NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lu-177 dotatate for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using Lu-177 dotatate in the NHS in England. The appraisal committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: July 2017

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using Lu-177 dotatate in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: **24 August 2017**

Second appraisal committee meeting: **27 September 2017**

Details of membership of the appraisal committee are given in section 6.

Lu-177 dotatate was originally appraised as part of NICE's technology appraisal guidance on everolimus and sunitinib (TA449), a multiple technology appraisal (MTA). NICE could not release any recommendations on Lu-177 dotatate because it did not have a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use. To avoid delaying TA449 Lu-177 dotatate was removed from the MTA, to be considered separately by the committee.

1 Recommendations

1.1 Lu-177 dotatate is not recommended, within its marketing authorisation, for treating unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours in adults.

1.2 This recommendation is not intended to affect treatment with Lu-177 dotatate that was started in the NHS before this guidance was published. Adults having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

NETs can affect the pancreas, gastrointestinal tissue and lungs and are difficult to diagnose and treat. They can significantly affect emotional health and often mean that people are unable to work.

Clinical trial evidence shows that Lu-177 dotatate is effective for treating midgut gastrointestinal NETs compared with octreotide long-acting release. However, the results of an indirect comparison of Lu-177 dotatate with everolimus and best supportive care were very uncertain because the trials included were not comparable.

Cost-effectiveness estimates for Lu-177 dotatate compared with everolimus and best supportive care were much higher than what NICE normally considers acceptable, that is, between £20,000 and £30,000 per quality-adjusted life year gained. Lu-177 dotatate does not meet NICE's criteria to be considered a life-extending treatment at the end of life. Therefore, it cannot be recommended.

Lu-177 dotatate is not suitable for use within the Cancer Drugs Fund because it is unlikely to be cost effective at its current price. Collecting outcome data from patients in the NHS would not add useful information to the current evidence from the clinical trial.

2 The technology

	Lu-177 dotatate (Lutathera, AAA)
Marketing authorisation	The Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorisation for Lu-177 dotatate for 'unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults.'
Recommended dose and schedule	Lu-177 dotatate is administered as an intravenous infusion. A single cycle consists of 4 infusions of 7.4 GBq The recommended interval between 2 infusions is 8 weeks (±about 1 week).
Price	Anticipated list price is commercial in confidence.

3 Committee discussion

The appraisal committee (section 6) considered evidence from a number of sources. See the committee papers for full details of the evidence.

Clinical need and current practice

People with NETs will welcome new treatment options because of high unmet need

3.1 The committee understood that neuroendocrine tumours (NETs) can affect the pancreas, gastrointestinal tissue and lungs. They are difficult to diagnose and treat, can significantly affect emotional health and often mean that people are unable to work. It also heard from a patient expert that there is increasing frustration among people with advanced progressive NETs because of the recent restriction on targeted treatments that were previously available through the Cancer Drugs Fund. The patient expert explained that Lu-177 dotatate is a very effective treatment with tolerable side effects, which allowed people to live a relatively normal life. The committee concluded that there is a recognised need for treatment for NETs at different sites.

Everolimus, sunitinib and best supportive care are appropriate comparators

3.2 The committee heard from the clinical experts that managing NETs in the NHS follows the European Neuroendocrine Tumor Society's guidelines. For treating pancreatic NETs causing symptoms (functional NETs) in people with progressive disease, options include everolimus and Lu-177 dotatate. For non-functional pancreatic NETs, the guidelines suggest Lu-177 dotatate or chemotherapy for progressive disease after offering everolimus or sunitinib. For treating functional and non-functional advanced gastrointestinal NETs in people with progressive disease, the guidelines suggest Lu-177 dotatate as an option with everolimus, and interferons. The clinical experts explained that although interferons may be considered in people with progressive disease, they are not routinely used in England because of their toxicity. The clinical experts further explained that chemotherapy is sometimes used if people have symptoms because of the bulk of their disease (mainly people with high disease burden with a Ki-67 proliferative index of around 20% or more, that is, grade 3 tumours). This is most often people with pancreatic NETs; chemotherapy is rarely used for people with well-differentiated gastrointestinal NETs. The committee agreed that interferons and chemotherapy are not relevant comparators for Lu-177 dotatate. The

committee understood that at the time of the committee discussion, everolimus was not available in clinical practice, and sunitinib was only available through the Cancer Drugs Fund, meaning that treatment options were limited to best supportive care. However, NICE has recently issued technology appraisal guidance for everolimus and sunitinib. The committee therefore concluded the relevant comparators for Lu-177 dotatate are sunitinib, everolimus and best supportive care for pancreatic NETs, and everolimus and best supportive care for midgut gastrointestinal NETs.

