National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression [ID858]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Imaging Equipment	Yes, this topic is appropriate for NICE appraisal as there are limited treatment options for patients with this rare disease. Over the past three years, there has been a high level of national and international support for Lu-177 DOTATATE. This is demonstrated by the endorsement of Lu-177 DOTATATE as a therapeutic option by the European Neuroendocrine Tumour Society (ENETS), the British Society of Gastroenterology and the European Society for Medical Oncology (ESMO) in their treatment guidelines (Öberg et al. 2012, Pavel et al. 2016, Ramage et al. 2012).	Comments noted.
	Novartis	This topic is highly appropriate given that neuroendocrine tumours (NETs) is a disease area that has not been previously assessed by NICE. There is an urgency for the institute to review this topic to ensure that patients receive access to effective medicines in an area where there is a clear unmet clinical need, particularly in NETs of lung origin.	Comments noted.

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	Pfizer	Pfizer consider it appropriate for this topic to be referred to NICE for appraisal.	Comment noted.
Wording	Imaging Equipment	Yes, the remit broadly does reflect the intended license.	Comment noted.
	Novartis	The wording of the remit is appropriate i.e. unresectable or metastatic neuroendocrine tumours with disease progression and reflects the interventions included in the scope.	Comment noted.
	Pfizer	People with unresectable or metastatic neuroendocrine tumours and whose disease has progressed represent a heterogeneous population [1]. It is now accepted that pancreatic neuroendocrine tumours (NETs) and non-pancreatic NETs (often termed 'carcinoid') should be regarded as separate clinical entities, despite sharing many characteristics. Grade 3 pancreatic NETS are further deemed by the clinical community as a separate tumour type, not covered in the clinical data/marketing authorisation for either everolimus or sunitinib. Furthermore, the marketing authorisations of both everolimus and sunitinib are restricted to the subpopulation of patients with pancreatic NETs only of Grade 1 and 2 as per WHO classification (or Ki67<20% (a marker of tumour proliferation) [2, 3]. Therefore, Pfizer recommend the remit reflects the need to differentiate treatment of pancreatic NETs from carcinoid tumours as follows: "To appraise the clinical and cost effectiveness of everolimus, lutetium-177 DOTATATE and sunitinib within their marketing authorisation for treating unresectable or metastatic neuroendocrine tumours of pancreatic or non-pancreatic origin"	Comments noted. This topic has been referred for appraisal with the current remit. The current remit is broad and does not exclude any possible population or indication for the treatments being appraised. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the marketing authorisations of the interventions.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Imaging Equipment	***Is the proposed approach of amending the remit to remove lanreotide appropriate?*** ***Is octreotide an appropriate comparator for this appraisal?*** We agree with the proposed approach of amending the remit to remove lanreotide from the appraisal and we would also propose that NICE remove octreotide as a comparator. Somatostatin analogues are not used in the patient population selected for this MTA. Octreotide has the same mechanism of action as lanreotide and is used in the same position in the treatment pathway. Unlike the interventions included in the scope, lanreotide and octreotide when used in this population of progressive patients, only aim to provide symptomatic relief rather than improve progression free survival. It is therefore accepted that if lanreotide is removed, octreotide should be removed as well. This was a consensus amongst stakeholders (clinical and industry) at the Stakeholder Information Meeting in Manchester on Tuesday 12 July 2016. The choice of relevant comparators in NICE appraisals are based on treatments most likely to be displaced in clinical practise. Neither octreotide/lanreotide would be displaced and would continue to be used for	Comments noted. Based on the feedback received at the stakeholder information meeting (SIM) and during consultation octreotide has been removed as a comparator in this appraisal.

