National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lutetium-177 DOTATATE for treating unresectable, somatostatin receptor-positive non-progressive gastroenteropancreatic neuroendocrine tumours

Response to consultee and commentator comments on the remit and scope

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	Advanced Accelerator Applications	Yes this topic is appropriate for NICE appraisal as there are limited treatment options for patients with this rare disease.	Comment noted.
	British Nuclear Medicine Society	Yes. This treatment is widely used in the UK and Europe. Although the treatment has been regarded as more useful for patients with documented progression of metastatic disease, there is increasing pressure to treat patients with no obvious evidence of progression as well. The principle of treating patients when they are fitter rather than when they have deteriorated and sometimes more significantly is a recognised issue in clinical practice.	Comment noted. This technology is also being considered for disease progression in a separate multiple technology appraisal alongside other treatments.
	Novartis Pharmaceuticals	The 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 ensure that patients receive access to effective	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Ltd	medicines.	
	Royal College of Pathologists	Yes, this is appropriate	Comment noted.
Wording	Advanced Accelerator Applications	Yes, the remit does broadly reflect the intended licence.	Comment noted.
	British Nuclear Medicine Society	No. Nuclear Medicine resources must be costed.	Comment noted. The wording of the remit is usually broad and does not describe the specific cost components of the cost-effectiveness analysis.
	Novartis Pharmaceuticals Ltd	The wording of the remit is appropriate ie unresectable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression	Comment noted.
	Royal College of Pathologists	Yes	Comment noted.
Timing Issues	Advanced Accelerator Applications	GEPNETs constitute a life-threatening disease, and functioning GEPNETs are associated with debilitating clinical symptoms. Therefore this appraisal should be reviewed by NICE so that guidance is available to the NHS in a timely manner.	Comment noted. NICE aims to provide draft guidance to the NHS for cancer drugs within 90 days of the marketing authorisation of the

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			technology.
	British Nuclear Medicine Society	Urgent. The number of treatments for adult neuroendocrine tumours has increased from 130 to 355 pa from 32007 to 2012 in the UK (Rojas et al Nuc Med Commun 36(8):761-765) and continues to increase. Cancer survival statistics support the concept of improving quality of life and this technology lends itself directly to such an approach.	Comment noted. NICE aims to provide draft guidance to the NHS for cancer drugs within 90 days of the marketing authorisation of the technology.
	Novartis Pharmaceuticals Ltd	As discussed previously, there is urgency for the institute to appraise this topic in a timely fashion in light of the limited treatment options for patients in this disease area	Comment noted. NICE aims to provide draft guidance to the NHS for cancer drugs within 90 days of the marketing authorisation of the technology.
	Royal College of Pathologists	Relatively important	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background	Advanced Accelerator	The background information is accurate.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
information	Applications		
	British Nuclear Medicine Society	Yes	Comment noted.
	Novartis Pharmaceuticals Ltd	The background information is described accurately	Comment noted.
	Royal College of Pathologists	Accurate	Comment noted.
The technology/ intervention	Advanced Accelerator Applications	The description of the technology is accurate, however the following text is suggested for inclusion: Mechanism of action / Pharmacodynamic effects: Lu-177 DOTATATE has a high affinity for subtype 2 somatostatin receptors (sst2) regardless of progression status. It binds to malignant cells which overexpress sst2 receptors. Lu-177 DOTATATE is a β- emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted tumour cells with a limited effect on neighbouring normal cells Lu-177 DOTATATE has been studied in a two clinical trials; the first was in a single arm study in people with unresectable, somatostatin receptor-positive neuroendocrine tumours with or without disease progression, and secondly, in people with inoperable, locally advanced or metastatic somatostatin receptor positive midgut neuroendocrine tumours (Ki67 ≤ 20%) with disease progression only, compared with octreotide long acting release (LAR). The	Comment noted. This section of the scope aims to provide a brief description of the technology; additional details may be included in the company's evidence submission, at the time of the appraisal. However, the scope has been amended to state that the treatment is designed to deliver radiation to the cells.

