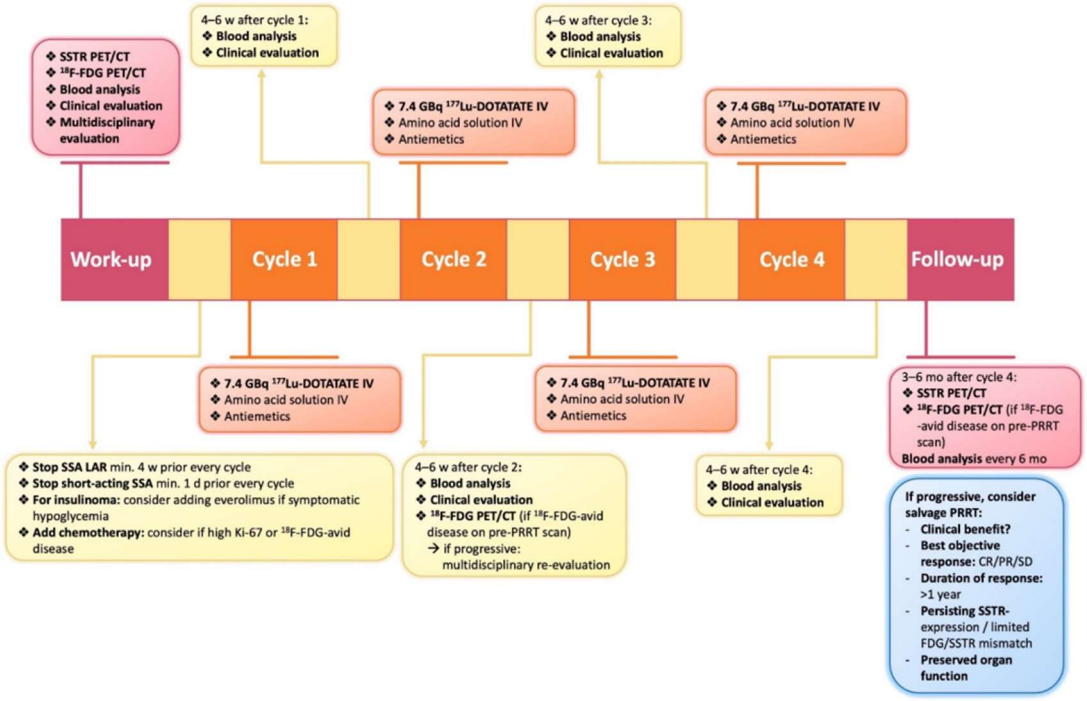

Figure 5 Proposed standardised PRRT scheme.

Source: Figure1, p4 from Bidakhvidi 2022
Abbreviations: CR = complete response; CT = computed tomography; FDG = Fluorodeoxyglucose; IV = intravenous; LAR = long-acting release; mo = month; SSA = somatostatin analogue; PET = positron emission tomography; PR = partial response; PRRT = peptide receptor radionuclide therapy; ^{177}Lu = ^{177}Lutetium

At its April 2023 meeting, PASC considered there was ambiguity in the description of the therapy, particularly with respect to number of cycles of treatment. PASC considered that a deviation from a total of four cycles (as per the NETTER-1 trial and current approvals in the USA and Europe) would require justification.

The applicant noted that in practice, deviations from four cycles of treatment will occur due to a multitude of factors but a standard course consists of four cycles. However, on rare occasions five cycles may be required if the tumour burden is high but this would only be considered rarely. They requested flexibility in the descriptor to accommodate these rare cases.

In August 2023, PASC noted that an induction cycle of ^{177}Lu-DOTA-octreotate therapy consists of four cycles but in rare cases, for patients with high tumour burden, five cycles may be given, and it had been requested that the MBS item descriptor should allow for these cases. It also noted that the applicant had requested MBS funding of the follow-up cycles after the induction cycle (see below). PASC noted the Department's advice that either the number of cycles could be unrestricted or that they could be restricted to a maximum of 6 cycles every 12 months. PASC considered that the number of cycles need not be specified in the item descriptor.

After the induction course, follow-up is usually conducted after a three-month interval when the patient's clinical, biochemical, and haematological status is assessed along with disease response assessment using SSTR imaging, and where applicable FDG PET/CT, formal CT, or MRI imaging to assess the response of each patient's ^{177}Lu-DOTA-octreotate therapy (see Table 6 for additional MBS items required post-treatment. No alterations for these item descriptors were requested).

Ongoing follow up requires personalisation depending on:

- the patient's tumour type and grade;
- the patient's prior treatment history;
- the response to therapy;
- the occurrence of persistent adverse events related to ^{177}Lu-DOTA-octreotate;
- the patient's clinical progress; and
- the results of biochemical monitoring test.

While not all modalities are required in every patient, the applicant noted that the most common items applied are MBS items 61647/61505 (^{68}Ga DOTA peptide PET with new item descriptor, see *Table 13*) and/or MBS item 56807 (see Table 6).

Table 6 MBS items for formal CT or MRI imaging used during follow-up post-^{177}Lu-DOTA-octreotate treatment.

Category 5 – Diagnostic Imaging Services
MBS item 56807 Computed tomography—scan of chest, abdomen and pelvis with or without scans of soft tissues of neck with intravenous contrast medium and with any scans of chest, abdomen and pelvis with or without scans of soft tissue of neck before intravenous contrast injection, when performed, not including a study performed to exclude coronary artery calcification or image the coronary arteries (R) (Anaes.).
Fee: $582.70
Category 5 – Diagnostic Imaging Services
MBS item 63546 MRI – multiphase scans of the liver (including delayed imaging, if performed) with a contrast agent, for diagnosis or staging, if: (a) the patient has: (i) known or suspected hepatocellular carcinoma; and (ii) chronic liver disease that has been confirmed by a specialist or consultant physician; and (b) the patient's liver function has been identified as Child Pugh class A or B; and (c) the patient has an identified hepatic lesion over 10 mm in diameter. For any particular patient—applicable not more than once in a 12-month period (R) (Contrast)
Fee: $558.80
Category 1 – Professional Attendances
MBS item 105 Professional attendance by a specialist in the practice of the specialist's specialty following referral of the patient to the specialist- an attendance after the first in a single course of treatment, if that attendance is at consulting rooms or hospital, other than a service to which item 16404 applies.
Fee: $46.15

Source: MBS online

Abbreviations: CT = computed tomography; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging; nca = no carrier added; ^{177}Lu = ^{177}Lutetium.

Progression/Consolidation cycles

Further treatment with ^{177}Lu-DOTA-octreotate may be instituted upon documentation of progression where: the individual (i) is willing to undergo further active treatment, (ii) has had a favourable response to the induction treatment course with no or clinically acceptable and self-limiting side-effects, and (iii) has suitable tumour characteristics demonstrated on SSTR imaging with or without FDG PET/CT imaging. Usually repeat ^{177}Lu-DOTA-octreotate treatments involve two administrations undertaken in the same manner as described for the induction cycle. Repeat treatments at documented progression can be undertaken until response failure is documented, unacceptable toxicity occurs, or alternative treatments offer the prospect of superior patient important outcomes. SPECT/CT imaging is not necessarily required after the repeat ^{177}Lu-DOTA-octreotate treatment; however other in-treatment and between-treatment assessments follow the induction cycle program with an identical three month follow schedule.

In some patients a two-administration consolidation course 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) NETs with rising tumour markers. The requirement for MDT referral for consolidation treatment with ^{177}Lu-DOTA-octreotate treatments will appropriately limit access to the medical service to patients most likely to benefit.

The applicant noted the evidence for retreatment cycles have been limited to retrospective institutional studies and generally reserved for patients who have responded symptomatically or by prolongation of the time to progression observed before initial treatment. In addition, objective radiologic response has not been a requirement for retreatment, and response rates and durability of response are generally less than observed with induction cycles, but patients can have ongoing disease control with intermittent retreatment.

The application provided one study investigating retreatment with ^{177}Lu-Dotatate after documented disease progression in the past six months, however, only two out of 47 patients had received ^{177}Lu-Dotatate as the initial treatment prior to ^{177}Lu-Dotatate re-treatment, the majority (45/47) received ^{90}Y-Dotatate as the initial treatment, potentially limiting its generalisability to this component of the protocol (Vaughn 2019). Although, a meta-analysis (Strosberg 2021) investigating the efficacy and safety of PRRT re-treatment in patients with advanced progressive GEP-NETs reported similar median PFS between patients who were initially treated with ^{177}Lu-Dotatate (12.26 months) and those with ^{90}Y-Dotatate (15.41 months) and later retreated with ^{177}Lu-Dotatate after disease progression. In addition, the safety profile of ^{177}Lu-Dotatate retreatment was similar to ^{177}Lu-Dotatate initial treatment.

The frequency of repeat ^{177}Lu-DOTA-octreotate treatment is necessarily highly variable but will be appropriately limited to achieve optimal outcomes when MDT referral is a mandatory requirement. In further discussions, the applicant's clinical expert noted that the optimal reimbursement strategy should anticipate highly variable treatment recommendations from MDTs or treating specialist, therefore funding each treatment cycle of ^{177}Lu-DOTA-octreotate as an independent episode is recommended.

In its consideration at the April 2023 meeting, PASC considered the potential for progression/consolidation cycles would need to be justified.