Clinical trial evidence

Lu-177 dotatate is effective for treating midgut gastrointestinal NETs

3.3 The clinical effectiveness evidence for Lu-177 dotatate came from the NETTER-1 clinical trial, which recruited people with inoperable, progressive, somatostatin receptor-positive, midgut gastrointestinal NETs. The trial was an open, randomised, parallel-group design comparing Lu-177 dotatate plus octreotide 30 mg with octreotide long-acting release (LAR) 60 mg. The committee acknowledged that the comparator in this trial was not considered established clinical practice. The hazard ratio for progression-free survival for Lu-177 dotatate compared with octreotide LAR was 0.21 (95% confidence interval [CI] 0.13 to 0.33). For overall survival, the hazard ratio for Lu-177 dotatate compared with octreotide LAR was 0.40 (95% CI 0.21 to 0.77). Median overall survival was not reached in both treatment arms at the time of data analysis. The committee concluded that Lu-177 dotatate is clinically effective for people with midgut gastrointestinal NETs compared with octreotide LAR.

The clinical trial only included people with midgut gastrointestinal NETs

3.4 The committee understood that the anticipated marketing authorisation for Lu-177 dotatate is for gastroenteropancreatic NETs, whereas NETTER-1 only recruited people with midgut gastrointestinal NETs. The clinical experts explained that in their experience, they do not expect much

difference in the efficacy of Lu-177 dotatate across the different tumour sites. The committee acknowledged that Lu-177 dotatate may be equally effective across different tumour sites, but concluded that its recommendations should be guided by evidence from the clinical trial that underpins the marketing authorisation.

Indirect and mixed treatment comparison

The company's mixed treatment comparison for pancreatic NETs is not appropriate for decision-making

3.5 The company did a mixed treatment comparison comparing Lu-177 dotatate with everolimus and sunitinib for advanced pancreatic NETs. The assessment group commented that the data for Lu-177 dotatate were taken from NETTER-1, which did not include any patients with pancreatic NETs so this comparison was not appropriate. The committee agreed that the company's mixed treatment comparison for pancreatic NETs was uninformative and that it would not consider it further.

NETTER-1 and RADIANT-4 are not fully comparable

3.6 The assessment group did an indirect treatment comparison for midgut gastrointestinal NETs comparing Lu-177 dotatate with everolimus and best supportive care, using data from NETTER-1 and RADIANT-4. For this comparison, it assumed that octreotide LAR 60 mg (the comparator arm in NETTER-1) was equivalent to best supportive care plus placebo (the comparator arm in RADIANT-4). Although the clinical experts considered this to be a reasonable assumption, they felt that octreotide LAR 60 mg was actually more effective than best supportive care plus placebo and that this assumption would underestimate the results for Lu-177 dotatate. The committee understood that RADIANT-4 included only people with non-functional tumours and that this was reflected in the marketing authorisation for everolimus. The committee was concerned that NETTER-1 included people with both functional and non-functional tumours, meaning that the 2 trials may not be comparable. It was also

concerned that NETTER-1 included only midgut gastrointestinal NETs, whereas RADIANT-4 included fore-, mid- and hindgut NETs. However, the committee noted that the assessment group used subgroup data from RADIANT-4 for midgut gastrointestinal NETs only, to match the population in NETTER-1. The clinical experts explained that there was no clear evidence of a difference in outcomes depending on the functional status of tumours. However, they acknowledged that there were variations in outcomes depending on tumour sites (for example, ileal tumours have a better prognosis than gastric or rectal tumours), so it was appropriate to use midgut gastrointestinal NETs subgroup data from RADIANT-4 for the comparison. The clinical experts highlighted that NETTER-1 specifically included patients with somatostatin receptor-positive tumours, whereas this was not an inclusion criterion for RADIANT-4. They stated that tumours respond differently to treatment based on somatostatin receptor status and this was the main concern in terms of the 2 trials' comparability. The committee concluded that there were important differences between NETTER-1 and RADIANT-4 and the results from any indirect comparison may be uncertain.

The assessment's group indirect comparison for midgut gastrointestinal NETs is preferred for decision-making

3.7 The committee noted that the company also presented an indirect comparison using the full gastrointestinal subgroup from RADIANT-4, which also included the RADIANT-2 trial of everolimus for functional tumours. The committee did not accept the company's indirect comparison because it introduced further uncertainty in addition to that identified in the assessment group's indirect comparison. In the absence of a more robust analysis, the committee accepted the assessment group's indirect treatment comparison as the preferred analysis for decision-making.

Lu-177 dotatate improved progression-free survival but overall survival benefit was unclear

3.8 The results of the assessment group's indirect comparison showed that, compared with everolimus, the hazard ratio for progression-free survival for Lu-177 dotatate was 0.37 (95% CI 0.19 to 0.69). The hazard ratio for overall survival cannot be reported, because the hazard ratio for everolimus compared with best supportive care on which the comparison is based is considered confidential by the company. The committee concluded that the evidence showed an improvement in progression-free survival with Lu-177 dotatate compared with everolimus for midgut gastrointestinal NETs, but the overall survival benefit was less clear because of the immaturity of the data. However, it noted that the results were uncertain given its concerns about the assumptions used in the indirect comparison (see sections 3.5 and 3.6).

