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Advising on new medicines for Scotland
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NHS SCOTLAND
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lutetium (^{177}Lu) oxodotreotide 370MBq/mL solution for infusion (Lutathera®)

SMC No 1337/18

Advanced Accelerator Applications

8 June 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

lutetium (^{177}Lu) oxodotreotide (Lutathera®) is accepted for use within NHS Scotland.

Indication under review: for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.

In an open-label, phase III study, lutetium (^{177}Lu) oxodotreotide significantly improved progression-free survival compared with a high dose somatostatin analogue in patients with progressive midgut neuroendocrine tumours.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chairman
Scottish Medicines Consortium

Published 9 July 2018

Indication

For the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults.[1]

Dosing Information

The recommended treatment regimen of Lutathera® in adults consists of four intravenous infusions of 7,400MBq each. The recommended interval between each administration is eight weeks which could be extended up to 16 weeks in case of dose modifying toxicity (DMT).[1]

For renal protection purpose, an amino acid solution must be administered intravenously during four hours. The infusion of the amino acid solution should start 30 minutes prior to start of Lutathera® infusion. Details are provided in the summary of product characteristics (SPC). Premedication with antiemetics should be injected 30 minutes before the start of the amino acid solution infusion.[1]

Lutathera® should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings and after evaluation of the patient by a qualified physician.

Before starting treatment with Lutathera®, somatostatin receptor imaging (scintigraphy or positron emission tomography [PET]) must confirm the overexpression of these receptors in the tumour tissue with the tumour uptake at least as high as normal liver uptake (tumour uptake score ≥ 2).[1]

Product availability date

4 December 2017

Lutathera® has been designated an orphan medicinal product by the European Medicines Agency (EMA)

Summary of evidence on comparative efficacy

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are a heterogeneous group of rare tumours arising from the diffuse neuroendocrine system, classified according to their embryonic origin in the gastrointestinal (GI) tract, pancreas or lungs. They are graded according to mitotic activity to low or intermediate (Grade 1 or 2 which are well- or moderately differentiated) and high (Grade 3 which is poorly differentiated) and subcategorised into functional (when the hypersecretion of biologically active substances results in clinical carcinoid symptoms) or non-functional (when these symptoms are absent). The somatostatin-2 (SST2) receptor is frequently over-expressed in NETs and provides a target for treatment.[2]

^{177}Lutetium oxodotreotide (hereafter referred to as Lutathera®) is ^{177}Lu-labelled somatostatin tumour-targeted peptide receptor radionuclide therapy (PRRT) agent. Oxodotreotide comprises the somatostatin peptide analogue, octreotate, which targets the SST2 receptors, coupled to the metal-ion chelating moiety DOTA, radiolabelled with the beta-emitting radionuclide, ^{177}lutetium. The high affinity for SST2 receptors delivers ^{177}lutetium to the cancer cells. ^{177}lutetium is a gamma-ray and β- emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm). This is sufficient to kill targeted tumour cells with a limited effect on neighbouring normal cells.[1-3]

The key evidence to support the use of Lutathera® in NETs comes from one randomised, open-label, phase III study (NETTER-1) in 229 patients with inoperable, metastatic or locally advanced, progressive midgut NET. Eligible patients were aged at least 18 years with centrally confirmed midgut NET with somatostatin receptors on target lesions. They had received a fixed dose of octreotide long-acting release (LAR) 20 to 30mg every three to four weeks for at least the previous 12 weeks and had evidence of disease progression (according to Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), They had Ki67 index of ≤20% (indicating low or intermediate [grade 1 or 2] disease) and had a Karnofsky performance score of ≥60. Patients were randomised equally to receive Lutathera® (four doses of 7,400MBq; one infused every eight weeks) plus best supportive care (BSC, which including octreotide LAR 30mg after each dose of Lutathera® and then every four weeks thereafter) or high dose octreotide (60mg every four weeks). Treatment with BSC in the Lutathera® group and high dose octreotide in the control group continued until disease progression, unacceptable toxicity or death. In the Lutathera® group, an intravenous amino acid solution was administered with the Lutathera® infusion for renal protection.[2, 3]

