MSAC Application 1744

^{177}Lutetium$_{(n.c.a)}$Octreotate treatment for advanced neuroendocrine and other high somatostatin receptor expressing tumours

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Instructions to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted. The separate MSAC Guidelines should be used to guide health technology assessment (HTA) content of the Application Form

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Applied Molecular Therapies Pty Ltd
Corporation name: Applied Molecular Therapies Pty Ltd
ABN: 70 625 535 551
Business trading name: AMT

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a consultant acting on behalf on an applicant?

☐ Yes
☒ No

(b) If yes what is the Applicant(s) name that you are acting on behalf of?

3. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☐ No

(c) Have you engaged a consultant on your behalf?

☐ Yes
☒ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

^{177}Lutetium$_{(nca)}$ Octreotate treatment for advanced neuroendocrine and other high somatostatin receptor expressing cancers

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Neuroendocrine Tumours (NET) arise in a range of tissues from cells that function to regulate bodily function by secreting bioactive compounds, particularly peptide hormones. NET and several other uncommon cancer types have high somatostatin receptor expression (H-SSTR), making this an attractive diagnostic and therapeutic target.

NET can be slowly or aggressively growing with excessive hormone secretion often adversely affecting NET patient's quality of life in lower-grade tumours, while high-grade tumours cause compromise of organ function and tissue integrity leading to premature death. Around 50% of patients have advanced and already incurable disease at diagnosis.

The long-acting formulations of the somatostatin analogues are the mainstay of symptomatic treatment for hormonal dysregulation and delay disease progression but eventually fail. Thereafter, the highly complex array of clinical management problems presented by advanced stage NET patients necessitates highly individualised care provided by experienced multi-disciplinary healthcare teams (MDT) to achieve optimal patient outcomes.

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

The service is a precision medicine approach for personaled treatment of patients with advanced NET and H-SSTR.

^{177}Lutetium(nca) Octreotate produced by TGA Licenced Manufacturer AMT is a GMP quality radiopharmaceutical administered by infusion to patients with progressive or symptomatic NET if molecular imaging techniques demonstrate much higher levels of somatostatin receptors on the majority tumours sites compared to normal tissues. Selective delivery of high radiation doses to NET tumour sites is the mechanism of action of ^{177}Lutetium(nca) Octreotate.

The initial treatment cycle most commonly comprises 4-5 ^{177}Lutetium(nca) Octreotate infusions given 6-8 weeks apart and responding patients may be re-treated multiple times if symptoms recur or further tumour progression occurs.

The wide spectrum of clinical management problems presented by patients with advanced NET and other H-SSTR cancer types means that experienced MDT provide the optimal pathway for assessing patient suitability for ^{177}Lutetium(nca) Octreotate and/or alternative treatments intended to control NET progression.

7. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service/technology:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

☒ A new item which also seeks to allow access to the MBS for a specific health practitioner group
☐ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
☐ A new item for a specific single consultation item
☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise:

N/A

8. What is the type of medical service/technology?

☒ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

N/A

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☒ No

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

N/A

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

N/A

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☐ Yes
☐ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

13. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: Gloves/giving sets/syringes/swabs/cannulas/ amino acid infusion/ [177Lu(nca)Octreotate injection

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer, or any other type of therapeutic good, please provide details

Type of therapeutic good: Sterile radioactive medicinal product
Manufacturer's name: Applied Molecular Therapies Pty Ltd
Sponsor's name: Applied Molecular Therapies

(b) Has it been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? If the therapeutic good has been listed on the ARTG, please state the ARTG identification numbers, TGA-approved indication(s), and TGA-approved purpose(s).

^{177}Lutetium(nca) Octreotate has not been listed on the ARTG.

(c) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

(d) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

No

15. (a) <u>If not listed on the ARTG</u>, is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☒ Yes. (Please see accompany letter from TGA to Australasian Association of Nuclear Medicine Specialists)
☐ No

(b) If the therapeutic good is <u>not ARTG listed</u>, is the therapeutic good in the process of being considered by TGA?

☐ **Yes (if yes, please provide details below)**
☒ **No**

(c) If **the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?**

☐ Yes (please provide details below)
☒ No

PART 4 – SUMMARY OF EVIDENCE

16. Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Randomised Controlled Trial	Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors	229 patients with well-differentiated, metastatic midgut NET randomised to 177Lu-Dotatate 7.4 GBq 8 weekly x 4 plus best supportive care including octreotide long-acting (Sandostatin-LAR) or augmented dose Sandostatin LAR (60mg versus 30mg 4-weekly). For primary endpoint 20 month PFS was 65% (177Lu-Dotatate) and 10.8% (control) with 14 deaths with 177Lu-Dotatate and 26 in control group (p=.004)	DOI: 10.1056/NEJMoa1607427	2017
2.	Prospective cohort study	Quality of Life in 265 Patients with Gastroenteropancreatic or Bronchial Neuroendocrine Tumors Treated with [177Lu-DOTA,Tyr3]Octreotate	Patients at a single institution had practitioner assessed Karnofsky score and self-assessed EORTC quality- of-life questionnaire (QLQ)–core module (C30) before and after 177LuDotate. GHS/QOL, KPS, and symptoms improved significantly after 177Lu-octreotate therapy, and there was no significant decrease in QOL in patients who had no symptoms before therapy.	DOI: 10.2967/jnumed.111.087932	2011

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	Prospective cohort study	Quality of life in patients with midgut NET following peptide receptor radionuclide therapy	70 patients with NET had performance scores and quality of life assessed before and after treatment with 177LuDotatate. Global health status emotional, cognitive functioning, pain and diarrhea improved significantly	doi: 10.1007/s00259-019-04431-3.	2019
4.	Cohort follow up study	Long-Term Efficacy, Survival, and Safety of [177Lu-DOTA,Tyr3]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors	Long-term follow-up documenting patients relevant outcomes of over 1200 patients with well differentiated gastroenteropancreatic or bronchopulmonary NET treated in single centre. PFS of 29 months and OS of 63 months. No therapy related chronic renal or hepatic failure. Myelodysplasia rate 1.5%, acute leukemia rate .7%	doi: 10.1158/1078-0432.CCR-16-2743ohert	2017
5.	Retrospective cohort outcome study	Long-term outcome of indigenous 177Lu-DOTATATE PRRT in patients with Metastatic Advanced Neuroendocrine Tumours: a single institutional observation in a large tertiary care setting	468 NET patients 177LuDotatate treated median follow up 46 months. 322 with progressive disease at treatment initiation had high disease control rate (CR + PR + SD) 93.5%, 88.5%, 89.1 and 87.9% on symptomatic, biochemical, RECIST 1.1 and PERCIST criteria. PFS and OS at 7 years 68.3% and 79.2%, respectively.	doi. org/ 10. 1259/ bjr. 20201041	2021