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		symptomatic relief in addition to the other interventions in this MTA. If NICE wish octreotide to be assessed, it should be in a separate STA, in line with lanreotide, for treating unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours without disease progression [ID 961]. In the pivotal trials of sunitinib, everolimus and Lu-177 dotatate, most or all of the patients had received and/or progressed on octreotide or lanreotide as a prior therapy. Lanreotide and octreotide have been licensed since 2001 and 1998 respectively, and are have been considered the standard of care in NETs as a first-line, therapy in non-progressive patients for many years.	
	Novartis	***Is the proposed approach of amending the remit to remove lanreotide appropriate?*** It is appropriate to remove lanreotide from the remit given that the remit of this appraisal is people with unresectable or metastatic NET whose disease has progressed. Current clinical guidelines (UKINETs1 and ENETs2) recommend the somatostatin analogues (SSA's) lanreotide and octreotide-LAR as first-line systemic therapies in the treatment of unresectable NETs, and everolimus, sunitinib and lutetium-177 DOTATATE (Lu-177) as second or third-line therapies following disease progression on a somatostatin analogue. Consequently lanreotide is received earlier in the treatment pathway prior to the other interventions included in this appraisal and is not an appropriate	Comments noted. Based on the feedback received at the stakeholder information meeting (SIM) and during consultation octreotide has been removed as a

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		comparator for these targeted therapies. We understand that the institute is proposing to conduct a separate appraisal for the SSA's3 and agree that this is the most appropriate approach. ***<u>Is octreotide an appropriate comparator for this appraisal?</u>*** Due to the rapidly evolving treatment landscape in NET, Octreotide-LAR is not an appropriate comparator for the interventions everolimus, lutetium-177 DOTATATE and sunitinib in this appraisal, because of the remit of this appraisal and the respective positioning of the interventions and comparators in the treatment pathway. As described previously, current clinical guidelines recommend the SSA's earlier in the treatment pathway, and the targeted therapies everolimus (GI, lung and pancreatic NET), sunitinib (pancreatic NETs) and Lu-177 (GI NETs) following disease progression on a SSA1, 2. Consequently, the SSA's are outside the remit of this appraisal (unresectable NET with disease progression). We acknowledge that at the time the pivotal trial for Lu-177 (NETTER-1)4 was initiated, the somatostatin analogues were considered the standard of care; however NETTER-1 compared Lu-177 plus 30mg octreotide LAR with 60mg octreotide-LAR, an unlicensed dose. Furthermore, following the results of the RADIANT-45 trial and the licensing of everolimus as a new treatment option for progressive metastatic GI (and lung) NETs, the treatment pathway in NETs has since evolved, with the SSA's no longer considered to be an	comparator in this appraisal.

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		appropriate comparator for Lu-177 in GI NETs. This is further supported by current clinical guidelines which position everolimus and Lu-177 as alternative treatment options for patients who progress on a SSA2, however we acknowledge that the evidence base for everolimus and Lu-177 is lacking, and in the absence of head-to head randomised clinical trials or a common comparator in RADIANT-4 and NETTER-1 trials, any comparisons between the two therapies are difficult. Finally, it should be noted that since current clinical guidelines considers a class effect for the SSA's2, If octreotide-LAR is to remain a comparator in this appraisal, then lanreotide should also be considered as a comparator, given that clinical opinion considers these therapies as interchangeable. Due to the paucity of data in this setting, it should be noted that the evidence base does not necessarily reflect current clinical practice.	
	Pfizer	Pfizer believe that all the relevant comparators have been identified. However, as outlined above, due to differences in marketing authorisation and evidence base the appropriateness of comparisons will need to be considered for each sub-population of interest, for example by tumour grade or location. ***Is the proposed approach of amending the remit to remove lanreotide appropriate?*** <u>Pfizer consider the proposed approach of removing lanreotide (Somatuline LA; Somatuline Autogel) appropriate:</u>	Comments noted. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the existing and anticipated marketing authorisations of the interventions.

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		Somatuline LA is indicated for “the relief of symptoms associated with neuroendocrine (particularly carcinoid) tumours.” [4]. Somatuline Autogel is indicated for “the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded**,** in adult patients with unresectable locally advanced or metastatic disease” [5] based on evidence in the CLARINET trial [6], and for the “treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours”. The marketing authorisation for lanreotide is broad but Pfizer will not compare sunitinib with lanreotide (Somatuline LA or autogel) as these are used for symptomatic relief in NET patients and in the PNET patients that sunitinib is indicated in, there is no evidence for the use of lanreotide autogel. The selection of this treatment clinically is based on whether the patient has a functional (symptomatic) PNET and a positive octreotide scan. Furthermore, the PNET patients in the CLARINET study [6] had non-progressive disease (Ki67 <2%) representing the patient at an earlier stage of their cancer and not comparable to the time where sunitinib may be selected as appropriate therapy for the patient (Ki67<20%). ***Is octreotide an appropriate comparator for this appraisal?*** Octreotide (Sandostatin LAR) is a potentially relevant treatment for a subgroup of patients included in the appraisal, but should not be compared to sunitinib. It is licensed for “treatment of patients with advanced neuroendocrine tumours of the midgut or of unknown primary origin where non-midgut sites of origin have been excluded” [7]. Patients were excluded from the pivotal PROMID trial if their primary tumour was within the pancreas, chest, or elsewhere. Therefore, octreotide (Sandostatin LAR) is not an	Based on the feedback received at the stakeholder information meeting (SIM) and during consultation octreotide has been removed as a comparator in this appraisal.