The primary outcome was progression-free survival (PFS) which was defined as time from randomisation to disease progression, assessed by independent central radiological review using RECIST version 1.1, or death for any cause. At the primary PFS analysis (cut-off date 24 July 2015), a PFS event had occurred in 18% (21/116) of Lutathera® and 62% (70/113) of octreotide 60mg LAR patients. The median PFS had not been reached in the Lutathera® group and was 8.5 months in the octreotide 60mg LAR group; hazard ratio 0.18 (95% confidence interval [CI]: 0.11 to 0.29). At an updated, post hoc PFS analysis (cut-off date 30 June 2016), a PFS event had occurred in 26% (30/117) of Lutathera® patients and 68% (78/114) of octreotide 60mg LAR patients. The median PFS was 28.4 months and 8.5 months respectively; hazard ratio 0.21 (95% CI: 0.14 to 0.33).[1, 2]

Overall survival was a secondary outcome and at the time of the primary PFS analysis (cut-off date 24 July 2015), 15% (17/116) of Lutathera® patients and 27% (31/113) of octreotide 60mg LAR patients had died. The median overall survival had not been reached in the Lutathera® group and was 27.4 months in the octreotide 60mg LAR group; hazard ratio 0.46 (95% CI: 0.25 to 0.83). At the updated analysis (cut-off date 30 June 2016), 24% (28/117) of Lutathera® patients and 38% (43/114) of octreotide 60mg LAR patients had died: median overall survival had not been reached and was 27.4 months respectively; hazard ratio 0.54 (95% CI: 0.33 to 0.86).[1, 2]

Objective response rate (ORR), defined as the proportion of patients with centrally assessed complete or partial responses, was achieved by 13% (15/116) of Lutathera® patients and 3.5% (4/113) of octreotide 60mg LAR patients, p=0.014) at the time of the primary PFS analysis (cut-off date 24 July 2015). This included one complete response in the Lutathera® group only. In responding patients, the median duration of response had not been reached in the Lutathera® group and was 1.9 months in the octreotide 60mg LAR group.[2]

Quality of life was assessed using the European Organisation for Research and treatment of Cancer Quality of Life core questionnaire (EORTC QLQ-C30) and the European Organisation for Research and treatment of Cancer Quality of Life core questionnaire for gastrointestinal neuroendocrine tumours (EORTC QLQ-G.I.NET21) questionnaires. Results, presented in abstract form, indicate that there were clinically and statistically significant improvements in scores for global health status and diarrhoea and a trend towards improvement in pain scores in the Lutathera® group compared to the octreotide 60mg LAR group.[10]

Supportive evidence was provided from a single-centre, single-arm, open-label, phase I/II study (ERASMUS) performed in the Erasmus Medical Centre in Rotterdam, Holland between January 2000 and December 2012. It assessed the efficacy and safety of Lutathera® used on a compassionate use basis in patients with somatostatin receptor positive tumours and histologically proven GEP- or bronchial-NETs and a Karnofsky performance score of ≥50. All patients received four intravenous doses of Lutathera® (7,400MBq) at six to thirteen week intervals to a maximum cumulative dose of 29.6GBq.[2]

A total of 1,214 patients were enrolled but the main analysis was performed in the subgroup of 811 Dutch patients since they had the most complete and accurate data. This included 360 patients who had received at least one treatment and had a baseline tumour assessment (FAS population). Results of efficacy outcomes for the total FAS population and by primary NET origin are detailed in the table 1 below. Approximately half of the FAS population were reported to have progressive disease at baseline and available results are also presented in the table 1 below.[2]

Table 1: ERASMUS results for the FAS population and for the FAS population with progressive disease where available[1, 2, 4]