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
6.	Retrospective cohort outcome study	Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN) - a single-institution retrospective analysis	28 patients with G3 NET -25/28 FDG-avid. Most had ^{177}Lu-Dotate treatment and 20 with radiosensitising chemotherapy. 79% treated for disease progression after prior chemotherapy. Median follow-up was 29 months. Median PFS was 9 months for all patients. with median OS of 19 months.	doi.org/10.1007/s00259-017-3821-2	2017
7.	Retrospective cohort outcome study	Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients	69 patients received 177Lu- or 90Y Dotatate or Dotatoc or DOTATOC, 22 adjuvant chemotherapy. For Ki-67 less 55% (53 patients) median PFS was 11 mo and median OS was 22 mo. Ki-67 index greater than 55% (11 patients had 4 months median PFS and 7 months median OS.	DOI: 10.2967/jnumed.118.215848	2019
8.	Retrospective cohort outcome study	Subacute haematotoxicity after PRRT with 177Lu-DOTA-octreotate: prognostic factors, incidence and course	Haematological toxicity (grade 3/4) occurred in 34 of 320 patients and lasted more than 6 months in 15. Risk factors were: poor renal function, white blood cell (WBC) count<$4.0x10^9$/l, age over 70 years, extensive tumour mass and high uptake on somatostatin receptor imaging.	DOI 10.1007/s00259-015-3193-4	2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
9.	Retrospective	Multi-centre PRRT toxicity study	807 patients from multiple centres in Europe evaluating acute and long-term toxicity. Treatment with 90Y and 90Y+177Lu was more likely to result in nephrotoxicity than treatment with 177Lu alone (33.6 %, 25.5 % and 13.4 % of patients, respectively; p<0.0001). Nephrotoxicity (any grade), transient and persistent, occurred in 279 patients (34.6 %) and was severe (grade 3+4) in 12 (1.5 %). Myelodysplastic syndrome occurred in 2.35 % of patients	DOI 10.1007/s00259-014-2893-5	2015
10	Retrospective cohort study	Retreatment with peptide receptor radionuclide therapy in patients with progressing neuroendocrine tumours: efficacy and prognostic factors for response	29 patients were re-treated (PRRT2) with 90Y-dotatate and 18 patients with 177Lu-dotatate after initial peptide receptor radionuclide therapy . Median PFS after PRRT2 was 17.5 months. There was no statistically significant difference in median PFS related to radiopharmaceutical. 71 months median overall survival from commencement of first PRRT cycle.	doi. org/ 10. 1259/ bjr. 20180041	2018
11.	Retrospective cohort study	Analysis of efficacy and safety of PRRT in bronchpulmonary NET at 2 ENETS Centres of Excellence	48 patients with typical and atypical lung carcinoid tumours with progressive metastatic disease. At a median follow-up of 42 mo, the median PFS and OS were 23 mo (95% CI, 18–28 mo) and 59 mo (95% CI, 50-not reached [NR]), respectively. Disease control rate was 88% by RECIST or Ga-68 DOTATE PET/CT. Of patients with stable disease by RECIST, those with partial response on ^{68}Ga-DOTATATE PET/CT had a longer OS than those with no response, NR versus 52 mo (95%CI, 28–64), hazard ratio 0.2 (95% CI, 0.1–0.6), P = 0.001.	DOI: 10.2967/jnumed.120.260760	2022

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
12.	Retrospective cohort	Efficacy of Peptide Receptor Radionuclide Therapy (PRRT) for Functional Metastatic Paraganglioma and Phaeochromocytoma.		Journal of Clinical Endocrinology and Metabolism 2017 Sep 1;102(9):3278-3287	2017
13.	Retrospective cohort	Initial Experience With Gallium-68 DOTA-Octreotate PET/CT and Peptide Receptor Radionuclide Therapy for Pediatric Patients With Refractory Metastatic Neuroblastoma	Small series of children with advanced neuroblastoma treated with palliative intent demonstrating effective control of symptoms, evidence of response and low toxicity	10.1097/MPH.0000000000000411	2016
14.	Systematic Review and Meta-Analysis	The therapeutic efficacy of 177Lu-DOTATATE/DOTATOC in advanced neuroendocrine tumors	22 studies (1758 patients) were included Pooled Disease Response Rates were 33.0%, 35.0%, and 25.0% and pooled Disease Control Rates were 79.0%, 83.0% and 82.0% for RECIST, RECIST 1.1 and SWOG criteria respectively.	doi.org/10.1097/MD.0000000000019304	2020

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
15.	Expert Society Clinical Guidelines	ENETS consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues.	Evidence based guidelines developed by the European Neuroendocrine Tumour Society detailing the role of biosimilars in the treatment of NET	https://doi.org/10.1159/000475526.	2017
16.	Expert opinion	Unmet needs in the international neuroendocrine tumor (NET) community: assessment of major gaps from the perspective of patients, patient advocates and NET health care professionals.		Leyden S, Kolarova T, Bouvier C, et al. Int J Canc 2020; 146:1316e23.	2020

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
17.	Expert opinion	Consensus on molecular imaging and theranostics in neuroendocrine neoplasms.	Focus group of oncologists, gastroenterologists and nuclear medicine specialists convened by European Association of Nuclear Medicine to the document current state-of-art opinions on the use of theranostic approaches in neuroendocrine neoplasia. Consensus supported use of peptide receptor radionuclide therapy (PRRT) as second line therapy at first disease progression in all patients with G1-2 [68Ga] Ga-DOTA-SSA positive gastrointestinal NET and in a subset of patients with NET G3 (Ki67 > 20%) provided all [18F]FDG positive lesions exhibit [68Ga]Ga-DOTASSA uptake. PRRT rechallenge was also supported for prior responders.	doi: 10.1016/j.ejca.2021.01.008	2020
18	Expert Clinical Guidelines	Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Contemporary practice guidelines compiled by experts in the field for the European Society of Medical Oncology. Includes comprehensive descriptive text and multiple algorithms detailing optimal clinical pathways for NET patients with a variety of tumour types, tumour grades and clinical indications	doi.org/10.1016/j.annonc.2020.03.304	2020

17. Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.

	Type of study design	Title of research	Short description of research	Website link to research	Date
1.	Prospective phase I trial	PARLuNET (NCT05053854)	Phase I dose-escalation trial of Lu-DOTATE plus the PARP-inhibitor talazoparib as a DNA-damage repair modifying agent. Prior preclinical data suggesting significantly enhanced radiosensitivity (Cullinane et al. Scientific Reports 2020;10(1):10196) Currently recruiting into dose level 2	No results available	Recruitment will likely complete in 2022

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

18. List all appropriate professional bodies/organisations representing the health professionals who provide the service. For MBS-related applications ONLY, please attach a brief 'Statement of Clinical Relevance' from the most relevant college/society.