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		latter trial, NETTER-1, did not include non-progressive patients. The method of action of the therapy is the same in progressive and non-progressive patients.	
	British Nuclear Medicine Society	Not sufficient. The statement '[Lu-177 DOTATATE] kills tumour cells by binding to a specific type of somatostatin receptor, called sst2 receptors, which are overexpressed by the malignant cells' does not mention that the treatment delivers radiation to these cells. As such, the effectiveness of treatment depends on the radiation dose delivered and therefore the level localisation.	Comment noted. The scope has been amended to state that the treatment is designed to deliver radiation to the cells.
	Novartis Pharmaceuticals Ltd	The intervention is defined appropriately	Comment noted.
	Royal College of Pathologists	Yes	Comment noted.
Population	Advanced Accelerator Applications	Yes the population has been accurately defined.	Comment noted.
	British Nuclear Medicine Society	Yes. Although the current cohort is correctly identified. The clinical urgency for cancer teams is to provide guidance also for the patient population with documented progression of disease.	Comment noted. This technology is also being considered for disease progression in a separate multiple technology appraisal alongside other

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			treatments.
	Novartis Pharmaceuticals Ltd	The population is defined as adults with unresectable, somastatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression; however there is limited clinical evidence to support an appraisal of lutetium-177 DOTATATE in this patient population. The only phase III clinical trial supporting the registration of lutetium-177 DOTATATE (NETTER-1) included patients with progressed disease and is therefore outside the remit of this current appraisal. Furthermore, clinical evidence for patients without disease progression is limited to a single arm phase I/II trial, which included patients with or without disease progression and is not as a robust source of evidence to conduct an appraisal for patients with non-progressed disease. We are aware that lutetium-177 DOTATATE in patients with somastatin receptor-positive gastroenteropancreatic neuroendocrine tumours with disease progression is subject to a separate appraisal (ID858). Given the limited evidence base for lutetium-177 DOTATATE in patients without disease progression, we suggest that the institute terminate this current appraisal (ID857) and only appraise lutetium-177 DOTATATE according to the available evidence in patients with progressive disease.	Comment noted. NICE has received a formal referral to appraise this technology for this indication. Any decision to proceed or terminate the appraisal will be guided by the marketing authorisation of the technology or any other factors identified by the marketing authorisation holder of the technology.
	Royal College of Pathologists	Yes	Comment noted.
Comparators	Advanced Accelerator Applications	We recommend that aside from watchful waiting/ observational protocol that only treatments affecting the neuroendocrine tumours are included i.e. somatostatin analogues in the list of comparators and that symptomatic relief for functional tumours are excluded. This is because specific symptomatic treatment for functional tumours is not administered in isolation but given	Comment noted. Stakeholders agreed that these comparators were appropriate at this point in the treatment

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		adjunctively with SSAs or Lu-177 DOTATATE.	pathway. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal.
	British Nuclear Medicine Society	An alternative treatment, although not commercially available, is Y-90 DOTATATE (used in 6 UK centres in 2012). I-131 mIBG has been widely used in the past. Some centres are also using Y90 microsphere therapies for liver predominant disease.	Comment noted. Treatments that are not commercially available would not normally be included as comparators. Please see the Guide to the Methods of Technology Appraisal for details on how appropriate comparators are selected.
	Novartis Pharmaceuticals	The draft scope proposes octreotide-LAR (long-acting release formulation) and lanreotide as comparators for lutetium-177 DOTATATE in GI NETs without disease progression, and lanreotide for pancreatic NETs without	Comment noted. Stakeholders agreed

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	Ltd	disease progression. These analogues are inappropriate comparators for the following reasons: • As described previously, the evidence base for lutetium-177 DOTATATE in patients without disease progression is limited. • There is no phase III randomised clinical trial of octreotide-LAR in the stable disease setting (patients without disease progression) • Lanreotide is the only somatostatin analogue with robust clinical evidence in non-progressive disease (CLARINET[1]), however in UK clinical practice and in current European NET guidelines[2], PRRT therapy is often initiated following disease progression on a somatatostatin analogue. • Consequently the NETTER-1 and CLARINET trials cannot be used for any clinically meaningful comparison.	that these comparators were appropriate at this point in the treatment pathway. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal.
	Royal College of Pathologists	Yes	Comment noted.
Outcomes	Advanced Accelerator Applications	Yes.	Comment noted.
	British Nuclear Medicine Society	Yes	Comment noted.
	Novartis	The outcome measures to be considered are appropriate.	Comment noted.

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	Pharmaceuticals Ltd		
	Royal College of Pathologists	Yes	Comment noted.
Economic analysis	Advanced Accelerator Applications	We are in early stages of planning our economic case so cannot comment yet.	Comment noted.
	British Nuclear Medicine Society	Economic analysis must take full account of the patient journey including nuclear medicine costs, including radiopharmacy, imaging, dosimetry and nursing as well nuclear medicine physician resources. The BNMS can provide full costings.	Thank you for your comments. Consultees are encouraged to provide all relevant evidence in their written submissions.
	Novartis Pharmaceuticals Ltd	The economic analysis is appropriate and consistent with the NICE reference case.	Comment noted.
Equality and Diversity	Advanced Accelerator Applications	There are no equity issues to raise.	Comment noted.
	British Nuclear Medicine Society	No issues	Comment noted.
	Novartis	No Comment	Comment noted.