	ORR	PFS (months)	OS (months)
FAS Dutch population with or without progressive disease			
All GEP-NET (n=360)	45% (162/360)	28.5	61.2
Pancreatic NET (n=133)	61% (81/133)	30.3	66.4
Foregut NET (n=12)	58% (7/12)	43.9	-
Midgut NET (n=183)	33% (61/183)	28.5	54.9
Hindgut NET (n=13)	46% (6/13)	29.4	-
Bronchial NET (n=19)	37% (7/19)	18.4	50.6
FAS Dutch population with progressive disease*			
All GEP-NET	-	29.8	60.2
Pancreatic NET	-	35.6	80.7
Midgut NET		28.4	49.0

ORR=objective response rate; PFS=progression-free survival; OS=overall survival; FAS=full analysis set; GEP-NET=gastroenteropancreatic neuroendocrine tumours; NET=neuroendocrine tumours.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the NETTER-1 study, a treatment emergent adverse event was reported in 95% (106/111) of Lutathera® and 86% (95/110) of octreotide 60mg LAR patients and these were considered treatment-related in 86% (95/111) and 31% (34/110) of patients respectively. Serious adverse events occurred in 26% (29/111) and 24% (26/110) of patients respectively. Study discontinuation due to adverse events was reported in 6.3% (7/111) of Lutathera® and 9.1% (10/110) of octreotide 60mg LAR patients and due to treatment-related adverse events in 4.5% (5/111) and no patients respectively.[3]

The most commonly reported adverse events in the Lutathera® and octreotide 60mg LAR groups respectively were: nausea (59% versus 12%); vomiting (47% versus 10%); fatigue or asthenia (40% versus 25%); diarrhoea (29% versus 19%); musculoskeletal pain (29% versus 20%), abdominal pain (26% versus 26%); thrombocytopenia (25% versus 0.9%); lymphopenia (18% versus 1.8%); decreased appetite (18% versus 8.2%); headache (16% versus 4.5%); peripheral oedema (14% versus 7.3%) and anaemia (14% versus 5.4%).[3]

The incidence of individual grade 3 or 4 adverse events were reported as generally similar in the two treatment groups. However the following haematological grade 3 or 4 adverse effects were reported with Lutathera® and no octreotide 60mg LAR patients: lymphopenia (9.0%), thrombocytopenia (1.8%), leukopenia (0.9%) and neutropenia (0.9%).[3]

In the ERASMUS study, safety information was not recorded routinely, and safety analyses presented were produced in a re-evaluation of patient data. In the full Dutch population (n=811), 14 cases (1.7%) of myelodysplastic syndrome (MDS) were diagnosed and were considered possibly or probably related to the treatment. In two of these cases, the patients received two extra treatments (exceeding 29.7 GBq) and in both cases the MDS was considered related to the additional treatments. The incidence of serious renal disorders related to Lutathera® was 0.4% (three cases) in this Dutch population.[2]

Summary of clinical effectiveness issues

GEP-NET patients with early stage disease are often asymptomatic or present with poorly defined symptoms. Consequently, at the time of confirmed diagnosis, a significant percentage of GEP-NET patients have hepatic metastases. However patients with grade 1 or 2 GEP-NETs can have a prolonged or intermediate prognosis. Typically, the clinical management involves a multi-modal approach including surgery, embolisation, chemo-embolisation, radiotherapy and medical treatment with chemotherapy and somatostatin analogues.[2]

In patients with progressive disease following somatostatin analogues, the most likely treatments are sunitinib and everolimus. Sunitinib has a marketing authorisation for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.[5] Everolimus has marketing authorisation for the treatment of unresectable or metastatic, well- or moderately-differentiated NETs of pancreatic origin in adults with progressive disease and for unresectable or metastatic, well-differentiated (grade 1 or grade 2), non-functional NETs gastrointestinal or lung origin in adults with progressive disease.[6] There are few other treatment options for patients with advanced disease. Clinical experts consulted by SMC highlighted an unmet clinical need for effective and well tolerated therapies in this rare tumour type. Lutathera® is the first PRRT medicine with marketing authorisation in the UK. Lutathera® meets SMC orphan criteria.