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		appropriate comparator for sunitinib in patients with tumours of pancreatic origin.	
	British Nuclear Medicine	We support the removal of Lanreotide LAR from the above MTA. ***Rationale*** Whilst Lanreotide LAR has been shown to have significant anti-proliferative tumour effect over placebo in the CLARINET study (Caplin et al, 2014), current guidelines (ENET3 Guidelines 2016) support the ise of this systemic therapy (and the similar drug ocretodie LAR) as a means of controlling the symptoms from functionally active neuroendocrine neoplasms such as carcinoid syndrome and symptoms arising from functionally active pancreatic NETs. In addition, in the case of patients with refractory symptoms, these patients may have already undergone maximal dose escalation of this drug, prior to any documented anatomical disease progression. The recent guidelines also state that it is current practice to combine SSA with other therapies in functionally active neuroendocrine neoplasms, when the latter have been used second line. As outlined above, in accordance with current guidelines, many patients are already receiving Lanreotide prior to disease progression, or continue to receive it in conjunction with other therapeutic agents included in the assessment. We therefore consider it inappropriate in include lanreotide in	Comments noted. Based on the feedback received at the stakeholder information meeting (SIM) and curing consultation lanreotide has been removed as an intervention in this appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		the MTA with everoiimus, sunitinib and lutetium-177 Dotatate and support its omission. References 1. Lanreotide in metastatic enteropancreatic neuroendocrine tumours. Caplin et al. NEJM; 371:224-233 2. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Pavel et al, Neuroendocrinology 2016; 90: 172-185	
	NCRI/RCP/RCR /ACP	***Is the proposed approach of amending the remit to remove lanreotide appropriate?*** Our experts are supportive of the change. Excluding both octreotide and lanreotide is sensible as they are generally used in different clinical situations from those where everolimus, sunitinib and PRR T are indicated ***Is octreotide an appropriate comparator for this appraisal?*** No.	Comments noted. Based on the feedback received during the stakeholder information meeting (SIM) and during consultation lanreotide has been removed as an intervention and octreotide has been removed as a comparator in this appraisal.
Additional	Novartis	References	Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
comments on the draft scope		1. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012;61:6-32. 2. Pavel M, O'Toole D, et al ENETs Consensus Guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchialneuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology Jan 2016 3. Communication from NICE, July 2016 4. Ruszniewski P. Abstract LBA6 NETTER-1 phase III: Progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-Dotatate.Presented at ECCO/ESMO 2015 5. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016:968-77.	
	Pfizer	References 1) Kulke et al. 2011. Future directions in the treatment of neuroendocrine tumors: Consensus report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting. J Clin Oncol 29:934-943. 2) SPC Sutent, 2016. http://www.medicines.org.uk/emc/medicine/18531 Accessed August 2016. 3) SPC Afinitor, 2016. http://www.medicines.org.uk/emc/medicine/22281. Accessed August 2016. 4) SPC Lanreotide (somatuline LA), 2016. http://www.medicines.org.uk/emc/medicine/877/SPC/Somatuline+LA.	Comments noted.

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		Accessed August 216 5) SPC Lanreotide (autogel), 2016. https://www.medicines.org.uk/emc/medicine/25104. Accessed August 2016 6) Caplin ME, et al. July 2014. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. NEJM; 371:224-233 7) SPC Octreotide, 2016. http://www.medicines.org.uk/emc/medicine/20029. Accessed August 2016.	