Comparator(s)

The application has nominated (p33) alternative active and supportive care strategies as the comparator for ^{177}Lu-DOTA-octreotate. The application explains that although the targeted therapies everolimus and sunitinib (PBS funded for GEP-NETs and lung-NETs) would be considered the most relevant comparators to ^{177}Lu-DOTA-octreotate for NET patients who failed 1L SSA therapy, nominating these drugs as 'appropriate comparators' would lead to serious misconception about how best treatment outcomes are achieved for patients with advanced NETs. In this context the choice between ^{177}Lu-DOTA-octreotate and alternative treatment is more often a sequencing decision rather than binary choice, further highlighting the complexity that comes with the highly heterogeneous nature of advanced NETs and the importance of an experienced MDT to guide patient treatment management. Moreover, as ^{177}Lu-DOTA-octreotate treatment and "appropriate comparators" are very often used in sequence in patients with NETs the healthcare resource utilisation in properly evaluated patients is largely similar.

In discussions with the applicant, the applicant's clinical expert emphasised that virtually all patients with advanced NET die from their disease or complications. Therefore, the majority of patients will receive all treatments that have shown efficacy in their particular tumour type, extent, grade, and symptomatic status with the recommended sequencing of the interventions highly dependent on clinical experience, given a lack of direct RCT evidence of many potential comparators.

The application proposes ^{177}Lu-DOTA-octreotate as an add-on therapy rather than replacement of comparator management strategies, hence the more reasonable comparator would be 'alternative active and supportive care strategies'.

This is potentially supported by the NETTER-1 trial (Strosberg 2017) which provides a comparison of ^{177}Lu-Dotatate plus supportive care (LAR octreotide 20/30 mg) with high-dose (60mg) LAR octreotide in patients with progressive advanced or metastatic SSTR-positive midgut NETs who are receiving fixed dose 20 or 30 mg octreotide LAR at least 12 weeks prior to receiving the intervention. However, as mentioned earlier, the applicant noted that LAR octreotide use is considered on a case-by-case basis and is not entirely reflective of standard supportive care, especially for other NET types. The Lutathera® Product Information (FDA) follows the regimen of the NETTER-1 trial, prescribing octreotide therapy alongside PRRT. However, octreotide is a life-long hormone treatment for patients with NETs and therefore is not considered a co-administered product with PRRT.

There is currently no evidence that compares ^{177}Lu-DOTA-octreotate with everolimus or sunitinib to support the sequencing of ^{177}Lu-DOTA-octreotate in patients eligible and deemed appropriate to receive these treatments options. Two relevant ongoing RCTs include:

- NCT02230176: Antitumor Efficacy of Peptide Receptor Radionuclide Therapy With ^{177}Lutetium - Octreotate Randomized vs Sunitinib in Unresectable Progressive Well Differentiated Neuroendocrine Pancreatic Tumour: First Randomized Phase II (expected completion date October 2023).
- NCT04665739: Randomized Phase II Trial of Lutetium Lu-177-Dotatate Versus Everolimus in Somatostatin Receptor Positive Bronchial Neuroendocrine Tumors (expected completion date July 2024).

The following was presented to provide a representation of the potentially relevant comparators for each component of the proposed tests and the intervention, *as considered by PASC at the April 2023 meeting*:

Component	Comparison
^{68}Ga-DOTA-octreotate PET/CT	No ^{68}Ga-DOTA-octreotate PET/CT
FDG PET/CT	No FDG PET/CT
^{177}Lu-DOTA-octreotate	Long-acting SSA (unlabelled) – octreotide depot and lanreotide Target therapies-everolimus and sunitinib Chemotherapy Best supportive care strategies
Post-treatment SPECT/CT (if included)	No post-treatment SPECT/CT

At its April 2023 meeting, PASC considered that the appropriate comparator for ^{68}GA-DOTA-octreotate was not "no testing". However, PASC also acknowledged that alternative comparators were not suitable. For example, "PRRT Predictive Quotient (PPQ)" was not generally accepted or available and immunohistochemistry (IHC) for tumour SSTR-2 expression was not practicable. In August 2023, PASC noted there was no current comparator for ^{68}Ga-DOTA-octreotate PET/CT as ^{111}In-pentetreotide [Octreoscan®] was considered superseded.

PASC agreed that the comparator for FDG PET/CT was no FDG PET/CT (following SSTR imaging) at the April 2023 meeting. Given the role of FDG PET/CT in this group of patients, as already noted, PASC is requested to consider whether FDG/PET should be removed from the clinical management algorithm (which reflects the nominated 'exemplars'). These patients currently have access to FDG PET/CT and given PASC advice that the wording of the currently FDG MBS item (61612) is unlikely to require rewording, then this access will remain available without change. That is, there is unlikely to be any substitution.

At the April 2023 meeting, PASC discussed the appropriate comparators for ^{177}Lu-DOTA-octreotate therapy, nominating the following:

- *Long-acting SSA (unlabelled) – octreotide depot and lanreotide*
- *Targeted therapies – everolimus and sunitinib*
- *Chemotherapy – capecitabine + temozolomide (CAPTEM); folinic acid + fluorouracil + oxaliplatin (FOLFOX); folinic acid + fluorouracil + irinotecan (FOLFIRI); carboplatin + etoposide*
- *Best supportive care*

However, PASC also questioned whether these represented comparators or whether treatment with ^{177}Lu-DOTA-octreotate therapy would occur after failure of these treatments, leaving only best supportive care as a relevant comparator.

At the August 2023 meeting, PASC considered that best supportive care may be the most relevant comparator given that ^{177}Lu-DOTA-octreotate therapy would most likely be offered after the failure of the nominated comparator treatments. PASC noted that:

a) No guidelines consider PRRT as first-line treatment (versus alternative first-line treatments such as unlabelled SSA, targeted treatment [everolimus, sunitinib] or chemotherapy).

b) *The NETTER-1 trial compared ^{177}Lu-DOTATATE plus octreotide LAR (30mg/4week) to octreotide LAR alone (60mg/4week).*
c) *No published RCTs of PRRT versus targeted treatment or chemotherapy currently exist, therefore only naïve comparisons are possible. There are several current comparative clinical trials of which one [NCT02230176: ^{177}Lu versus sunitinib 37.5mg/day] has a completion date of October 2023 but others are scheduled for completion even later.*

PASC also stated in April 2023 that should the MBS listing be restricted to ^{177}Lu(nca)-DOTA-octreotate, then ^{177}Lu(ca)- DOTA-octreotate would be a relevant comparator (to demonstrate superiority of ^{177}Lu(nca)-DOTA-octreotate versus ^{177}Lu(ca)-DOTA-octreotate).

PASC agreed that the appropriate comparator for post-therapy SPECT/CT was no post-therapy SPECT/CT at its April 2023 meeting.

Table 7 lists the current comparative clinical trials that include ^{177}Lu-DOTA-octreotate PRRT.

Table 7 Current comparative clinical trial with ^{177}Lu-DOTA-octreotate

Identifier	Trial Name	Population	Intervention	Comparator	Completion
NCT02230176	OCCLURANDOM	Unresectable, progressive, well-differential pNET, Phase II	^{177}Lu-DOTATATE 7.4 GBq x4	Sunitinib 37.5,g/d	Oct 2023
NCT03049189	COMPETE	Inoperable, progressive GET-NET, Phase III	^{177}Lu-DOTATATOC 7.5+0.7 GBq x4	Everolimus 10mg/d	June 2029
NCT03972488	NETTER-2	Metastatic or locally advanced inoperable G2 or G3 GET-NET	1st-line^{177}Lu-DOTATATE 7.4 GBq x4 plus octreotide LAR 30mg q 4 wk	Octreotide LAR 60mg q 4 wk	July 2027
NCT04665739	N/A	Metastatic bronchial carcinoid tumour (well-/moderately diff. , low/intermediate grade). Phase II	^{177}Lu-DOTATATE (activity not stated) x4	Everolimus	July 2024
NCT04919226	COMPOSE	Unresectable G2 or G3 GEP-NET; Phase III	1st or 2nd line ^{177}Lu-DOTATATE 7.4 GBq x4	Best standard of care • CAPTEM • Everolimus • FOLFOX	Sep 2026
NCT05247905	N/A	G1, G2 or well-diff G3 pNET unresectable/metastatic, Phase III	^{177}Lu-DOTATATE (activity NS) q 8wk x4	CAPTEM q 4wk x 12	Oct 2033

Source: Developed by PASC
CAPTEM=Capecitabine+temoxolomide; FOLFOX=folinic acid+fluorouracil+oxaliplatin; GEP-NET=gastroenteropancreatic neuroendocrine tumour; pNET=pancreatic NET; diff=differentiated; q= every: wk= week

Reference standard (for investigative technologies only)

No reference standards for SSTR-PET/CT imaging were nominated.

In the assessment of ^{68}Ga-DOTA-octreotate PET/CT, the MSAC 1479R PSD noted (p2) that while the gold standard for the diagnosis of GEP-NETS is histopathology, the evidence presented in 1479R to support the diagnostic accuracy of ^{68}Ga-DOTA-octreotate PET/CT, consisted of a composite reference standard which

included the results from histopathology and/or conventional imaging and/or clinical follow-up of at least one year (MSAC 1479R, 2017).

At the April 2023 meeting, PASC considered that immunohistochemistry (IHC) for SSTR-2 expression as the appropriate reference standard for ^{68}Ga-DOTA-octreotate .

At the April 2023 meeting, PASC considered there was no appropriate reference standard for FDG PET/CT.

Clinical utility standard (for co-dependent investigative technologies only)

The clinical utility standard for SSTR-PET/CT in this application was ^{68}Ga-DOTA-octreotate SSTR-PET/CT imaging or OctreoScan® SPECT/CT.