In the pivotal NETTER-1 study, in patients with advanced midgut NETs, Lutathera® significantly improved the primary outcome, PFS, compared with octreotide 60mg LAR.[2, 3] However this may not be a relevant comparator for clinical practice in Scotland. At the time of the primary analysis, the data in the Lutathera® group were immature with only 18% of Lutathera® patients having had a PFS event. Although median PFS had not been reached, the results significantly favoured Lutathera®. The post-hoc updated analysis confirmed that PFS was statistically significantly and clinically improved with Lutathera® compared with octreotide 60mg LAR.[2] Available results for the secondary outcome of overall survival are immature but significantly favour Lutathera®. The EMA noted that 30 patients in the octreotide 60mg LAR group received Lutathera® under a different programme and acknowledged the implications on overall survival[2]. Final overall survival results are awaited.[1, 2]

The key evidence for GEP-NETs for patients with pancreatic, foregut and hindgut NET comes solely from the results of the ERASMUS study which is limited by its single-arm, compassionate use design. While ERASMUS included the whole GEP-NETs population reflecting the marketing authorisation, the numbers of patients with foregut and hindgut tumours was small (n=12 and 13 respectively). In addition, a further subgroup of approximately half of the FAS population of ERASMUS had progressive disease reflecting the licence. The European Medicines Agency (EMA) noted that although the numbers of patients with foregut and hindgut NETs were small, the results appeared to be in-line with pancreatic and midgut NETs and were considered supportive for these subpopulations given that the rare nature of the disease.[1, 2]

Patients with brain metastases were excluded from both studies. Therefore, efficacy results of Lutathera® cannot be extrapolated to patients with known brain metastases, for which individual benefit-risk must be assessed.[1, 2]

Patients are required to have adequate renal function before treatment with the proposed dosing regimen of Lutathera® to maximize elimination and prevent unnecessary radiation exposure to the whole body. Somatostatin analogue peptides used in PRRT are known to be partially retained in the kidney and the kidney is described as a “critical organ” for radiotoxicity. During the studies and according to the marketing authorisation, Lutathera® is administered with an amino acid solution to significantly reduce (by about half) the radiation absorbed dose to the kidneys, limiting possible kidney toxicities. Without adequate renal function, the co-infusion of amino acid solution could not be effective.[1, 2]

The risk of developing MDS and acute leukaemia is noted in the SPC, along with potential risks and or predictive factors. The EPAR notes that post-authorisation safety data to investigate secondary malignancies will be collected.[1, 2]

The SPC notes that hormonal crises due to excessive release of hormones or bioactive substances may occur after Lutathera® treatment and that overnight hospitalisation for observation may be required for some patients.[1]

There are no direct data comparing Lutathera® with everolimus and sunitinib. The submitting company performed a matching adjusted indirect comparison (MAIC) to compare Lutathera® with everolimus, sunitinib and BSC in patients with pancreatic (P)-NETs using three studies, including ERASMUS for Lutathera® (the only evidence in P-NET patients). Lutathera® was compared with everolimus, sunitinib and BSC in terms of PFS and overall survival using patient-level data (reweighted based on some, but not all, prognostic factors and effect modifiers) from the ERASMUS study. Limitations include concern that the prediction models and subsequent matching may be poor and that the sample sizes after matching were small. A mixed treatment comparison (MTC) was also performed to compare Lutathera® with everolimus in patients with gastrointestinal (GI)-NETs to support sensitivity analysis in the economic analysis. This used two studies, including NETTER-1 for Lutathera®, and assumed the equivalence of octreotide LAR 60mg and BSC. Limitations include differences between the patient study populations in relation to the types of NETs, somatostatin receptor and functioning/non-functioning status and previous treatments. The hazard ratios for the MTC results for PFS and overall survival had wide credible intervals making it difficult assess the true value of the comparison between Lutathera® and everolimus.