Australasian Association of Nuclear Medicine Specialists

Royal Australian and New Zealand College of Radiologists

19. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

Clinical Oncology Society of Australia

Royal Australian College of Physicians

Royal Australian College of Surgeons

Endocrinology Society of Australia

Royal Australian and New Zealand College of Radiologists

20. List the consumer organisations relevant to the proposed medical service (noting there is NO NEED to attach a support letter at the 'Application Lodgement' stage of the MSAC process):

NeuroEndocrine Cancer Australia

Cancer Council Australia

Cancer Voices

21. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

There is no alternative identical or biosimilar *GMP quality* product available in Australia for this treatment indication

Non-GMP quality, extemporaneously compounded product is manufactured in several locations around Australia for supply to patients using both no carrier added (nca) and carrier added (ca) ^{177}Lutetium and is used for this treatment indication

Biosimilar non-GMP quality radiopharmaceuticals that are, or have been used in Australia for this treatment indication are

^{177}Lutetium(ca and nca)Octreotide

^{90}Ytrium Octreotate and Octreotide

^{111}Indium DTPA-Octreotate and Octreotide

NOVARTIS sponsors a GMP quality ^{177}Lutetium(ca and nca)Octreotate radiopharmaceutical product for use in a similar treatment indication in the European Union and United States of America, but it is unknown whether the company intends to sponsor supply of their product to the Australian healthcare system.

22. Nominate two experts that can be contacted about the proposed medical service, and current clinical management of the condition:

REDACTED

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

23. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease (in terms of both morbidity and mortality):

NET is a malignancy that originates in neuroendocrine cells normally located in many regions of the body but primarily the digestive and respiratory tracts.

NET may be sporadic or may occur as part of familial Multiple Endocrine Neoplasia Syndromes (MEN 1 and 2)

Approximately 20% of NET retain the capacity to secrete clinically significant quantities of functional peptide hormones and may present with associated syndromic features, e.g. carcinoid syndrome, Werner-Morrison syndrome etc.

H-SSTR tumours 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) or autonomic nervous system)paraganglioma) and may also demonstrate dysregulated production of physiologically active molecules, particularly catecholamines.

The natural history of the disease is highly variable and dependent several key tumour characteristics

- *location of the primary tumour.* Localised tumours may produce major morbidity and cause death depending on their location and potential for ablation by surgery and/or radiotherapy

  The location of the primary tumour also commonly defines the cell type of origin of the NET or H-SSTR and in conjunction with the site of tumour origin these characteristics strongly influence the range of tumour behaviours and consequently management options and patient outcomes

- *whether the tumour is localised or metastatic.* Metastatic NET is present in approximately 50% of patients at first diagnosis, and in most patients who have metastatic NET and H-SSTR the condition is ultimately their cause of death.

- *the rate of tumour cell replication.* NET Grade is a classification dependent upon pathological estimation of a Ki-67 index. G1, or Low grade tumours, have Ki-67 less than 3% and G2, or Intermediate grade tumours, have Ki-67 of 3-20%.
  G3, or High grade tumours, have a Ki-67 of 21-100% with the G3 tumours category more recently divided into Well differentiated NET and Poorly differentiated neuroendocrine carcinoma (NEC), with G3 WD-NET generally having a Ki-67 index of 21-55% with NEC typically having Ki-67 >55%.
  Higher tumour grades have more rapid tumour growth and shorter average overall survival duration with shortest overall survival of 6-18 months for patients with NEC.
  NET patients with metastatic disease not uncommonly have some heterogeneity of tumour grade at different metastatic sites and the range of tumour grades in any individual may not be static for the duration of their illness. There is a strong tendency for patients to develop for less differentiated tumours, higher grade tumour associated with more rapid disease progression and symptomatic deterioration during the course of their illness.
  In general tumour grade is reflected by metabolic imaging characteristics with decreasing somatostatin receptor imaging positivity and increasing FDG PET 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.
No formal system of tumour grading for H-SSTR has been implemented but the intensity of uptake of 68Ga-Dotatate PET/CT, referred to as the modified Krenning score 3 and 4, has been shown to correlate with strong staining on immunohistochemistry. Moreover, FDG PET/CT intensity is also associated with a higher rate of tumour cell replication and degree of tumour differentiation. These factors influence the natural history of these tumours and heterogeneity is also a common feature in these tumours.

- *the type and quantity of peptide hormone secretion.* Patient outcomes may be strongly influenced by excessive hormone secretion as the adverse effects of hormone secretion can be the dominant factor diminishing an individual NET or H-SSTR patient's quality of life and not infrequently their survival even when they have lower grade slowly growing tumours.
For example lower grade slowly growing NET 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 great morbidity related to diahorrea and malabsorption that is impossible to ameliorate with pharmacological and/or supportive treatments and may be disabled by bronchospasm. Intractable diahorrea is also a cause of serious morbidity in rare patients secreting vasoactive intestinal peptide (VIP). Diabetes, skin rash and steatorrhoea can cause major morbidity in rare 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.

  Although severe syndromes of hormone excess with fatal outcome are rare less severe syndromes of hormone excess are not uncommon within the NET population and patients with indolent G1 tumours may experience many years of poor quality of life due to poor control of the manifestation of their tumours' hormone secretion and/or the adverse effects of associated treatments.

- *Response to treatments applied and associated adverse effects of treatment*

Although, as a group, NET, including those with H-SSTR, and the other H-SSTR tumours 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 or H-SSTR 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.

From those perspectives the burden of disease associated with NET and H-SSTR is increased when patients are managed without access to guidance by an experienced MDT.

24. Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):

Treatment with ^{177}Lutetium(nca) Octreotate may be indicated for several patient groups who already have been diagnosed with NET or H-SSTR tumours who most commonly will have previously received one of more forms of local ablative or systemic therapy for their advanced disease.

1. 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

2. 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 Everolimus and/or Sunitinib
3. 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 chemotherapy
4. 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
5. Patients with NET who are experiencing reduced quality of life due to pain that is refractory to other therapies
6. Patients with NET who require systemic therapy but cannot tolerate treatment with somatostatin antagonists, the targeted agents Everolimus and Sunitinib, or chemotherapy
7. Patients with NET in whom neoadjuvant treatment may facilitate successful localised curative intent ablative therapies
8. Patients with advanced malignancy characterised by high somatostatin receptor expression such as neuroblastoma, phaeochromocytoma and paraganglioma whose outcomes may be improved by ^{177}Lutetium(nca) Octreotate treatment

Suitability for ^{177}Lutetium(nca) Octreotate treatment requires demonstration of high concentration of somatostatin receptors at all, or the majority of, tumour sites by imaging with suitable somatostatin targeting radiopharmaceuticals (SSTR imaging) using PET or SPECT scanning. For some patients with G2 tumours and patients with G3 tumours ^{18}FDG PET 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 tumourcidal/tumourostatic therapy.