Where ^{68}Ga-DOTA-octreotate PET/CT was performed in the studies cited in the application, the modified Krenning score (5-point scale) was used: 0=no uptake, 1=very low uptake, 2=uptake no more than the liver, 3=uptake greater than the liver, 4=uptake greater than the spleen. A SSTR-positive status on PET/CT was based on a modified Krenning score ≥3 (i.e., tumour uptake greater than liver uptake). Where OctreoScan® was used in the studies cited by the application, the Krenning score (4-point scale) was used: 1=uptake less than liver, 2=uptake is approximately equal to liver, 3=uptake is greater than liver, and 4=uptake is greater than kidney and spleen. Strosberg et al. performed a Phase 3 trial (NETTER-1 trial) which provides the best evidence for the efficacy of ^{177}Lu-DOTA-octreotate in advanced midgut neuroendocrine tumours graded tumours (Strosberg 2017). Patients were included in the study if they had somatostatin receptors on all target lesions as determined by somatostatin receptor scintigraphy. Target lesions were identified via CT or MRI. Although the Krenning scale was used, thresholds to determine eligibility for ^{177}Lu-DOTA-octreotate were not nominated.

At the April 2023 meeting, PASC agreed that the clinical utility standard for SSTR-PET/CT was ^{68}Ga-DOTA-octreotate or OctreoScan® SPECT/CT with a Krenning score ≥2. PASC also noted that there is no evidence to support "blind" use of PRRT without prior documentation of SSTR expression – that is, positive SSTRI is (currently) a requirement for PRRT.

The clinical utility standard for FDG PET has not been nominated by the applicant.

At the April 2023 meeting, PASC noted that no clinical utility standard for FDG PET was specified by the applicant. PASC acknowledged the prognostic value of FDG PET, specifically, that 'discordant' NETs (with FDG uptake > SSTRI uptake) have a poorer prognosis than SSTRI positive/FDG negative NETs. However, PASC also noted there is no established threshold of "discordance" beyond which PRRT is contraindicated. The applicant has also suggested that eligibility for PRRT should include that there are no more than three sites of discordance of tumours >2 cm or that it should be left to the discretion of the MDT. In follow up written advice (email 14th July 2023), the applicant clarified that these are often value judgements in which a MDT considers all available information to determine the likely course of treatment, and as such determining a level of discordance will not assist in that process. They therefore re-iterated that this is a decision best left to the MDT (item 872 case conference).

In its April 2023 meeting, PASC noted that the appropriate assessment questions are:

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

The clinical utility of both SSTR PET/CT and FDG PET/CT is likely to be confined to the organs with the most commonly occurring NETs as that is where the evidence is likely to be generated. Where the NEN is primarily located can affect survivability but may not reflect disease burden. Therefore, the generalisability of the evidence provided in relation to one organ, to other organs will need to be considered.

For ^{68}Ga-DOTA-octreotate PET/CT, PASC noted in August 2023 that Octreoscan® is a valid clinical utility standard: Results of studies based on Octreoscan® uptake (using the Krenning score) need to be translated to ^{68}Ga-DOTA-octreotate uptake (using the modified Krenning score) for the assessment report.

Outcomes

Test accuracy

No outcomes for the two tests (^{68}Ga-DOTA-octreotate PET/CT or FDG PET/CT) were nominated.

In discussions, the applicant agreed that the pre-requisite tests identified are applied as predictive biomarkers for response to a specific highly targeted therapy. The tests are not being used to determine diagnostic accuracy, hence, metrics such as sensitivity, specificity, positive and negative predictive values, area under the curve of the receiver operating characteristic curve, are not relevant to this application.

Moreover, the MSAC 1479R meeting minutes noted (p2) that no serious adverse events were associated with the use of ^{68}Ga-DOTA-octreotate PET/CT imaging (MSAC 1479R, 2017).

Other characteristics such as intra-/inter-observer agreement across SSTR-PET/CT and FDG PET/CT would be relevant outcomes as variation in the classification of SSTR status will likely influence change in management. The purpose of the addition of the FDG PET/CT is not to change the classification of SSTR status but to identify metabolically active disease in areas that express lower or no somatostatin receptors on receptor-based imaging. The status of the disease identified by the FDG PET/CT may not result in change in management but change in management may be due to the MDT determining that a patient is not currently suitable for PRRT rather than a reassessment of their SSTR classification.

At the 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, suggesting that this may be improved by using uptake quantification (for example SUV ratios). This may be a difficult outcome to evaluate. The purpose of combining ^{68}Ga-DOTA-octreotate followed by FDG PET/CT is that less differentiated NENs often co-express SSTRs and glucose-transporters and the uptake of ^{18}F-FDG can show areas that are hypermetabolic. For these patients, the use of dual imaging can potentially provide a better picture of metabolic spatial intra- and inter-tumour heterogeneity of the disease, especially in higher-grade tumours. For MSAC Assessment Report purposes, the imaging is designed to measure slightly different targets: the uptake of SSTR agonists in receptor-based imaging correlates closely to SSTR2 receptor expression (and this is shown to correlate

with overall survival), the target for PRRT therapy. But the FDG avidity, reflects increased tumour metabolic activity and is used for prognostic utility for NETs. Combined, the two PET/CT studies provide a better overall picture of the patient's disease and help predict response to PRRT and suitability for this treatment given the status of their disease. Therefore intra-/inter-observer variability between ^{68}Ga-DOTA-octreotate and FDG PET/CT may not be relevant to determining test outcomes and suitability for PRRT treatment.

It is reported that the interpretation of dual modality imaging in multifocal and heterogenous tumours can be difficult, which appears to be the reason that the applicant has recommended MDT guided imaging and treatment. Measures of joint results of FDG and SSTR based imaging in a single combined parameter have not yet been developed. A scoring system (the NETPET Grading System) has been proposed that correlates with overall survival (Chan 2017), but it appears to yet be validated.

Change in management

The purpose of ^{68}Ga-DOTA-octreotate PET/CT imaging is to assess the eligibility for treatment with ^{177}Lu-DOTA-octreotate. Therefore, a result below the nominated threshold (i.e., below 3 for the modified Krenning score) would mean that patients are not eligible for ^{177}Lu-DOTA-octreotate treatment.

Relevant outcomes would be the proportion of patients who meet the nominated thresholds of ^{68}Ga-DOTA-octreotate PET/CT imaging who then proceed to ^{177}Lu-DOTA-octreotate treatment.

It was noted in discussions with the applicant that patients with higher grade NETs, in particular G2 tumours with Ki-67>10% and G3 tumours with Ki-67<55%, can reflect decreased SSTR expression which would lower the proportion of higher-grade NET patients eligible for ^{177}Lu-DOTA-octreotate treatment based on SSTR-positive status on SSTR-PET/CT imaging. As FDG PET/CT is recommended for these subgroups of patients (in addition to those who progress in less than 6 months and those with abnormal lesions on CT/MRI without H-SSTR), an additional outcome would include the proportion of patients with G2 (Ki-67>10%) or G3 (Ki-67<55%) NETs who have a FDG PET/CT scan.

At the April 2023 meeting, for change in management outcomes, PASC considered the following were relevant:

- *Proportion of patients considered eligible for PRRT following ^{68}Ga-DOTA octreotate PET/CT*
- *Proportion of SSTRI-positive patients considered ineligible for PRRT following FDG PET/CT*

The literature notes that ^{18}F-FDG PET/CT positive NENs that display low avidity on SSTR imaging are potentially high-grade, metabolically active and aggressive tumours with more rapid progression of disease and a worse prognosis (Kayani 2008; Nilica 2016; Chan 2017; Reccia 2023). Therefore, the outcomes nominated may not be informative to how these tests are used in current clinical practice. Something which the utilisation data will need to consider.

Oncologic and patient outcomes

The outcomes nominated in the application (p33) include:

- Quality of life.
- Disease response i.e., symptomatic control of excess hormone secretion, bone pain, objective response rate' (measured by RECIST v.1.1 or repeat SSTRI) and disease control rate, tumour biomarkers.

- Survival duration (overall and progression free).
- Related Treatment Emergent Adverse Effects.

At the April 2023 meeting, PASC agreed with the clinical outcomes proposed, however expanded on the 'disease response' category, adding 'objective response rate' (measured by RECIST v.1.1 or repeat SSTRI) and 'disease control rate'. PASC also considered that measurement of tumour biomarkers should be encompassed under 'disease response'.

At the August 2023 meeting, PASC noted that the outcomes were as specified.

Assessment framework (for investigative technologies)

No trials were identified that compared the efficacy of ^{177}Lu-DOTA-octreotate and standard supportive care in patients who were:

- SSTR-PET/CT positive and SSTR-PET/CT negative.

As noted above, there is no evidence to support "blind" use of PRRT without prior documentation of SSTR expression – that is, positive SSTRI is (currently) a requirement for PRRT.

Similarly, no trials were identified that compared the efficacy of ^{177}Lu-DOTA-octreotate and standard supportive care in a subgroup of patients with higher-grade NETs (i.e., Ki-67>10%) who were:

- SSTR-PET/CT positive and FDG-PET/CT positive;
- SSTR-PET/CT negative and FDG-PET/CT positive; and
- SSTR-PET/CT positive and FDG-PET/CT negative.

Hence, a linked evidence approach will likely be required to establish the proposed requirement for (i) the threshold for a positive SSTR status on ^{68}Ga-DOTA-octreotate PET/CT (modified Krenning score ≥3) (ii) SSTR/FDG mismatch, and the implications of these characteristics on intermediate and health outcomes as result of treatment with ^{177}Lu-DOTA-octreotate.