Clinical experts consulted by SMC consider Lutathera® to be a therapeutic advancement in this disease area where few effective treatment options currently exist. They highlighted impressive improvements in PFS and median overall survival together with minimal toxicity.

Before starting treatment with Lutathera®, somatostatin receptor imaging (scintigraphy or positron emission tomography [PET]) must confirm the overexpression of these receptors in the tumour tissue with the tumour uptake at least as high as normal liver uptake (tumour uptake score ≥ 2).[1] This is part

of the routine management of patients with GEP-NET. It should be noted that there are considerable service implications associated with the handling and administration of radiopharmaceuticals within nuclear medicine departments. Receipt, storage, use, transfer and disposal are subject to regulations and/or appropriate licences of competent official organisations. Although these processes are likely to already be in place, there are likely to be implications associated with the administration of an additional agent.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group and clinical specialist representation was held to consider the added value of Lutathera®, as an orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- The majority of patients with GEP-NETs are diagnosed late and there are limited available treatments for patients with progressive disease following somatostatin analogues.
- The debilitating symptoms of GEP-NETs, particularly diarrhoea, flushing, extreme fatigue and pain, have a severe impact on daily living and negatively affect the quality of life of patients, their families and carers.
- Lutathera® is an innovative, targeted treatment which addresses an unmet need. Clinicians noted that, compared with high dose octreotide LAR, it has shown a remarkable improvement in progression-free survival from 8 to 28 months. They also advised that Lutathera® has produced durable symptomatic, radiological and biochemical responses.
- Lutathera® must be administered with an amino acid solution for renal protection. Clinicians advised that a new formulation of amino acid solution is now available which is associated with a lower rate of adverse events than reported in the NETTER-1 study and has greatly improved the tolerability of this treatment.
- Lutathera® is expected to be better tolerated than available targeted therapy. This, together with improved control of NET disease and symptoms, would allow patients to regain control of life, allow them to enjoy family life, care for children and continue to work. This has the potential to have a major impact on improving quality of life, both physically and emotionally.
- It was noted that Lutathera® treatment will need to be administered in a specialist centre by a team familiar with radionuclides. However, based on experience of a local feasibility study, the PACE participants anticipated that the delivery of Lutathera® will be straightforward.

Additional Patient and Carer Involvement

We received patient group submissions from the NET Patient Foundation and The Ann Edgar Charitable Trust. The NET Patient Foundation is a registered charity and the Ann Edgar Charitable Trust is a charitable trust. The NET Patient Foundation has received 14% pharmaceutical company funding in the past two years with none from the submitting company. The Ann Edgar Trust has not received any funding from pharmaceutical companies in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis which compared Lutathera® against best supportive care (BSC), everolimus and sunitinib in unresectable or metastatic GEP-NETs with disease progression. In the economic analysis, the GEP-NET population was separated into GI-NET patients, where Lutathera® was compared against BSC, and P-NET patients where the comparators included BSC, sunitinib and everolimus. It is worth noting that BSC reflected use of octreotide in both patient populations, and a sensitivity analysis versus everolimus was also presented for the GI-NET population.

A partitioned survival model was used to evaluate the cost-effectiveness of Lutathera® versus the comparators. The model included three health states: progression free survival (PFS), post-progression survival (PPS) and death. All patients started the economic analysis in the PFS health state and patients could remain in a health state, progress to a worse health state, or die, in the analysis. The time horizon used in the model reflected 20 years.

The clinical data used in the analysis included the NETTER-1 study, the ERASMUS study, and a MAIC. The NETTER-1 study included head to head data for Lutathera® versus BSC and was used to model the efficacy of each treatment in the GI-NET population. The ERASMUS study was used to inform the efficacy of Lutathera® in P-NET patients; however ERASMUS was a single arm study and therefore the relative efficacy of the comparators required the MAIC. Specifically, the application of the MAIC included re-weighting patient level data from the progressive P-NET Dutch population from ERASMUS, to produce survival data which were considered reflective of a population aligned with the comparator trials.