The applicants propose that Medicare funding for ^{177}Lutetium(nca) Octreotate requires referral from a Multi-Disciplinary Team (MDT) experienced in managing patients with NET. This proposal is closely aligned with Neuroendocrine Carcinoma Australia's view that all patients with NET should have management guided by an experienced MDT. This referral pathway to ^{177}Lutetium(nca) Octreotate treatment recognises that early involvement of an expert MDT is highly desirable for maximal attainment of patient important outcomes. NET patients present a highly heterogeneous range of clinical problems and no single clinician has the expertise required to effectively and efficiently optimise management decisions at all stages of NET patients' treatment.

Early MDT guidance facilitates optimal investigation and treatment targeted to the needs of each patient. Effective guidance from an MDT usually requires extensive information including some or all of the following details:

- tumour pathology including tumour grade/ Ki-67 index
- current clinical features
- patient co-morbidities
- prior treatment history
- patient's treatment objectives and preferences
- serial imaging including appropriately timed SSTR imaging and CT and/or MRI depending on the nature and location of the patient's NET
- FDG PET/CT imaging in selected patients depending on the type of malignancy, tumour Grading, disease stage and clinical progress
- biochemical details of tumour status including chromogranin assays and assays relevant to particular form of excessive hormone secretion by a patient's NET
- background biochemical parameters including renal and liver function
- haematological parameters

PART 6b – INFORMATION ABOUT THE INTERVENTION

25. Describe the key components and clinical steps involved in delivering the proposed medical service/technology:

The theranostic specialist who supervises ^{177}Lutetium(nca) Octreotate therapy will often be a member, or regular attendee, of the MDT 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}Lutetium(nca) 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}Lutetium(nca) Octreotate treatment effects is current
- obtain formal patient consent for ^{177}Lutetium(nca) Octreotate treatment

26. On occasions due to equity of access considerations it is foreseeable that the patient referred for ^{177}Lutetium(nca) Octreotate will not be known to the supervising specialist and in that situation the specialist would be required to ensure that the MDT has properly identified patient suitability for the treatment by reviewing all the relevant patient details. The diagram below illustrates typical key components and clinical steps involved in ^{177}Lutetium(nca) Octreotate treatment (extracted from Bidakhvidi,N et al; doi.org/10.3390/ cancers14010129 (Open Access)**]**

^{177}Lutetium(nca) Octreotate administration is mostly conducted as an outpatient procedure. 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.

Upon attendance at the administration facility suitably equipped and staffed to undertake the delivery of the ^{177}Lutetium(nca) Octreotate radiopharmaceutical. Preferably such facilities would meet the standards specified in the appended document Australasian Association of Nuclear Medicine Specialists Position Statement on Practice of Theranostics in Australia -Version 1, dated February 2021 (AANMS Theranostics Position Paper). At a suitable facility the patient would have 2 intravenous cannulas inserted with appropriate process to ensure that extravasation of the radiopharmaceutical will not occur.

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.

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}Lutetium(nca) Octreotate administration to reduce kidney uptake of the radiopharmaceutical and continued for 3-4 hours after infusion of ^{177}Lutetium(nca) Octreotate, which is undertaken using a separate infusion pump and the second cannula.

The patient is monitored for vital signs and adverse reactions during the infusions of ^{177}Lutetium(nca) Octreotate and amino acid solution and for at least 3 hours following these infusions. Occasionally treatment emergent symptoms require additional medication or slowing the rate of the infusions.

At the completion of the ^{177}Lutetium(nca) 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.

For research purposes after each ^{177}Lutetium(nca) 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) provides optimal patient evaluation.

For routine clinical practice, when H-SSTR has been confirmed by obligatory pre-treatment PET or SPECT scanning, a single time point post ^{177}Lutetium(nca) Octreotate treatment SPECT/CT scan is ideally performed to identify “super-responders” after 2 treatment cycles. These patients have a high degree of tumour site early following treatment commencement and are unlikely to benefit further from proceeding to complete full “induction cycle” as the treatment target has already been largely ablated.

A typical induction, or initial treatment cycle of ^{177}Lutetium(nca) Octreotate involves 4 administrations of radiopharmaceutical separated by intervals of 6-8 weeks. In patients with a high disease burden at diagnosis and a favourable but incomplete response to 4 cycles of treatment, a further cycle of treatment may be considered worthwhile.

Older patients, particularly strong treatment responders may also receive abbreviated treatment schedules and the interval between ^{177}Lutetium(nca) Octreotate administrations may be adjusted to allow for haematological recovery if toxicity occurs. For G1 tumours in particular, cycles may be separated by up to 12 weeks.

After the induction course, follow-up is usually conducted after a 3-month interval when the patients 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}Lutetium(nca) Octreotate therapy.

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}Lutetium(nca) Octreotate
- the patient's clinical progress
- the results of biochemical monitoring test

27. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Currently GMP quality ^{177}Lutetium(nca) Octreotate manufactured by AMT does not have a trademark component however this is being investigated and is likely to associated with an Australian registered trademark Internationally, a similar radiopharmaceutical agent known as Lutathera is sponsored by Novartis.

28. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

29. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency)?

Determining patient suitability for ^{177}Lutetium(nca) Octreotate treatment requires confirmation that H-SSTR is present at all, or most tumour sites. This assessment must be done with either 68Ga Octreotate PET/CT or Octreoscan SPECT/CT imaging technique. These assessments require patient to attend a suitably equipped facility, imposing some limitation of patient access. The distribution of suitable imaging centres is more widespread than suitable ^{177}Lutetium(nca) Octreotate treatment centres and so this limitation is not seen as a major restriction to patient access for the proposed treatment. However, the current MBS for 68Ga Octreotate PET/CT or Octreoscan SPECT/CT imaging do not contemplate the use of these procedures for assessing suitability for ^{177}Lutetium(nca) Octreotate treatment. Accordingly, the wording of the MBS Item descriptors would need to be appropriately altered *or* the fee for these obligatory imaging procedures to determine patient suitability for treatment would need to be incorporated in the ^{177}Lutetium(nca) Octreotate treatment fee otherwise the out-of-pocket costs for the requisite pre-treatment imaging assessments would likely constrain patient accessibility for ^{177}Lutetium(nca) Octreotate treatment. The applicants consider that expanding the indications currently contemplated in the respective diagnostic imaging MBS Item descriptors to be the preferred method for allowing patient selection for ^{177}Lutetium(nca) Octreotate treatment.