At the April 2023 meeting, PASC considered that appropriate assessment questions for this application were:

- *What is the clinical utility of ^{68}Ga-DOTA-octreotate PET/CT for the selection of patients with progressive, advanced, metastatic or inoperable NETs 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 NETs with known H-SSTR expression for ^{177}Lu-DOTA-octreotate therapy?*
- *What is the safety, effectiveness and cost effectiveness of ^{177}Lu-DOTA-octreotate vs alternative active and supportive care in patients with advanced NETs or other H-SSTR tumours as identified by ^{68}Ga-DOTA-octreotate PET/CT?*
- *What is the safety, effectiveness and cost effectiveness of ^{177}Lu(nca)-DOTA-octreotate vs ^{177}Lu(ca)-DOTA-octreotate in patients with advanced NETs or other H-SSTR tumours as identified by ^{68}Ga-DOTA-octreotate PET/CT?*

PASC clarified at the April 2023 meeting that the first three questions refer to the selection of patients for, and safety, effectiveness and cost-effectiveness of ^{177}Lu-DOTA-octreotate therapy (either ^{177}Lu(nca)-DOTA-octreotate or ^{177}Lu(ca)-DOTA-octreotate, since the evidence base does not draw a distinction). PASC noted that the final question is relevant only insofar as the application is to be restricted to ^{177}Lu(nca)-DOTA-octreotate as there are some plausible claims relating to differences between these two products with respect to radiation protection and waste disposal. The applicant was to provide further information to address this question. It should be noted that Australia has been using radiopharmaceuticals for therapy for several decades and specialist centres are likely well equipped to manage the additional radioactive waste from ^{177}Lu(ca), but additional information is required to inform this issue.

In discussions with the applicant, given the heterogenous nature of NETs and the complexities in patient management, an exemplar approach using pancreatic NETs was proposed to illustrate the flow of patients who go on to receive ^{177}Lu-DOTA-octreotate treatment. Pancreatic NETs were chosen on the basis they are (i) among the most common NETs (see Table 4) and (ii) there are PBS-listed therapies for this condition (everolimus and sunitinib).

Proposed exemplar approach

In its consideration at the April 2023 meeting, PASC agreed that an 'exemplar' approach to the economic evaluation would be appropriate. However, PASC considered that both pancreatic NETs and midgut NETs should be included. The basis of recommending inclusion of midgut NETs was the following:

- *Pancreatic and midgut NETs together account for 27% of NETs in the Australian population.*
- *Best available evidence (NETTER-1) was derived from patients with midgut NETs.*
- *There are PBS-subsidised agents for therapy of pancreatic and midgut NETs (including everolimus and sunitinib for the former and octreotide and lanreotide for the latter).*
- *The ESMO Clinical Practice Guideline encompasses pancreatic and midgut NETs.*

Caution is considered to be necessary in the use of exemplars for the economic evaluation of NETs. Although the exemplars chosen may reflect common NETs, and therefore availability of evidence, where the primary tumours are located can affect survivability but also may not reflect disease burden in NET patients.

PASC noted the concern raised by an independent expert that although the location of the primary tumour may affect survivability, it may not reflect disease burden, so the nominated exemplars of pancreatic and midgut NETs may not be generalisable to other NETs; however, PASC noted:

a) the purpose of exemplars is to evaluate the proposal for typical or more common population/intervention settings for which there is the most clinical evidence, then to extrapolate the findings of the evaluation to other population/intervention settings (close enough to the exemplars).
b) the disease burden has been defined in the population (i.e., "locally advanced or metastatic, and inoperable neuroendocrine tumours [NETs] with documented disease progression or uncontrolled symptoms related to their NET").

PASC re-affirmed that the assessment should use pancreatic and midgut NETs as exemplars to evaluate the proposal.

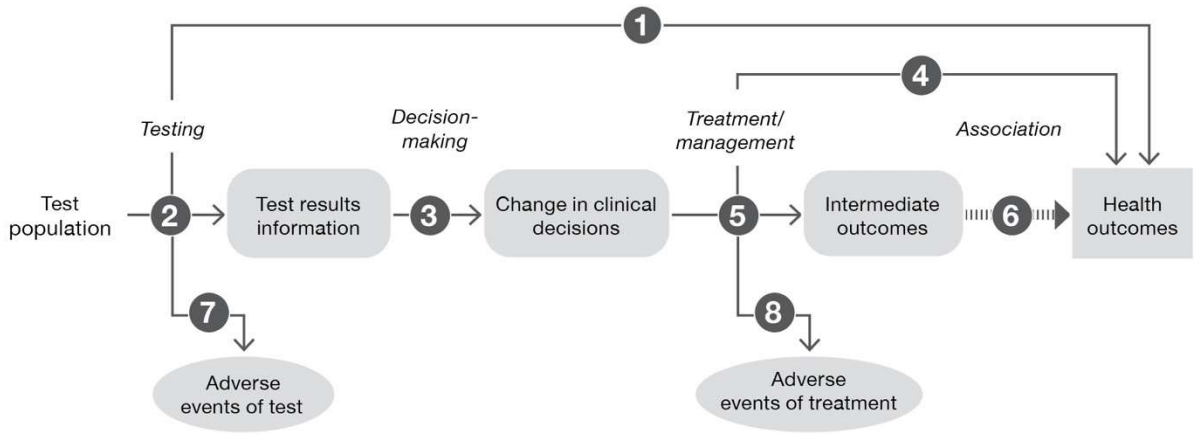

Figure 6 Generic assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Clinical management algorithms

The clinical management algorithms presented in the application are presented in Figure 7 and Figure 8.

Clinical management based on current best management guidelines (ESMO; Pavel 2020) was presented in the application where it was explained that as ^{177}Lu-DOTA-octreotate treatment is already in use in Australia in multiple locations and has regulatory approval in the USA and European Union it did not provide a 'proposed' clinical management algorithm. The clinical algorithms presented demonstrate how current best practice guidance recommends the integration of ^{177}Lu-DOTA-octreotate treatment (PRRT) with other potentially effective treatments for patients with advanced NET and H-SSTR malignancies and for patients with carcinoid syndrome.

Moreover, the application stated that these algorithms illustrate well the complexity of optimal management strategies for patients with advanced NET and H-SSTR malignancies who may exhibit a wide variety of individual and changing clinical circumstances, so emphasising the desirability of requiring MDT referral for ^{177}Lu-DOTA-octreotate treatment.

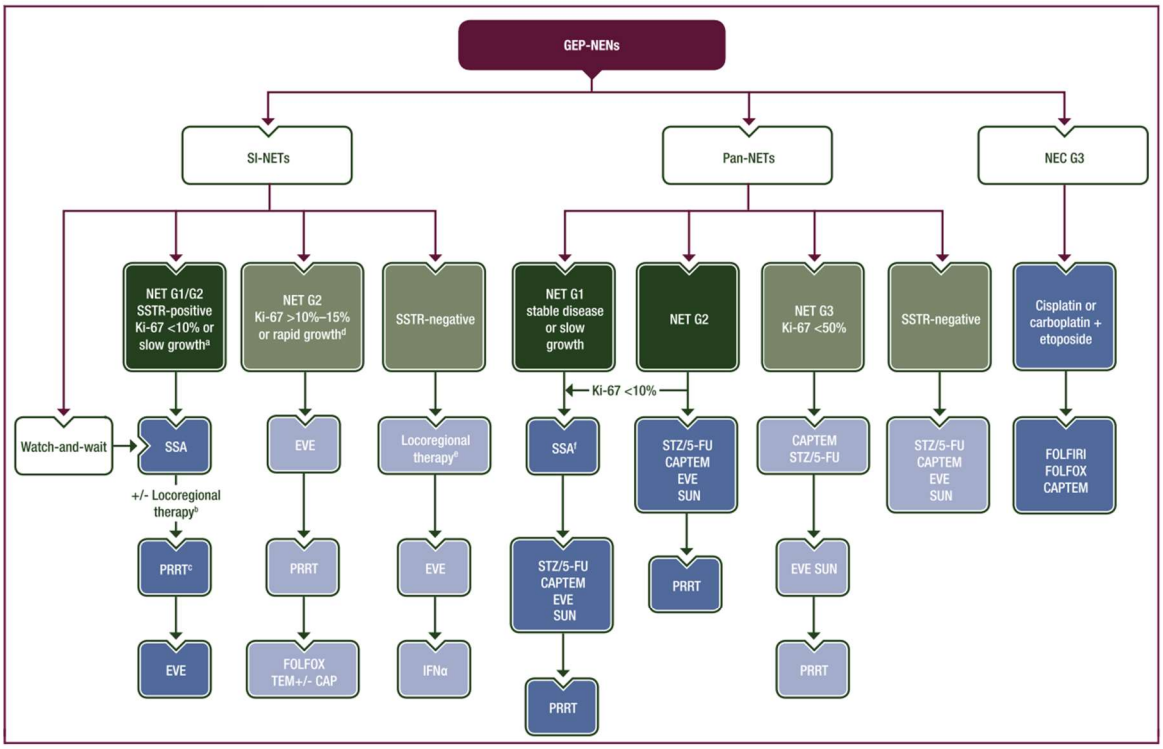

Figure 4. Systemic therapy in GEP-NENs.
The stratification factors are not predictive, but prognostic.
A watch-and-wait approach is recommended in asymptomatic low-grade tumour patients with absence of morphological progression. Locoregional therapy may be considered as an alternative approach to systemic 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.