The economic analysis also required the extrapolation of shorter term study data over the duration of the economic model using parametric functions. In the GI-NET and P-NET populations the PFS and OS data were mainly extrapolated using Weibull functions, apart from the comparison with sunitinib which used the exponential curve, with treatment effect captured as a hazard ratio.

Utility values were taken from a published study and the utility values for PFS and PPS were 0.771 and 0.612 respectively. Disutilities due to adverse events were included in the analysis.

Medicine costs were included in the analysis as were administration, monitoring and adverse event costs.

A PAS is in place for both sunitinib and everolimus and these were included in the results used for decision-making by the SMC by using an estimate of the PAS price of sunitinib and everolimus. The estimate of the PAS price for sunitinib was based on information that is in the public domain.

The base case results in the GI-NET population and selected sensitivity analyses were as follows:

Table 2: Base case results GI-NET

Comparator	Inc. Costs	Inc. QALY	ICER
BSC	£35,701	1.33	£26,830

Table 3: Selected sensitivity analysis versus BSC (GI-NET patients)

Analysis	ICER
5 year time horizon	£47,013
Medicine costs of Lutathera® plus octreotide	£38,181
10 year time horizon	£35,986
MTC Lutathera® versus octreotide	£34,478
MTC Lutathera® versus everolimus	£39,169 (everolimus at list price)

The base case results in the P-NET population and selected sensitivity analyses were as follows:

Table 4: Base case results P-NET

Comparator	Inc. Costs	Inc. QALY	ICER
Sunitinib	£34,269	1.96	£17,487
Everolimus	£37,472 (everolimus at list price)	1.44	£26,103 (everolimus at list price)
BSC: using data from sunitinib study	£65,452	2.61	£25,068
BSC: using data from everolimus study	£50,293	1.68	£29,964

Table 5: Selected sensitivity analysis versus BSC, sunitinib and everolimus (P-NET patients)

Analysis	Sunitinib	Everolimus	BSC*	BSC**
5 year time horizon	£26,904	£40,597 (everolimus at list price)	£37,273	£48,073
Medicine costs of Lutathera® plus octreotide	£36,644	£46,161 (everolimus at list price)	£37,686	£47,138
100% dose intensity	£22,822	£33,490 (everolimus at list price)	£29,149	£36,303
10 year time horizon	£16,923	£27,887 (everolimus at list price)	£26,774	£33,123

* using data from sunitinib study
** using data from everolimus study

The results presented do not take account of the PAS for everolimus but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for everolimus due to commercial confidentiality and competition law issues and hence the results are presented for these comparisons using the list prices of Lutathera® and everolimus.

The main weaknesses were:

- The NETTER-1 study and the indirect comparison estimated hazard ratios which captured the relative treatment effect for Lutathera® versus the comparators. The extrapolation of shorter term trial data over the duration of the time horizon (using parametric functions) also included estimating a hazard ratio in order to apply a treatment effect in the economic model over the longer term. However the hazard ratios presented in the clinical data/indirect comparison were not always consistent with the hazard ratios estimated in the long term extrapolation used in the economic evaluation. The company suggested that the variation in the hazard ratios between the clinical data/indirect comparison versus the economics were a result of the different methods used to estimate treatment effects i.e. cox-regression versus parametric functions (specifically the Weibull or exponential functions). The SMC Statistical Advisor noted differences in results may be expected due to the various methods employed by the company; however the inconsistency in the estimated treatment effect may also be considered a weakness.
- Lutathera® is a radiopharmaceutical and the company did not initially provide enough detail or comprehensively discuss how the costs and resource use related to radiopharmaceuticals were captured in the analysis. However, following consideration of SMC Clinical Expert responses and additional information subsequently provided by the company, the economic analysis adequately captured the costs of delivering Lutathera®.
- In NETTER-1 patients received Lutathera® plus octreotide (30mg) and the economic model omitted the cost of concomitant octreotide (i.e. BSC).
- The time horizon used in the analysis reflected 20 years which may be considered long in relation to the median overall survival in the ERASMUS study.