It is proposed that ^{177}Lutetium(nca) Octreotate administration should be limited to patients referred by a formally-convened MDT that has expertise in the management of patients with NET. Treatments of other advanced H-SSTR malignancies should be referred from appropriate specialist practitioners such as endocrinologists or surgeons for phaeochromocytoma/paraganglioma or paediatric oncologists for neuroblastoma.

Specialists supervising the ^{177}Lutetium(nca) Octreotate administration should be suitably trained and accredited, optimally adhering to the recommendations of the AANMS Theranostics Position Paper.

Administering facilities performing ^{177}Lutetium(nca) Octreotate should be suitably staffed, equipped and licenced to ensure the safe administration of therapeutic radiopharmaceuticals, optimally conforming to the recommendations of the AANMS Theranostics Position Paper. These recommendations can be readily implemented at a scale that is sufficient to enable equitable access to patients who have been referred for ^{177}Lutetium(nca) Octreotate treatment.

Restricting Medicare funding for ^{177}Lutetium(nca) Octreotate administration to appropriately credentialled facilities and theranostic specialists, as proposed, will necessarily involve some limitation to patient access and increase the travel and dislocation burden particularly for patients in regional and rural areas. However, the applicants consider that the disadvantages of limiting ^{177}Lutetium(nca) Octreotate administration as specified in this application is more than compensated for by the benefit patients derive from a service delivery model that maximises quality of care.

The therapeutic is a sterile radioactive therapeutic product with a 4-day expiry from the time of manufacture. This product characteristic will not materially limit the availability of ^{177}Lutetium(nca) Octreotate treatment throughout Australia as the sponsors have well established logistics capability.

^{177}Lutetium(nca) Octreotate treatment after MDT referral will commonly be undertaken by an induction cycle of 4-5 infusions at 6-12 but typically 8-weekly intervals and a post treatment review 3 months later.

Further treatment with ^{177}Lutetium(nca) Octreotate may be instituted upon documentation of progression where the individual is willing to undergo further active treatment, has had a favourable response to the induction treatment course with no or clinically acceptable and self-limiting side-effects and has suitable tumour characteristics demonstrated on SSTR imaging with or without FDG PET/CT imaging. Usually repeat ^{177}Lutetium(nca) Octreotate treatments involve 2 administrations undertaken in the same manner as described for the induction cycle. SPECT/CT imaging is not necessarily required after the repeat ^{177}Lutetium(nca) Octreotate treatment however other in treatment and between treatment assessments follows the induction cycle program with an identical 3 month follow schedule.

Repeat treatments at documented progression can be undertaken occur until response failure is documented, unacceptable toxicity occurs or alternative treatments offer the prospect of superior patient important outcomes.

The frequency of repeat ^{177}Lutetium(nca) Octreotate treatment is necessarily highly variable but will be appropriately limited to achieve optimal outcomes when MDT referral is a mandatory requirement.

In some patients a 2 administration consolidation course of ^{177}Lutetium(nca) 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) NET with rising tumour markers. The requirement for MDT referral for consolidation treatment with ^{177}Lutetium(nca) Octreotate treatments will appropriately limit access to the medical service to patients most likely to benefit.

30. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

Administration of an amino acid infusion is required to reduce uptake of the product in the kidneys immediately prior to ^{177}Lutetium(nca) Octreotate administration.

Attendance of healthcare professionals skilled in the administration of therapeutic radiopharmaceuticals and associated patient care requirements is mandatory. A credentialled theranostic specialist should be available for consultation during the procedure and 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 administration facility.

31. If applicable, advise which health professionals will primarily deliver the proposed service:

See above. ^{177}Lutetium(nca) Octreotate administration requires the availability of a theranostic specialists appropriately credentialled for the administration of therapeutic radiopharmaceuticals, a nuclear medicine technologist and a trained nurse.

32. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

No

33. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

The applicants propose that the service should only be delivered by theranostic specialists trained and appropriately credentialled for the administration of therapeutic radiopharmaceuticals.

The decision to deliver the service to individual patients should be a shared decision between the patient and theranostic specialists following referral from a MDT with specific expertise in the management of NET patients and patients with related cancers demonstrating H-SSTR.

It is also proposed that the Medicare funded service should only be provided at appropriately equipped and qualified theranostic centres as detailed in the AANMS Theranostics Position Paper.

34. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

The proposed service should only be supplied by theranostic specialists who are trained and appropriately credentialled for the administration of therapeutic radiopharmaceuticals. The AANMS Theranostics Position Paper provides excellent guidance on optimal training of theranostic specialists.

35. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> relevant settings):

- ☒ Inpatient private hospital (admitted patient)
- ☒ Inpatient public hospital (admitted patient)
- ☒ Private outpatient clinic
- ☒ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☐ Laboratory
- ☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

The applicants propose that private or public organisations could satisfy the proposed centre of excellence requirements for Medicare funded service provision.

Generally, the service can be delivered to outpatients on a same day basis over period of 6-8 hours.

Rarely patients may require access to inpatient service to enable safe management of hormone excess syndromes that are pre-existing or have a significant risk of being precipitated as a result of administration.

36. Is the proposed medical service intended to be entirely rendered in Australia?

☒ Yes
☐ No

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

37. Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service):

This question is not directly relevant to the current Australian healthcare environment given the long history of ^{177}Lutetium(nca) Octreotate biosimilar use in Australia for patients with advanced NET and H-SSTR malignancies. Despite the lack of Medicare funding experienced specialists have increasingly referred these patients for treatment with ^{177}Lutetium(nca) Octreotate biosimilar treatment when they judge that better treatment outcomes are likely.

Currently treatment with ^{177}Lutetium(nca) Octreotate biosimilars is conducted at several sites throughout Australia including (Melbourne/Sydney/Brisbane/Adelaide/Perth). Treatment using this agent was first delivered in 2005 at the Peter MacCallum Cancer Centre and soon after at Fremantle Hospital in Western Australia. The Peter MacCallum Cancer Centre and Royal North Shore Hospital in Sydney have been accredited by the European Neuroendocrine Tumour Society as Centres of Excellence. Funding for ^{177}Lutetium(nca) Octreotate treatment in Australia is currently only provided by patients or by State healthcare systems.