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

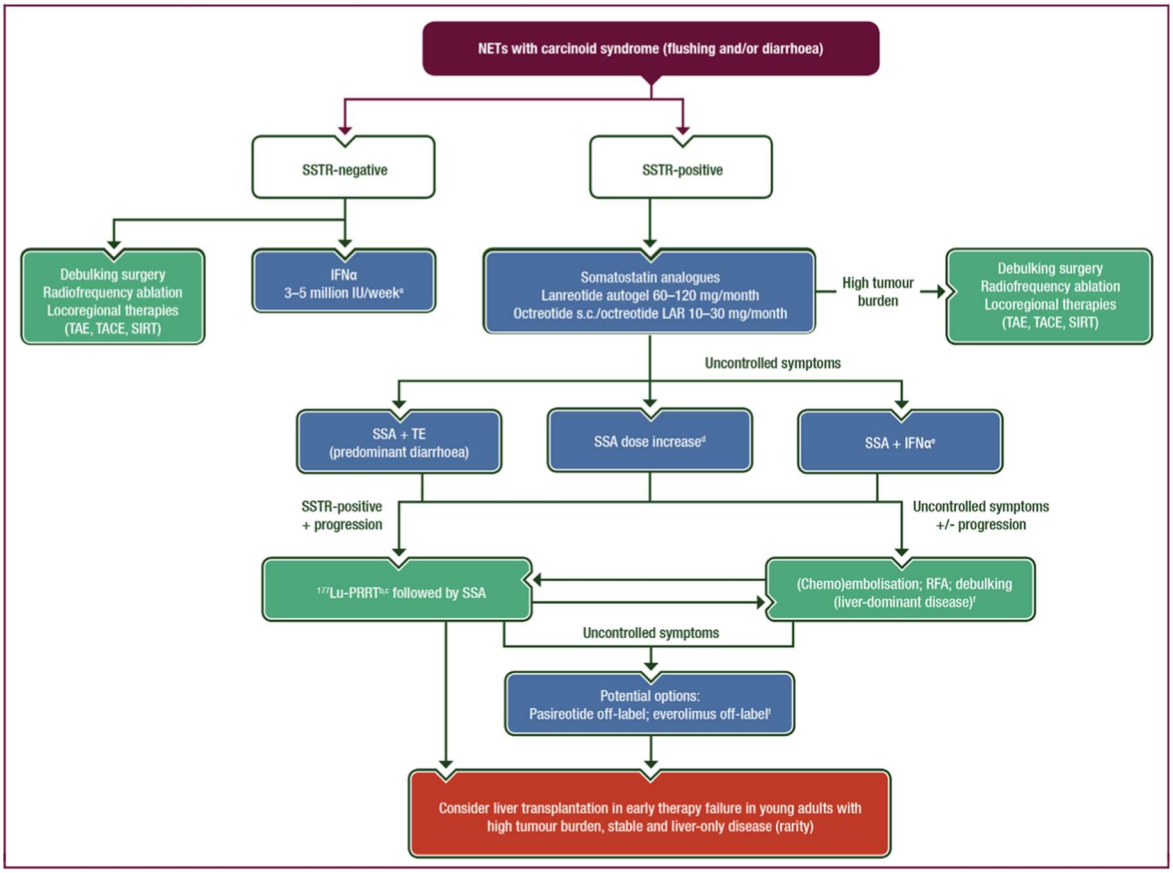

Figure 3. Therapeutic approach in NETs with carcinoid syndrome.
^{177}Lu, lutetium-177; IFN-α, interferon alpha; LAR, long-acting release; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; s.c., subcutaneous; SIRT, selective internal radiotherapy; 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.

Figure 8 ESMO Clinical management algorithm for advanced/metastatic NETs with carcinoid syndrome[2]
Source: Figure 3, p851 from ESMO guidelines (Pavel 2020)

At the April 2023 meeting, PASC discussed the proposed clinical management algorithm presented in the PICO and those subsequently provided by the applicant. PASC questioned the inclusion of those who were SSTR negative OR those with grade 3 NET/NEC, as these are not germane to the application. PASC also requested the applicant propose (and justify) a "FDG positive" threshold beyond which PRRT is not the preferred option for patients with H-SSTR tumours demonstrated on SSTRI. As above, the applicant suggested that eligibility for PRRT should include that there should be no more than three sites of discordance of tumours >2 cm or that decisions regarding eligibility should be left to the discretion of the MDT. The applicant has re-iterated their preference that these decisions are left to the MDT.

PASC suggested an amended clinical management algorithm (see Figure 9). The algorithm highlights thresholds for eligibility for PRRT. This includes a modified Krenning score of ≥3 and the threshold for FDG/SSRI discordance (<2 lesions). However, these thresholds are for the purposes of the assessment report. In clinical practice, an MDT will provide the guidance for individual patient management.

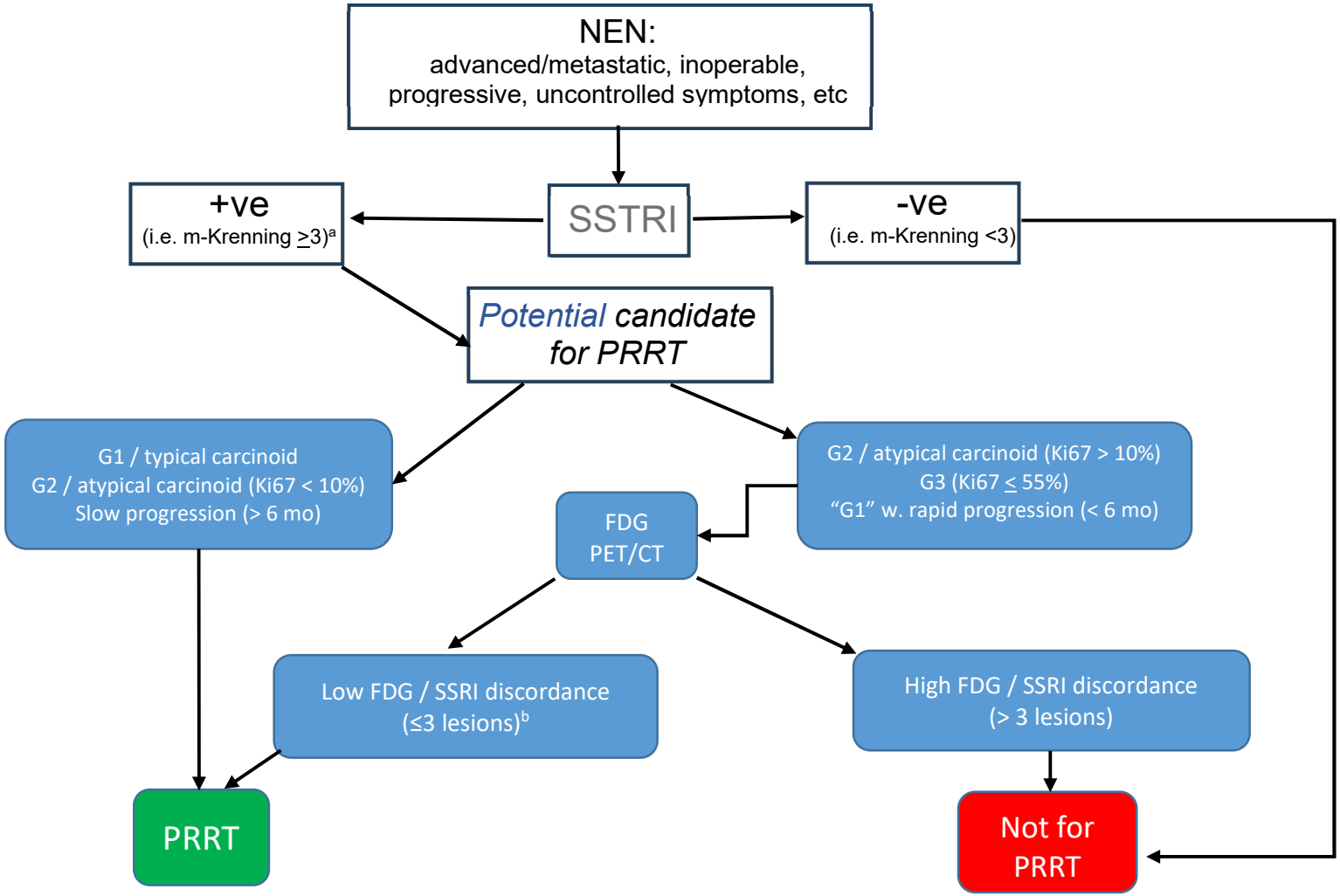

Figure 9 Reduced clinical management algorithm for G1 and G2 carcinoids and G3 pulmonary NECs

Source: Developed by PASC

CT = computed tomography; G1 = grade 1; G2 = grade 2; G3 = grade 3; FDG = Fluorodeoxyglucose;; m-Krenning = modified Krenning score; NEC = neuroendocrine carcinoma; NEN = neuroendocrine neoplasm; PET = positron emission tomography; PRRT = peptide receptor radionuclide therapy; SSTR = somatostatin receptor

[a] Patients with demonstrated high concentration of somatostatin receptor expressions (H-SSTR) at all, or the majority of, tumour sites [b] No more than3 sites of discordance where the tumour is greater than or equal to 2 cm in size.

Proposed economic evaluation

Table 8 provides a guide for determining which type of economic evaluation is appropriate. Based on the clinical claim of superior health outcomes for effectiveness, and an inferred clinical claim of noninferior safety, a cost-effectiveness or cost-utility analysis would be appropriate. *PASC agreed at the April 2023 meeting, on the basis on the claim of superior effectiveness and noninferior safety, that a cost-effectiveness or cost-utility analysis would be appropriate.*

Table 8 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Table 9 summarises the health resources identified as being relevant in the delivery of the intervention.