The Committee also considered the benefits of Lutathera® in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission and a substantial improvement in quality of life. In addition, as Lutathera® is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted Lutathera® for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Additional information: guidelines and protocols

The Scottish Neuroendocrine Tumour Group published 'Consensus guidelines for the management of patients with neuroendocrine tumours' in February 2015 and updated the guidance in July 2015.[8] The guideline was developed by NHS Scotland, with financial support for publication provided by Novartis. This recommends somatostatin analogues for the first-line medical treatment of NETs. Everolimus may be considered in patients with progressing pancreatic NETs where the tumour is well or moderately-differentiated and the patient is of PS 0, 1 or possibly 2 with adequate organ function. Sunitinib may be considered in patients with progressing pancreatic NETs where the tumour is well -differentiated and the patient is of PS 0 or 1 with adequate organ function. Interferon-alfa should be reserved as a second-line agent for symptomatic relief in patients who fail to tolerate or show no benefit from somatostatin analogue therapy. In terms of chemotherapy, the guideline notes that there is wide variation in the chemosensitivity of different types of NET. Anatomical location, grade and proliferation index help to determine the choice of chemotherapy and timing of interventions. The guideline also notes that radiolabelled somatostatin analogues (DOTATOC and DOTATATE) can be used to treat patients with significant disease demonstrated on 111In-octrotide scintigraphy and acceptable renal function. However, there are currently no Scottish centres that routinely offer this treatment. Radionuclide therapy

is recommended. All radionuclide treatments must occur within purpose-built facilities under the supervision of trained staff with expertise in the care of patients undergoing treatment with radiopharmaceuticals. However, at the time of publication there were no Scottish centres that routinely offer this treatment.

This guideline predates the marketing authorisation for everolimus for GI- and lung-NETs and for Lutathera®.

The European Neuroendocrine Tumour Society (ENETS) published "ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site" in January 2016.[9] This generally recommends somatostatin analogues as first-line systemic therapy and everolimus and sunitinib as a first-line therapy, when somatostatin analogues are not as option. Everolimus or sunitinib are generally recommended after failure of somatostatin analogues or chemotherapy in pancreatic NET. In intestinal NET, everolimus may be used as a second-line therapy after failure of somatostatin analogues or as a third-line therapy after failure of PRRT. Data from the NETTER-1 study in midgut NET support the recommendation of PPRT as a second-line treatment option in intestinal NET if the general requirements for PRRT are fulfilled and as an alternative option to everolimus.

The National Institute for Health and Care Excellence (NICE) issued a multiple technology appraisal on the use of everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease in June 2017. This guidance, which recommends the use of sunitinib and everolimus within their marketing authorisations, is valid for NHSScotland.[7]

Additional information: comparators

Everolimus and sunitinib

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
Lutathera®	Four intravenous infusions of 7,400MBq administered at eight week intervals	71,500
Everolimus	10mg orally daily continuously	2,495 (4 weeks)
Sunitinib	37.5mg orally daily continuously	2,354 (4 weeks)

Doses are for general comparison and do not imply therapeutic equivalence. Costs for Lutathera® are from the company submission. Costs for everolimus and sunitinib are from eMIMS on 12 March 2018. The median duration of everolimus treatment in the pivotal GI-NET and P-NET studies was approximately 40 weeks. The median duration of sunitinib treatment in the pivotal P-NET study was approximately 20 weeks. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated that 308 patients would be eligible for treatment in year 1 reducing to 60 in year 5 to which confidential uptake rates were applied.

The gross impact on the medicines budget was estimated to be £428k in year 1 rising to £1.0m in year 5. As other medicines are expected to be displaced the net medicines budget impact is expected to be £421k in year 1 rising to £818k in year 5.

Following consideration of SMC Clinical Expert responses patient numbers may be overestimated in year 1.

*Other data were also assessed but remain commercially confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 April 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.