The increasing utilisation of ^{177}Lutetium(nca) Octreotate treatment and commissioning of new treatment centres throughout Australia has resulted largely from accumulated local experience of highly favourable patient outcomes from selective implementation of this treatment. Increasing use of ^{177}Lutetium(nca) Octreotate treatment also reflects accumulating published evidence of efficacy mainly from retrospective studies and prospective registry type studies. More recently the NETTER-I Phase III randomised controlled trial has demonstrated the superiority of 177 (nca) Lutetium Octreotate treatment over somatostatin antagonist treatment and supported regulatory approval in the USA and European Union. Although the NETTER-1 study included only patients with mid-gut tumours, (i.e. neuroendocrine tumours of appendix, ileum, cecum and ascending colon), the subsequent indication for 177(nca)Lutetium Octreotate treatment was extended to also include pancreatic NET in the European Union.

Although PBS funded drugs Everolimus and Sunitinib are the most relevant comparators for ^{177}Lutetium(nca) Octreotate treatment for NET patients who have failed first line somatostatin antagonist treatment nominating these drugs as "appropriate comparators" invites a serious misconception about how best treatment outcomes are achieved for patients with advances NET and H-SSTR malignancies.

The unfortunate reality is that these patients have terminal malignancy and current treatments are not curative. Many patients will require treatment with *both* ^{177}Lutetium(nca) Octreotate treatment and "comparator to maximise the quality and duration of their lives. That is, ^{177}Lutetium(nca) Octreotate should not be considered as a "replacement" for comparator management strategies but rather as a valuable addition to the therapeutic armamentarium for patients with advanced NET.

In that context it is apparent that any choice between ^{177}Lutetium(nca) Octreotate and alternative treatment is more often sequencing decision rather than binary choice, a concept easily demonstrated by considering the management pathway charts provided in the Appendices.

In view of this decision-making complexity caused by the highly heterogeneous nature of advanced NET and H-SSTR malignancies, the highly variable clinical courses of different individuals and the difficulty developing high level evidence underlines the imperative for engaging experienced MDT's to guide every patient to the right treatment at the right time.

It is highly likely that the absence of Medicare funding has resulted in lower than optimal rates of ^{177}Lutetium(nca) Octreotate treatment utilisation and the implementation of this treatment in a less than ideal sequence with "comparator" treatments that are currently PBS funded.

As ^{177}Lutetium(nca) Octreotate treatment and "appropriate comparators" are very often used in sequence in patients with NET and associated H-SSTR malignancies the healthcare resource utilisation in

properly evaluated patients is largely similar. Many patients are able to reduce or cease use of Sandostatin LAR or Somatuline therapy, which is PBS-subsidised at a cost unknown to the applicants and similarly, targeted treatments with Everolimus and sunitinib are presumed to have high and ongoing monthly costs. ^{177}Lutetium(nca) Octreotate treatment, if amortised over the long progression free survival and low utilisation of secondary healthcare resources make this treatment a relatively cost-effective alternative.

38. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☐ Yes
☒ No

39. (a) Will the proposed medical service/technology be used in addition to, or instead of, the nominated comparator(s)?

☒ In addition to (i.e. it is an add-on service)
☐ Instead of (i.e. it is a replacement or alternative)

(b) If yes, please outline the extent to which the current service/comparator is expected to be substituted

See the response to 36- in most patients the proposed medical service will be used in addition to current services and comparators however the sequence of utilisation will vary for different patients

PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)s

40. Define and summarise the CURRENT clinical management pathway (algorithm) that patients follow when they receive the COMPARATOR service (i.e. the landscape before the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current clinical management pathway), but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g. pharmaceuticals, diagnostics and investigative services, etc.).

As ^{177}Lutetium(nca) Octreotate treatment is already in use in Australia in multiple locations and has regulatory approval in the USA and European Union it is not helpful to consider "the landscape *before* the proposed service is introduced".

As most patients will receive both ^{177}Lutetium(nca) Octreotate treatment and comparator treatments during the course of their advanced incurable malignancy, there will be little difference is healthcare resource utilisation. It is probable that patients whose management is guided by an experienced MDT will achieve better treatment outcomes with more efficient use of overall health care resources.

2 algorithms extracted from ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of Gastropancreatic neuroendocrine neoplasms [Pavel, M et al; doi.org/10.1016/j.annonc.2020.03.304 (Open Archive)] have been extracted below to demonstrate how current best practice guidance recommends the integration of ^{177}Lutetium(nca) Octreotate treatment (PRRT) with other potentially effective treatments for patients with advanced NET and H-SSTR malignancies and for patients with carcinoid syndrome.

The applicant contends that the best practice algorithms included here illustrate well the complexity of optimal management strategies for patients afflicted 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}Lutetium(nca) Octreotate treatment.