Table 9 Health Resources identified in the delivery of the intervention

Medical Service Type	Always required (Yes/No)	Frequency	Cost
^{177}Lutetium Octreotate	Yes	7.4 GBq per IV Infusion 4 infusions at 6-12 week intervals	$8,000/cycle
^{177}Lutetium Octreotate Consolidation	?	The need for this is yet to be justified 2 cycles proposed	$8,000/cycle
Whole body ^{68}Gallium (^{68}Ga)-octreotate PET/CT	Yes (as for MBS Item 61647)	1	$953
CT	Yes MBS Item 61505	1	$100.00
FDG PET/CT Imaging	No MBS 61612 (rare or uncommon cancers)	1	953.00
CT	No MBS Item 61505	1	$100.00
Theranostic Specialist	Yes, consultation pre-treatment costs (MBS 110)	1	$167.75
Specialist attendance theranostic centre for ^{177}Lutetium Octreotate infusion	Yes MBS Item 13950 (requires alteration)	1 per cycle	$118.30
Nurse specialist	Yes	1 per cycle	
Non-admitted patient	Yes		
Amino acid infusion	Yes	1	Applicant to provide fee
SPECT/CT	Recommended 24 hours after MBS Item 61462*/61505	4	$129/$100
Follow-up testing-3 months			
^{68}Ga-DOTA Pet Study	Yes	1	$953
CT	Yes (61505)	1	$100
MRI Scans of the liver	Yes ((item 63546))	1	$578.90
biomarkers			

NOTE: Not every patient will receive all these tests

* PASC has recommended that SPECT/CT be included into the cost of the infusion rather than amending a current MBS item but this awaits a final decision.

Source: Pg 36 of the application

Proposal for public funding

The application proposed a single MBS item for the therapeutic intervention (p38) but indicated a number of other MBS items would also require amendment. Although indicating required amendments to a range of existing MBS items, the application did not provide proposed wording for most requests. The proposed new item descriptors which have been drafted by the applicant are presented in the tables below.

At the April 2023 meeting, PASC noted a requirement for an MBS item associated with an MDT. PASC questioned whether the current MBS items (items 871 and 872) would be applicable for the proposed MDTs or whether MBS items should be developed specifically for these MDTs (like MBS items 6080 and 6081 for

Transcatheter Aortic Valve Implantation (TAVI)). The applicant responded that Item 872 looked appropriate as an MDT Item (email 14th July 2023).

At the August 2023 meeting, PASC noted that the current MBS case conferencing items 872 & 871 are considered sufficient for MDT meetings, but also noted that:

a) These items do not define which professionals should be involved in a "formally convened neuroendocrine tumour multidisciplinary board" (in the item descriptor) and this will need to be resolved.
b) AANMS feedback was that items 872 & 871 are under-reimbursed.

In its consideration in April 2023, PASC discussed the proposed item descriptors in the PICO, those subsequently provided by the applicant, those suggested by the Department and those further proposed by PASC.

Table 10 presents the MBS item for pre-treatment specialist consultation; no changes required or requested.

Table 10 MBS item proposed by the applicant for theranostic specialist pre-treatment consultation.

Category 1 – Professional Attendances
MBS item 110 Professional attendance at consulting rooms or hospital, by a consultant physician in the practice of the consultant physician's specialty (other than psychiatry) following referral of the patient to the consultant physician by a referring practitioner-initial attendance in a single course of treatment.
Fee: $161.90

Source: MBS online
Abbreviations: MBS = Medicare Benefits Schedule

For administration of ^{177}Lu-DOTA-Octreotate, the application proposed amendment to MBS item 13950 for administration, see Table 11.

Table 11 Current and proposed MBS item for administration of ^{177}Lu-DOTA-octreotate treatment

Category 3 – Therapeutic Procedures	**Proposed amendment, if any**
MBS item 13950 Parenteral administration of one or more antineoplastic agents, including agents used in cytotoxic chemotherapy or monoclonal antibody therapy but not agents used in anti-resorptive bone therapy or hormonal therapy, by or on behalf of a specialist or consultant physician—attendance for one or more episodes of administration.	MBS item XXXX Parenteral administration of radiopharmaceutical therapy with attendance by a credentialled Theranostic specialist for one episode of administration.
Fee: $114.20	Fee: $114.20

Source: MBS online; episode=cycle
Abbreviations: MBS = Medicare Benefits Schedule

Notably, the descriptor for MBS item 13950 currently includes parenteral administration of antineoplastic agents such as agents used in cytotoxic chemotherapy or monoclonal antibody therapy and does not include radionuclide therapy (see Table 11 under Proposal for public funding). In further discussions, the applicant highlighted the cost for supervision and administration per cycle of radionuclide therapy could be bundled.

At the April 2023 meeting, PASC noted the applicant's amendment to item 13950 to include "Parenteral administration of radiopharmaceutical therapy with attendance by a credentialled Theranostic specialist for one episode of administration". However, PASC noted that, for Application 1686 (^{177}Lutetium PSMA I&T for metastatic castrate resistant prostate cancer), MSAC advised that the cost of radiopharmaceutical administration should be included in the item fee; PASC considered that the cost of ^{177}Lu-DOTA-octreotate administration should also be included in the item fee for the treatment (see last dot point following Table 15). Table 12 below shows the current MBS item descriptors for ^{68}Ga DOTA peptide PET imaging (item 61647) and the additions proposed by the applicant to allow for its intended use. Item 61647 is often billed with item 61505, it is considered that the wording for item 61505 would not require amendment.

Table 12 Current and proposed MBS items for ^{68}Ga DOTA peptide PET

Category 5 – Diagnostic Imaging Services	**Proposed addition**
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)	For the evaluation of somatostatin receptor expression in patients with known metastatic or unresectable primary neuroendocrine neoplasia who have been deemed to be candidates for peptide receptor radionuclide therapy (PRRT) by a formally-convened neuroendocrine tumour multidisciplinary board or require follow-up for recurrent symptoms or imaging progression after PRRT but would remain candidates for retreatment based on prior benefit
Fee: $953.00	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	

Source: MBS online
Abbreviations: CT = computerised tomography; Ga = Gallium; MBS = Medicare Benefits Schedule; PET = positron emission tomography; SPECT = single photon emission tomography; SSTR = somatostatin receptor.

At the April 2023 meeting, PASC noted the proposed new item for ^{68}Ga-DOTA-octreotate outlined by the Department:

> *Whole body ^{68}Ga DOTA peptide PET study for the evaluation of somatostatin receptor expression in patients with known metastatic or unresectable primary neuroendocrine neoplasia who:*
> *a) are considered suitable for peptide receptor radionuclide therapy (PRRT) by a formally-convened neuroendocrine tumour multidisciplinary board; or*
> *b) require follow-up for recurrent symptoms or imaging progression after PRRT but remain candidates for treatment based on prior benefit. (R)*
> *Fee: $953.00 75%: $714.75 85% $859.80**

And noted this differed to the description of the population:

"locally advanced or metastatic, and inoperable NETs with documented disease progression or uncontrolled symptoms related to their NET".

At the August 2023 PASC meeting, PASC recommended that existing MBS item 61647 needed revision/replacement. Specifically, the relevant radiopharmaceutical product should be a ^{68}Ga-DOTA-octreotate or somatostatin receptor 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 PRRT;
d) Evaluation of response to therapy;
e) Evaluation of suspected recurrent/metastatic disease in known SSA-avid (H-SSTR) NEN.

PASC 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 MDT.

The proposed new MBS Item for ^{68}Ga DOTA peptide PET Study to determine SSTR expression, *suggested by PASC at the August 2023 meeting* is below (Table 13).

Table 13 Proposed MBS Item for ^{68}Ga DOTA peptide PET Study to determine SSTR expression

Category 5 – Diagnostic Imaging Services
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 r 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

Table 14 presents the current MBS item descriptors for FDG PET/CT imaging. It is considered that the wording for item 61612 would not require amendment. *At is April 2023 meeting, PASC agreed that the item descriptor for FDG PET/CT would likely not require amendment or a new item, noting that whole body FDG PET for treatment response and recurrence for rare or uncommon cancers was currently under consideration by MSAC. PASC further noted that the incidence threshold of less than 12 cases per 100,000 persons per year definition for rare cancers would apply.*

Table 14 Current and proposed MBS items for FDG PET imaging

Category 5 – Diagnostic Imaging Services
MBS item 61612 Whole body FDG PET study for the initial staging of eligible cancer types, for a patient who is considered suitable for active therapy, if: (a) the eligible cancer type is: (i) a rare or uncommon cancer (less than 12 cases per 100,000 persons per year); and (ii) a typically FDG-avid cancer; and (b) there is at least a 10% likelihood that the PET study result will inform a significant change in management for the patient Applicable once per cancer diagnosis (R)
Fee: $953.00

Source: MBS online
Abbreviations: FDG = Fluorodeoxyglucose; MBS = Medicare Benefits Schedule; PET = positron emission tomography

It is noted that MBS Item 61612 does not require referral from an MDT.

In its consideration at the April 2023 meeting, PASC noted that there was no MBS item fee associated with amino acid infusion, nor are the amino acids PBS-listed and agreed with the applicant's proposal that the cost for amino acid infusion may be incorporated into the per cycle fee for ^{177}Lu-DOTA-octreotate treatment (see last dot point following Table 15).