Economic models

The assessment group's economic model is the most appropriate for decision-making

3.9 The committee discussed the economic models presented by the company and the assessment group for midgut gastrointestinal NETs. Both models were partitioned survival models with health states corresponding to pre-progression, post-progression and death. The models were driven by the indirect treatment comparison of Lu-177 dotatate with everolimus, although the assessment group's model also included a comparison with best supportive care. The committee preferred the assessment group's indirect treatment comparison to the company's (see section 3.6), and agreed that best supportive care should be included as a comparator in the analyses. The committee therefore concluded that the assessment group's economic model was the most appropriate for decision-making.

All relevant costs associated with Lu-177 dotatate have been included in the economic model

3.10 The committee questioned whether there would be additional costs for administering Lu-177 dotatate given that it is a radionuclide. It heard from the clinical experts that the initial scans needed to identify people with somatostatin receptor-positive tumours are part of standard care. They also stated that although people having Lu-177 dotatate usually stay overnight in hospital, some are discharged the same day. The assessment's group base case assumed that most patients stay overnight. In response to the company's comments on the assessment report, the assessment group produced scenario analyses that explored Lu-177 dotatate being administered in a day-case setting. The impact of this assumption on the assessment group's base-case incremental cost-effectiveness ratio (ICER) was minimal and in the assessment group's opinion, was uncertain based on clinical expert opinion. The company commented that supportive care costs should not be included in the Lu-177 dotatate arm of the model. The assessment group considered the company's comment to be reasonable and provided scenario analyses that exclude supportive care costs for Lu-177 dotatate. This also had minimal impact on the ICER. The committee also noted the comment from the expert evidence submissions that no additional resources will be needed for Lu-177 dotatate because several centres in England have been providing it for some time. The committee was satisfied that all relevant costs associated with Lu-177 dotatate had been captured.

Cost-effectiveness results

3.11 The assessment group's base-case results, which were used in the committee's decision-making, include the confidential patient access scheme discount for everolimus. As such, the exact cost-effectiveness results cannot be reported here.

Lu-177 dotatate is not cost effective for treating midgut gastrointestinal NETs

3.12 The committee considered the cost effectiveness of Lu-177 dotatate compared with everolimus and best supportive care for midgut gastrointestinal NETs. In both cases, the deterministic and probabilistic ICERs were much higher than £30,000 per quality-adjusted life year (QALY) gained. Because of this, the committee concluded that Lu-177 dotatate is not a cost-effective use of NHS resources for treating somatostatin receptor-positive midgut gastrointestinal NETs in people with progressive disease.

Innovation

All significant health-related benefits were captured in the analyses

3.13 The committee heard from both the patient and clinical experts that Lu-177 dotatate is an important new treatment option that represents a major change in managing NETs. The committee noted the company's comment that Lu-177 dotatate addresses a significant unmet need for people with inoperable NETs whose disease has progressed on somatostatin analogues. However, the committee concluded that there were no additional health benefits that had not been captured in the QALY calculations.

End-of-life considerations

3.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods.

Lu-177 dotatate did not meet NICE's end-of-life criteria and could not be recommended

3.15 The committee heard from the clinical experts that average life expectancy for people with advanced midgut gastrointestinal NETs was around 5 to 6 years. Survival of less than 24 months, as would be necessary to meet NICE's first end-of-life criterion, is not seen in practice.

The committee noted that the extrapolated survival was 58.8 months for best supportive care and 69.0 months for everolimus, meaning that the criterion for short life expectancy of 24 months was not met. For the second criterion of extension to life of at least 3 months compared with current NHS treatment, the difference in extrapolated survival for Lu-177 dotatate compared with best supportive care and everolimus was 21.1 months and 10.9 months respectively. The committee considered that the second criterion was met. However, because the criterion for short life expectancy was not met, the committee concluded that Lu-177 dotatate did not meet the end-of-life criteria for midgut gastrointestinal NETs. Because the end-of-life criteria did not apply, the committee could not recommend Lu-177 dotatate as an option for treating somatostatin receptor-positive midgut gastrointestinal NETs after disease progression.

Cancer Drugs Fund considerations

Lu-177 dotatate did not meet the criteria for use in the Cancer Drugs Fund

3.16 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. It noted that the most plausible ICERs for Lu-177 dotatate were much higher than that considered to be a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained), and so Lu-177 dotatate did not have plausible potential to satisfy the criteria for routine use. The committee also considered that although there were uncertainties in the evidence, the clinical-effectiveness evidence from NETTER-1 was relatively robust (see section 3.3) and there were no clinical uncertainties that could be addressed by collecting outcome data from patients in the NHS, which could be used to inform a subsequent update of the guidance. The committee concluded that Lu-177 dotatate did not meet the criteria to be considered for use in the Cancer Drugs Fund for somatostatin receptor-positive midgut gastrointestinal NETs.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, appraisal committee
July 2017

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ross Dent and Stuart Wood

Technical Leads

Nwamaka Umeweni

Technical Adviser

Kate Moore

Project Manager

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