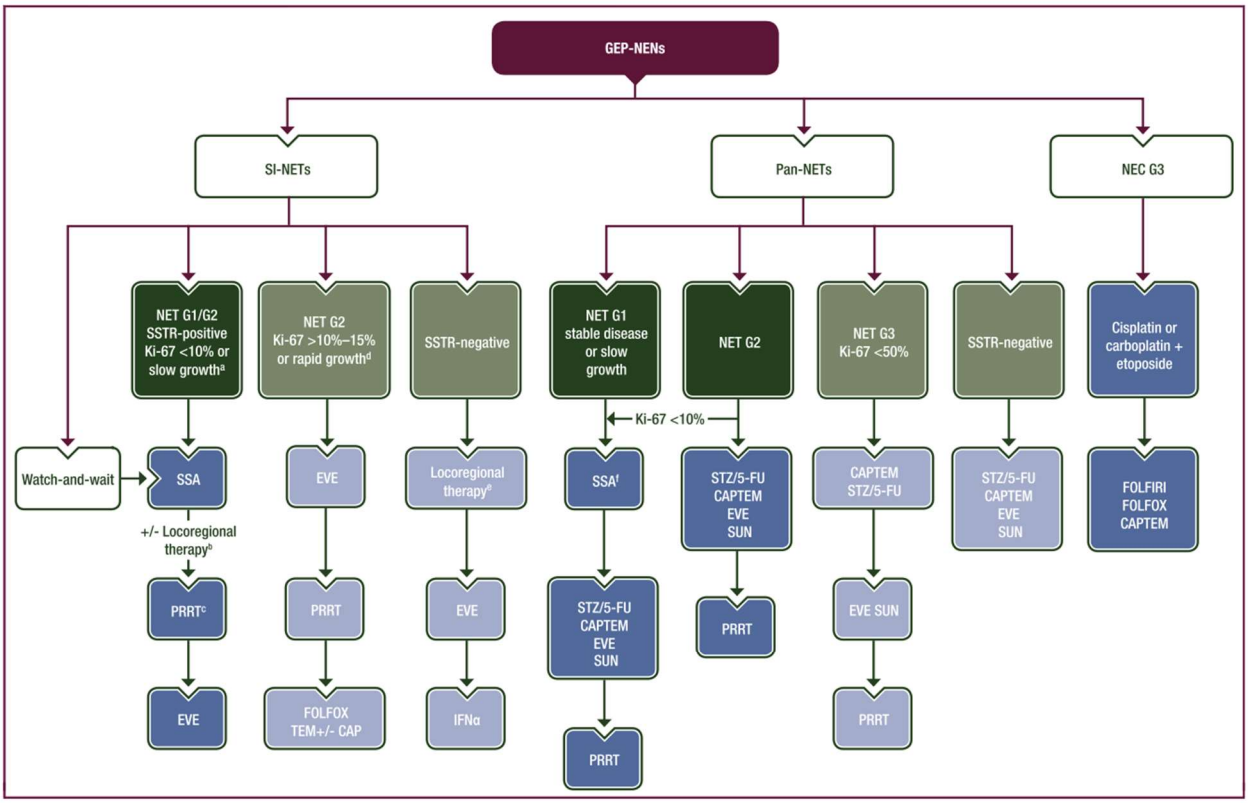

Figure 4. Systemic therapy in GEP-NENs.
The stratification factors are not predictive, but prognostic.
A watch-and-wait approach is recommended in asymptomatic low-grade tumour patients with absence of morphological progression. Locoregional therapy may be considered as an alternative approach to systemic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

Source: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of Gastropancreatic neuroendocrine neoplasms [Pavel, M et al; doi.org/10.1016/j.annonc.2020.03.304 (Open Archive)]

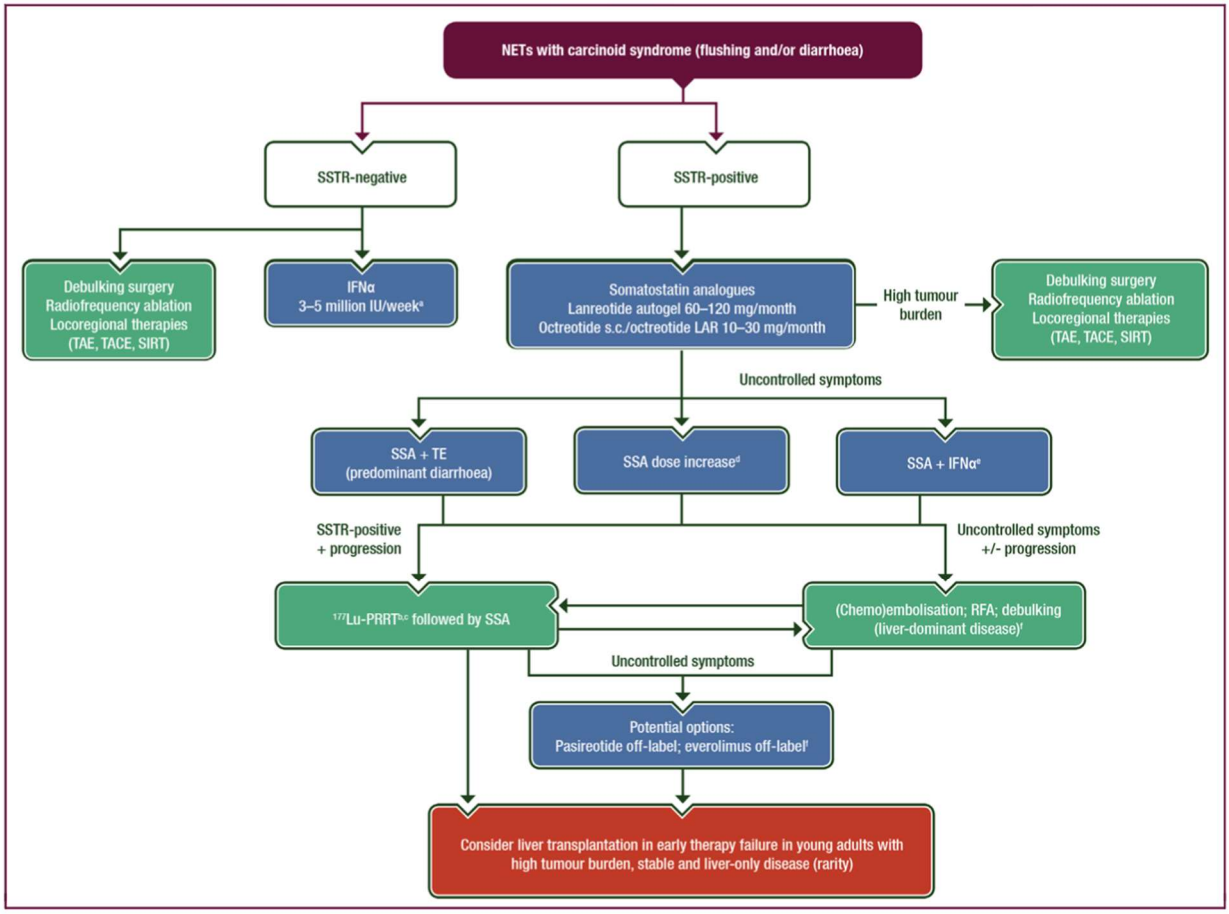

Figure 3. Therapeutic approach in NETs with carcinoid syndrome.
^{177}Lu, lutetium-177; IFN-α, interferon alpha; LAR, long-acting release; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; s.c., subcutaneous; SIRT, selective internal radiotherapy;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

Source: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of Gastropancreatic neuroendocrine neoplasms [Pavel, M et al; doi.org/10.1016/j.annonc.2020.03.304 (Open Archive)]

41. Define and summarise the PROPOSED clinical management pathway (algorithm) that patients would follow <u>after</u> the proposed service/technology is introduced, including variation in health care resources.

Please see response to 39.

<u>PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES</u>

42. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

In suitable patients ^{177}Lutetium(nca) Octreotate treatment improves patient's quality of life

In suitable patients ^{177}Lutetium(nca) Octreotate treatment results in greater reduction of morbidity related to excessive secretion of hormonal products than relevant comparator treatments

In suitable patients ^{177}Lutetium(nca) Octreotate treatment results in improved progression free and overall survival duration than relevant comparator treatments

^{177}Lutetium(nca) Octreotate treatment has less severe and less frequent related treatment emergent adverse effects than relevant comparator treatments

^{177}Lutetium(nca) Octreotate treatment does not increase kidney or other organ dysfunction at a greater rate than relevant comparator treatments

^{177}Lutetium(nca) Octreotate treatment results in a greater incidence (2-3% incidence) than relevant comparator treatments of myelodysplastic syndrome that may precede fatal blood dyscrasias

43. Please state what the overall clinical claim is:

Compared to alternative active and supportive care strategies ^{177}Lu(nca)octreotate treatment improves quality of life and extends the duration of life in suitable patients with H-SSTR defined by molecular imaging.