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	Pharmaceuticals Ltd		
Innovation	Advanced Accelerator Applications	Lu-177 DOTATATE is being used in clinical practice in England and is considered a valuable therapeutic option for patients with unresectable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression. This applies particularly in cases where: - [redacted]	Comment noted. If there are additional health effects associated with this treatment that are not captured in the QALY calculation, evidence may be provided in the submissions and will be considered by the committee accordingly.
	British Nuclear Medicine Society	The technology is innovative and as with many radiopharmaceutical therapy procedures under used. It offers the potential for a substantial cost-effective impact on health benefit.	Comment noted. If there are additional health effects associated with this treatment that are not captured in the QALY calculation, evidence may be provided in the submissions and will be considered by the committee accordingly.
	Novartis Pharmaceuticals Ltd	No Comment	Comment noted.

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	Royal College of Pathologists	Yes	Comment noted.
Other considerations	Advanced Accelerator Applications	No comment.	Comment noted.
	British Nuclear Medicine Society	A key question to consider is the administration schedule, as the effectiveness of Lu-177 DOTATATE is dependent on how it is used and the radiation doses delivered to tumours and to normal organs. The concept of recording administered radiation dose in the patient record needs to be reiterated.	Comment noted.
	Novartis Pharmaceuticals Ltd	No Comment	Comment noted.
Questions for consultation	Advanced Accelerator Applications	**Have all relevant comparators been included in the scope? In particular, which treatments are considered to be established clinical practice in the NHS for gastroenteropancreatic neuroendocrine tumours without disease progression?** According to the UK BSG guidelines for NETs, the only available treatment for patients with non-progressive unresectable GEP-NETs is watchful waiting in asymptomatic patients and somatostatin analogues in symptomatic patients prior to progression (Ramage et al. 2012). **The use of lutetium-177 DOTATATE is conditional on the presence of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours. Is the diagnostic testing for somatostatin receptor-positive**	Stakeholders agreed that these comparators were appropriate at this point in the treatment pathway. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been

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		neuroendocrine tumours considered to be established clinical practice in the NHS? Yes, it is established clinical practice in the NHS. There are over 40 hospitals in England conducting diagnostic testing with Tc-99m Tektrotyd, In-111 Octreotide or Ga-68 DOTATATE or DOTATOC. This is also in the guidelines (Ramage Gut 2012;61:6) **Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom lutetium-177 DOTATATE are expected to be more clinically effective and cost effective or other groups that should be examined separately?** No subgroup analysis has been decided at this point in time.	kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. Comment noted.
	British Nuclear Medicine Society	In answer to questions for consultation: Diagnostic testing with radiopharmaceuticals is standard practice. In particular, Ga-68 Peptide PET is increasingly used and could potentially inform personalised treatment. Evidence should include multi-centre trials to establish radiation doses.	Comment noted.
	Novartis Pharmaceuticals Ltd	*Have all relevant comparators been included in the scope? In particular, which treatments are considered to be established clinical practice in the NHS for gastroenteropancreatic neuroendocrine tumours without disease progression?* As discussed previously in the comparators section, the somatostatin analogues are inappropriate comparators for gastroenteropancreatic neuroendocrine tumours without disease progression. *The use of lutetium-177 DOTATATE is conditional on the presence of*	Stakeholders agreed that these comparators were appropriate at this point in the treatment pathway. Therefore in line with the Guide to the methods of

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		somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours. Is the diagnostic testing for somatostatin receptor-positive neuroendocrine tumours considered to be established clinical practice in the NHS? We believe that diagnostic testing for somatostatin receptor positive NETs is considered routine practice prior to treatment with lutetium-177 DOTATATE. We recommend this is verified by a NET clinical expert. *Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom lutetium- 177 DOTATATE are expected to be more clinically effective and cost effective or other groups that should be examined separately?* No comment	technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. Comment noted.
Additional comments on the draft scope	Advanced Accelerator Applications	[redacted] [redacted].	The information relating to the regulatory approval of technology has been noted and will remain confidential as requested.
	Novartis Pharmaceuticals Ltd	No comment	Comment noted.