In August 2023, PASC suggested the following descriptor for the proposed new MBS Item for the therapeutic intervention:

"^{177}Lutetium-somatostatin agonist therapy for patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine neoplasms (NEN) 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 tumour multidisciplinary board."

As noted previously, it is proposed that the number of cycles should not be specified in the item descriptor.

This item is inclusive of necessary patient preparation techniques such as the administration of an amino acid infusion, the preparation and administration of the radiopharmaceutical, immediate patient aftercare, and post-infusion single photon emission computed tomography, if performed.

PASC noted the following points regarding the proposed item descriptor:

a) The ^{177}Lutetium-somatostatin agonist as specified by definition excludes SSTR antagonists;
b) does not specify ^{177}Lu(nca) or ^{177}Lu(ca);
c) should include an explanatory note, to specify the provider's qualifications (i.e. theranostic specialist recognised by the Committee for Joint College Training of the RACP & RANZCR).

Table 15 presents the proposed MBS item descriptor for the therapeutic intervention, *suggested by PASC at the August 2023 meeting*.

Table 15 Proposed MBS item for ^{177}Lu-DOTA-octreotate

Category T3-Therapeutic Nuclear Medicine
MBS item XXXX *^{177}Lutetium-somastatin receptor agonist treatment for patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine tumours (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 tumour 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: $8,000.00 + additional costs to be provided by Applicant (see Attachment 1) to determine new fee

The requested fee is consistent with that requested for ^{177}Lu-prostate specific membrane antigen (^{177}Lu-PSMA; MSAC 1686). However, a distinction between the two is that the item descriptor for ^{177}Lu-PSMA included SPECT/CT 24 hours following injection, whereas the applicant for ^{177}Lu-DOTA-octreotate has specifically indicated they would like the follow-up SPECT/CT (if conducted) to be kept separate. Clinical advice was that the SPECT was usually done in the 24 hours following the infusion.

With respect to the item descriptor for therapy, PASC provided a further suggestion at the April 2023 meeting, specifically:

- *PASC considered a more 'generic' description of therapy may be appropriate with removal of reference to ^{177}Lu(nca)-DOTA-octreotate in the item descriptor and replacing it with "^{177}Lu-DOTA-octreotate " or "^{177}Lu-somatostatin receptor agonist". This may be subject to the demonstration of noninferiority or therapeutic equivalence between radiopharmaceuticals eligible for the proposed item descriptor. The applicant reiterated that the proposal was for ^{177}Lu(nca)-DOTA-octreotate specifically, and there was potential for use of ^{177}Lu(ca)-DOTA-octreotate if the descriptor was left more 'generic' as ^{177}Lu(ca)-DOTA-octreotate is much cheaper and prepared in some hospitals currently. The applicant also 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. While this may have implications for radioactive waste storage and disposal, the clinical advantages of "nca" vs. "ca" ^{177}Lu-DOTA-octreotate remain to be established.*
- *PASC considered the number of cycles should be limited to four (4) per 12 month period (as per the NETTER-1 trial).*
- *PASC suggested changes to the description of patients to be "for patients with histologically confirmed, locally advanced or metastatic, and inoperable neuroendocrine tumours (NETs) with documented disease progression or uncontrolled symptoms related to their NEN who:*

a) *Have high tumour somatostatin receptor expression demonstrated on whole body ^{68}Ga DOTA peptide PET study; and*
b) *Are considered suitable for peptide receptor radionuclide therapy (PRRT) by a formally-convened neuroendocrine tumour multidisciplinary board.*

- *PASC further stated the item should be inclusive of:*
  a) *Patient preparation (including cost of amino acid infusion);*
  b) *Radiopharmaceutical preparation and administration;*
  c) *Immediate aftercare; and*
  d) *Post-infusion single photon emission tomography (SPECT), if performed.*

PASC acknowledged that the requested fee may require reconsideration given the further inclusions.

At the August 2023 PASC meeting, PASC noted the applicant's revised bundled fee which was not evaluated before PASC. The applicant proposed fee of $10,431.05 for ^{177}Lu(nca)-DOTA-octreotate) produced under GMP was $400 higher than the revised bundled fee for ^{177}Lu(ca)-DOTA-octreotate ($10,031.05) produced under GMP. PASC queried whether the theranostic specialist pre-treatment consultation fee ($110) could be unbundled due to exiting MBS item 110/104, and whether the facility cost ($900) could also be unbundled. PASC advised the assessment should consider both fee structures (^{177}Lu(nca) and ^{177}Lu(ca)) for PRRT therapy with ^{177}Lu-DOTA-octreotate.

Table 16 presents the item descriptor for SPECT, which the application indicated was a requirement following each treatment, but the applicant has since indicated is not a necessary test. The application proposed MBS item 61462 for repeat SPECT imaging post- ^{177}Lu-DOTA-octreotate therapy, however the item descriptor for this item does not currently include MBS items 61647 (^{68}Ga DOTA peptide PET) or 61369 (^{111}In-octreotide SPECT) in the list of prerequisite scans. Unless the item descriptor is amended to include these two items, in the scenario where a patient is deemed to benefit from post-treatment SPECT/CT this may be associated with additional out-of-pocket costs to the patient. *PASC agreed at its April 2023 meeting that the item descriptor for repeat planar/SPECT imaging after therapy (item 61462 and 61505) would likely not require amendment or a new item but the cost of this could be accounted for in the item fee for the treatment – this is also consistent with MSAC's recommendation for Application 1686* (see last dot point following Table 15).

Table 16 Current and proposed MBS item descriptors for repeat SPECT/CT imaging

Category 5 – Diagnostic Imaging Services	***Proposed amendment***
MBS item 61462 Repeat planar and single photon emission tomography imaging, or repeat planar imaging or single photon emission tomography imaging on an occasion subsequent to the performance of item 61364, 61426, 61429, 61430, 61442, 61450, 61453, 61469 or 61485, if there is no additional administration of radiopharmaceutical and if the previous radionuclide scan was abnormal or equivocal (R)	*None suggested.*
Fee: $129.00	*Fee: $*
Category 5 – Diagnostic Imaging Services	***Proposed amendment***
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)	*No changed requested.*
Fee: $100.00	*Fee: $100.00*

Source: MBS online
Abbreviations: MBS = Medicare Benefits Schedule; SPECT = single photon emission tomography.

Other Issues

PASC considered the following additional issues with ^{177}Lu-DOTA-octreotate:

Implementation

PASC noted that the supply of ^{177}Lu worldwide is precarious.

- *The Australian Nuclear Science & Technology Organisation (ANSTO) is TGA-registered and supplies ^{177}Lu (nca) but if required ^{177}Lu (ca) can be sourced from overseas. PASC noted that ANSTO's ARTG listing (352151) is for $^{177}LuCl_3$ (not for ^{177}Lu-DOTA-octreotate) and does not specify "nca".*

PASC raised the following matters for additional consideration:

a) *If PRRT is MBS-funded, will "in-house" production —of either ^{177}Lu(nca)-DOTA-octreotate or ^{177}Lu(ca)-DOTA-octreotate —be eligible for reimbursement?*
b) *If so, will "in-house" production facilities need to demonstrate GMP compliance?*

PASC noted the department's advice that if MSAC supports the application the department would work through any implementation matters including what the appropriate requirements for MBS funding are.

PASC noted that the current items 872 & 873 were considered to be adequate for case conferencing by an MDT. PASC noted that it may be necessary to specify which professionals should be involved in the MDT for the purposes of reimbursement, most likely via an explanatory note to the proposed item.

Summary of public consultation input

At the April 2023 meeting, PASC noted and welcomed consultation input from 6 organisations. The organisations that 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)

The consultation feedback received was mostly supportive of public funding for ^{177}Lu(nca)-DOTA-octreotate treatment for advanced neuroendocrine tumours (NETs) and other high somatostatin receptor (H-SSTR) expressing tumours. The consultation feedback raised a number of concerns, predominately in relation to the patent status of the radiopharmaceutical, the fee, and the suggested incorporation of the AANMS position statement into policy.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included improved access and associated benefits, addressing the need for effective therapies, particularly for metastatic disease, and improved outcomes including prolonged periods of disease-free periods with minimum toxicity (compared with chemotherapy).

The main disadvantages of public funding received in the consultation feedback mainly related to the side effects of treatment. However, it was stated that these could be managed.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included: oncology, nuclear medicine physicians, endocrinology, surgery, palliative care, medical physics, social workers and dietician support services. RANZCR stated that they support the need for patient cases to be discussed by an expert MDT prior to treatment. The AANMS agreed and added that treatments of other advanced H-SSTR malignancies should be referred from appropriate specialist practitioners.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback ranged from agreeing to strongly agreeing with the proposed population(s). The AANMS stated that the proposed interventions should be available to all patients who have SSTR expressing tumours of satisfactory avidity on a ^{68}Ga-DOTA-peptide PET scan. Telix stated that they agreed with the proposed populations, however, that the target population is unclear. They add that the MBS item descriptor does not align with the population outlined in the application.

The consultation feedback ranged from disagreeing to strongly agreeing with the proposed comparator. The AANMS stated that the only well published comparator is high dose long acting somatostatin, they went on to state that there is a trial nearing completion comparing Lu-Dotatate to everolimus. They added that, currently, Lutate is used when most chemotherapy options are exhausted, so is an additional option rather than a direct competitor to other therapies. Telix stated that it is unclear what the proposed comparator is for each population.