44. List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Quality of Life

Symptomatic control of excess hormone secretion and bone pain

Survival Duration (overall and progression free)

Biomarkers relevant to patient important outcomes including Chromogranin A and specific hormones secreted to excess (insulin, gastrin, somatostatin, VIP, CARCINOID)

Related Treatment Emergent Adverse Effects

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

45. Estimate the prevalence and/or incidence of the condition in the proposed population:

Michael et al identified all NET from the Victorian Cancer Registry over four time periods: 1982–1989, 1990–1999, 2000—2009, and 2010–2019. Data collected included primary tumour site, histological grade, gender, overall survival (OS), and place of residence. Incidence data were analysed with the generation of annual standardized rates (ASR). OS was assessed for the entire cohort and between geographical regions.

The overall NET population (1982–2019) included 8,106 patients: over 60% grade 1/2 NENs, especially small bowel and colorectal. The number of new diagnoses increased over three-fold over time for the overall cohort and by tumoral categories. The ASR increased similarly, especially pancreatic NENs (4.3-fold) and differed between genders. The 5-year OS rates and median OS increased over time for the overall cohort: from 52% to 67% ($p < 0.001$). OS was greater for NEN patients residing in major cities relative to regional/remote areas ($p = 0.01$).

See: doi: 10.1111/ajco.13671.

46. Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:

In most patients and induction course of 177Lu (nca) Octreotate involves 4-5 administrations 6-12 weeks apart and this is the maximum number of services that would be usually administered to an individual patient in a single year.

47. How many years would the proposed medical service/technology be required for the patient?

This is highly variable in this heterogeneous disease and depends upon;

The individual patient response to the induction treatment cycle

The tumour grade and associated rate of tumour progression

The uncommon occurrence of treatment limiting adverse effects

The occurrence of tumour de-differentiation to forms that do not demonstrate high somatostatin receptor expression

The severity and tempo of patient symptoms of pain or related to the effects of excess hormone production.

Some patients, particularly patients with G1 and G2 tumours who respond well to ^{177}Lutetium(nca) Octreotate treatment, survive for over a decade when ^{177}Lutetium(nca) Octreotate treatment is used optimally in combination with best supportive care and other active treatments such as where indicated.

48. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

Data from Peter MacCallum Cancer Centre ENETS Centre of Excellence servicing predominantly Victoria and Tasmania approximately 300 PRRT administrations were performed in 2019 and 2020, with slightly lower numbers in 2021 due to COVID-19 limitations on Tasmanian travel and travel restrictions.

The administrations involved patients for induction ^{177}Lutetium(nca) Octreotate treatment (approximately 80% receiving 4 administrations), re-treatment (approximately 10% receiving 2 administrations) and “maintenance” (approximately 10% receiving one administration).

It could be projected on the basis of this data that approximately 55 patients would utilise the proposed medical service in the first year of operation at established centres serving a population base of approximately 7 million people, so approximately 200 patients per year would be projected to utilise the proposed service when a network of suitable centres for treatment was fully established across Australia. However, it is unlikely that *in the first year of operation* this projected total number of patients who

would ultimately utilise the service per year would be reached, therefore the applicant's estimate is that 150 patients would utilise the service in the first year of operation.

49. Estimate the anticipated uptake of the proposed medical service/technology over the next three years, factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors), as well as provide commentary on risk of 'leakage' to populations not targeted by the service.

See response 47. If the recommendation that access to the medical service is restricted to patients referred by a formally convened MDT with experience in management of NET patients, there is very little risk of 'leakage' to populations not targeted by the service.

PART 8 – COST INFORMATION

50. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The cost of ^{177}Lutetium(nca) Octreotate supply from AMT is $8000 per 7.4 GBq standard treatment dose.

Other costs related to providing the proposed medical service are identified in the attached Table and the applicants suggest that these services would be billed separately using existing or appropriately modified Item numbers that would allow the necessary associated services to be billed through the MBS.

Medical Service Type	Always required (Yes/No)	Aligned to existing Item number	Cost
^{177}Lutetium(nca) Octreotate supply costs	Yes	No	$8000
Imaging to confirm H-SSTR pre-treatment costs	Yes	61647/61505. Alteration of Item descriptor required	$953/$100
		61369/61505. Alteration of Item descriptor required	2015.75/100
FDG PET/CT imaging costs	No. Mainly required for patients with G3 NET who may be otherwise suitable for ^{177}Lutetium(nca) Octreotate treatment	61598 (rare tumour type)	$953/$100
Blood Tests required for suitability screening and in-treatment monitoring costs	Yes. Variable requirements depending on the type of NET	65070 (FBC)	$16.95
		66512 (Biochemistry)	$17.70
		66779 (5HIAA, adrenaline etc)	$39.95
		No. Chromogranin A	
Theranostic Specialist Consult ation pre-treatment cost	Yes	110	$161.90
Attendance at specialist theranostic centre for ^{177}Lutetium(nca) Octreotate cost	Yes	13950. Alteration of Item descriptor required	$114.20
Non-admitted patient facility cost	Yes	Yes. Alteration of Item descriptor required	
Amino Acid Infusion supply cost	Yes	No.	

SPECT/CT post ^{177}Lutetium(nca) Octreotate administration cost	No. Recommended after second ^{177}Lutetium(nca) Octreotate administration to identify hyper-responders	61642/61505. Alteration of Item descriptor required	$129/$100
Imaging to assess response to ^{177}Lutetium(nca) Octreotate treatment cost	Yes. Not all modalities are required in every patient. Most commonly Items 61647/61505 and/or 56807 are applied	61647/61505 with alteration of Item descriptor	$953/$100
		61369/61505 with alteration of Item descriptor	2015.75/100
		56807	$582.70
		63546	$558.80
Theranostic specialist consultation post-treatment cycle completion cost	Yes	105	$46.15

51. Specify how long the proposed medical service/technology typically takes to perform:

6-8 hours for each treatment administration

52. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and usage characteristics that defines eligibility for the medical service/technology.

Category T3-Therapeutic Nuclear Medicine
Item 16020 ^{177}Lutetium(nca) Octreotate treatment for patients with advanced Neuroendocrine Tumour and other High Somatostatin Receptor expressing tumours when recommended by an experienced Multidisciplinary Team Fee: $8,000

53. If public funding is sought through an alternative (non-MBS) funding arrangement, please draft a service description to define the population and usage characteristics that defines eligibility for the service/technology.

N/A