The consultation feedback ranged from disagreeing to strongly agreeing with the clinical claim. USANZ and Novartis questioned the therapeutic equivalence of ^{177}Lu-DOTATATE and ^{177}Lutetium(nca) Octreotate. Novartis stated that ^{177}Lutetium(nca) Octreotate (proposed intervention) and the Novartis product, ^{177}Lu-DOTATATE, may be two different drug products. They stated that there is no evidence to support the therapeutic equivalence of ^{177}Lu-DOTATATE and ^{177}Lutetium(nca) Octreotate which is not linked to a DOTA chelating moiety.

RANZCR stated that the application is clinically appropriate, reflects current best practice and the evidence is robust. Telix stated that the number of repeat doses is not clear.

Cost information for the proposed medical service

The consultation feedback ranged from disagreeing to strongly agreeing with the proposed service descriptor. Telix stated that it is not clear from the MBS item descriptor if the $8000 fee is for one dose, or whether one or more doses would be required. They went on to state that it is not clear if dosing is different per proposed population, and that MDT referral is not reflected in the MBS item descriptor.

The consultation feedback ranged from disagreeing to agreeing with the proposed service fee. ADIA stated that it is appropriate to allow practitioners to separately bill relevant items associated with delivering this therapy. They, however, added that, given the applicant has indicated the cost of the treatment dose is $8000, an MBS fee of $8000 is inappropriate as the MBS fee should be set to allow the provider to recover the cost of ^{177}Lutetium(nca) Octreotate to avoid significant out of pocket costs to patients. The AANMS stated that the proposed fee is in line with costs as delivered in public hospital settings in the metropolitan area. They added that the cost to deliver the proposed intervention in rural areas would be higher, and that the cost of radiopharmaceuticals is expected to increase from May 2023. Telix stated that the true cost of delivery is between $12,000-$15,000 per dose in 2023.

Additional comments

ADIA stated that, as no theranostic service is currently listed on Medicare, regulatory settings for Medicare-funded provision have not been determined. They added that incorporation of the *AANMS Position Statement on Practice of Theranostics in Australia* into legislation is inappropriate as these requirements would jeopardise provision of theranostics in private practice. RANZCR stated that they do not endorse the AANMS position statement as they do not believe it adequately establishes the required benchmarks for patient access to safe and high quality theranostics services.

Novartis noted that its ^{177}Lu-DOTATE is protected by a granted patent. Novartis queried why the proposed product is exempt from ARTG registration.

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.

As part of the consultation feedback for the August 2023 PASC meeting, organisations and specialists were asked for input on the key issues identified at the April 2023 PASC meeting, in addition to comments on these issues from the applicant. The targeted questions focused on the cost of providing ^{177}Lu-DOTA-octreotate therapy including required doses and pre and post treatment scans, eligibility of patients for

treatment and supply of ^{177}Lu-DOTA-octreotate therapy, in particular whether both carrier added (ca) and no-carrier added (nca) products should be considered in the intervention.

At the August 2023 PASC meeting, PASC noted and welcomed additional consultation feedback from 5 organisations and 2 individuals who are clinical experts and provide PRRT therapy in Australia. The 5 organisations that submitted input were:

- Medical Oncology Group of Australia (MOGA) and the Clinical Oncology Society of Australia (COSA)
- Australasian Association of Nuclear Medicine Specialists (AANMS)
- Australian and New Zealand Society of Nuclear Medicine (ANZSNM)
- NeuroEndocrine Cancer Australia (NECA)
- Australian Diagnostic Imaging Association (ADIA)

The consultation feedback received was largely supportive of public funding for ^{177}Lu-DOTA-octreotate treatment for advanced neuroendocrine and other high somatostatin receptor expressing tumours. The consultation feedback raised a number of concerns, predominately in relation to accessing the intervention and the MBS item descriptor and fee.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included reduction and control of the debilitating symptoms of neuroendocrine neoplasms (NENs) that include flushing, diarrhoea, asthma, nausea and heart palpitations and can enable return to normal routine and work. Public funding of this intervention also reduces the cost of treatment and allows safe, effective therapy to provide improved quality of life for patients.

The main disadvantages of public funding received in the consultation feedback included potential side effects of treatment including myelotoxicity, the potential for inequity in patient access due to geographical constraints and potential out of pocket costs should the MBS fee be inadequate.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included 68Ga-DOTA-octreotate PET/CT imaging and pre/post medications that can include amino acids, long/short acting octreotide and antiemetics.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback strongly agreed with the proposed population(s). All feedback noted that NENs are highly heterogeneous cancers and that patients are managed by a multidisciplinary team. The feedback stated that this therapy should be available to all appropriate patients identified by a multidisciplinary team.

The consultation feedback ranged from agreeing to strongly agreeing with the proposed comparator. ANZSNM stated that unfunded ^{177}Lutetium Octreotate therapy has been used in Australia for several years due to its superiority over non-radioactive somatostatin antagonists.

The consultation feedback ranged from agreeing to strongly agreeing with the clinical claim. ANZSNM stated that ^{177}Lutetium Octreotate therapy has been proven to have superior outcomes compared to non-radioactive somatostatin antagonists. MOGA and COSA stated the recent NETTER-1 trial has established Peptide Receptor Radionuclide Therapy (PRRT that includes 177Lutetium Octreotide therapy) as the

treatment of choice in this second-line setting for patients with midgut NENs and is supported by the forthcoming COSA NEN guidelines.

Cost information for the proposed medical service

The consultation feedback ranged from agreeing to strongly disagreeing with the proposed service descriptor. ADIA, AANMS, ANZSNM and the two clinical experts all disagreed with limiting the treatment to no carrier added (nca) ^{177}Lutetium. It was noted that carrier added ^{177}Lutetium is currently used in Australia with an excellent safety record, that there is no impact on the therapeutic outcome and that limiting the description to no carrier added could impact the supply and availability of ^{177}Lutetium in Australia. The two clinical experts expressed a preference for the item descriptor to be flexible regarding the number of cycles allowed per year to prevent potential out of pocket costs to patients. ADIA reiterated that as per their feedback in April, they disagree with the AANMS position statement regarding credentialling of theranostic specialists stating it would limit the service to metropolitan public hospital settings and impact regional and rural locations that currently provide the service.

The consultation feedback ranged disagreeing to agreeing with the proposed service fee. Almost all of the feedback commented that the proposed service fee would be insufficient to cover the cost of providing the therapy and that imaging post treatment should be covered by MBS funding.

Additional comments

In response to targeted questions, consultation feedback was provided on in-house radiopharmaceutical teams producing compounded ^{177}Lu(ca)-DOTA-octreotate. One clinical expert considered the practice was established and the product is made to a high standard with quality control performed before administration and did not consider there to be a clinically relevant difference between good manufacturing practice (GMP) and non-GMP products.

Consumer Feedback

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.

In August 2023, PASC also noted the consultation feedback from the April 2023 consideration. PASC noted that patent-related issues and the appropriateness of GMP exemptions were raised in the public consultation. PASC noted that these were implementation related matters that the Department would need to address. PASC noted that advising on TGA regulations and patent-related issues is not within its Terms of Reference and considered this to be matters for government.

Next steps

In August 2023, PASC noted the applicant's intent to proceed with a Department contracted assessment report (DCAR).

Applicant Comments on Ratified PICO

The AMT 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 and has not been assessed by TGA for quality, safety and efficacy. The AMT product is manufactured to GMP quality standards by a TGA licensed manufacturer.

It is noted the that the applicant and the clinical expert have repeatedly re-iterated their concern that patient safety will be jeopardised if MSAC supports funding for "in-house" production of therapeutic radiopharmaceuticals that are not produced by TGA licenced manufacturers (where GMP quality management systems and regular TGA audit is mandatory) or otherwise experienced radiopharmaceutical manufacturers who employ rigorous quality management systems.

The presentation of differing views on the merits of GMP/ non-GMP radiopharmaceutical production does not adequately reflect the input provided by the applicant and the applicant's nominated clinical expert. Quite simply, if there is no clinically relevant difference between GMP and non-GMP quality products the validity of the whole regulatory approach to pharmaceutical manufacture and supply in Australia is flawed and the economic costs associated with TGA licencing of manufacturers would not be justified on the basis of safety and quality of pharmaceuticals supplied to Australian patients.

Attachment 1

Bundled fee elements

Service Element	Suggested Fee	Comment
GMP ^{177}Lu (nca)DOTA-Octreotate Supply	$8000	AMT cannot supply for a lower cost
GMP ^{177}Lu (ca)DOTA-Octreotate Supply	$7600	AMT cannot supply for a lower cost
Delivery	$450	This is derived directly from fee suggested by AANMS for ^{177}Lu DOTA PSMA i&t therapy.
Theranostic Specialist pre Treatment Consult Fee	$167.75	This is 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 in the Theranostic Specialist is also a member and of the MDT recommending treatment and receives a fee for that attendance

Service Element	Suggested Fee	Comment
Theranostic Specialist Treatment Supervision and Follow-up Fee	$118.30	This is 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	This is derived directly from fee suggested by AANMS for ^{177}Lu DOTA PSMA i&t therapy
Nuclear Medicine Technologist	$200	This is derived directly from fee suggested by AANMS for ^{177}Lu DOTA PSMA i&t therapy
Amino Acid Infusion	$120	This is the cost to Peter MacCallum Cancer Centre from one commercial provider
Post-administration SPECT/CT scan	$400	This is derived directly from fee suggested by AANMS for ^{177}Lu DOTA PSMA i&t therapy
Radiation Safety Officer/Physicist	$75	This is derived directly from fee suggested by AANMS for ^{177}Lu DOTA PSMA i&t therapy. Probably 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**	

Source: provided by applicant in email on 04/08/23

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