NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease

The scope for this technology appraisal includes lutetium-177 dotatate (177Lu-dotatate). NICE cannot release any recommendations on 177Lu-dotatate until it has a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use. A separate document with the committee's recommendations will be released when this opinion is received.

1 Recommendations

1.1 Everolimus and sunitinib are recommended, within their marketing authorisations, as options for treating well- or moderately-differentiated unresectable or metastatic neuroendocrine tumours (NETs) of pancreatic origin in adults with progressive disease.

1.2 Everolimus is recommended, within its marketing authorisation, as an option for treating well-differentiated (grade 1 or grade 2) non-functional unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease.

1.3 Everolimus is recommended only when the company provides it with the discount agreed in the patient access scheme.

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. There is particularly high unmet need for people with NETs that affect the lungs.

Clinical trial evidence shows that everolimus and sunitinib are effective for treating pancreatic NETs compared with current treatment (best supportive care). Everolimus is effective for treating gastrointestinal and lung NETs compared with current treatment (best supportive care).

For treating pancreatic NETs, everolimus and sunitinib were recommended because they met NICE's end-of-life criteria. The cost effectiveness varied, from below £20,000 up to £30,000 per quality-adjusted life year (QALY) gained.

For treating gastrointestinal NETs, everolimus did not meet the end-of-life criteria but was recommended because it is cost effective, at below £20,000 per QALY gained.

For treating lung NETs, everolimus did not meet the end-of-life criteria. The cost effectiveness of everolimus varied, from below £20,000 up to £30,000 per QALY gained. It was recommended because of the cost-effectiveness estimates and the limited treatment options available for people with lung NETs.

NICE's end-of-life criteria are that life expectancy for people with the condition should be less than 24 months and that treatment should extend life by more than 3 months.

2 The technologies

	Everolimus (Afinitor, Novartis)	Sunitinib (Sutent, Pfizer)
Marketing authorisations	Everolimus has a marketing authorisation for 'unresectable or metastatic, well- or moderately differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease' and 'unresectable or metastatic, well differentiated (grade 1 or grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease'.	Sunitinib has a marketing authorisation for 'unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults'.
Recommended doses and schedules	Everolimus is taken orally, 10 mg once daily.	Sunitinib is taken orally, 37.5 mg once daily.
Prices	£2,673.00 per 30-tablet (10 mg) pack, (excluding VAT). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of everolimus with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.	£784.70 per 28-tablet (12.5 mg) pack (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts. A complex patient access scheme for sunitinib is available in the NHS for other indications. However, the company did not request approval from the Department of Health for it to be considered in this appraisal. This appraisal only considered the list price.

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 clinical experts explained that few treatment options are available for lung NETs, meaning there is particularly high unmet need for this group of people. 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 mostly 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 177Lu-dotatate. For non-functional pancreatic NETs, the guidelines suggest 177Lu-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 177Lu-dotatate as an option with everolimus, and interferons. The clinical experts explained that although interferons may be considered after disease progression, 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 a 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 understood that everolimus and 177Lu-dotatate are no longer available through the Cancer Drugs Fund. It was aware that only sunitinib is currently available through the Cancer Drugs Fund, meaning that current alternative treatment options are limited to best supportive care. The committee concluded that interferons and chemotherapy are not relevant comparators for everolimus and sunitinib, and that the most appropriate comparisons are of everolimus and sunitinib with each other and of both technologies with best supportive care for the specific sites covered by their marketing authorisations.

Clinical trial evidence

Everolimus and sunitinib are effective for treating pancreatic NETs

3.3 The clinical trial evidence for pancreatic NETs came from 2 double-blind, randomised controlled trials:

- RADIANT-3 (everolimus plus best supportive care compared with placebo plus best supportive care) and
- A6181111 (sunitinib plus best supportive care compared with placebo plus best supportive care).

The trials included people whose disease had progressed on surgery, radiotherapy, chemotherapy, somatostatin analogues and targeted therapies. The committee noted that only a small number of people had disease that progressed on targeted therapies, which included everolimus (in RADIANT-3) and sunitinib (in A6181111).The results from the clinical trials showed significant improvements in progression-free survival for both treatments, with hazard ratios of 0.35 (95% confidence interval [CI] 0.27 to 0.45) for everolimus compared with placebo and 0.42 (95% CI 0.26 to 0.66) for sunitinib compared with placebo. The committee noted that the overall survival results were confounded by high levels of crossover in the comparator arms of both trials (73% in RADIANT-3 and

69% in A6181111). Both companies used the rank-preserving structural failure time model to adjust for crossover, which resulted in hazard ratios of 0.60 (95% CI 0.09 to 3.95) for everolimus compared with placebo and 0.34 (95% CI 0.14 to 1.28) for sunitinib compared with placebo. The median overall survival gain for sunitinib compared with placebo was 25.4 months, but this could not be determined for everolimus compared with placebo after adjusting for crossover. The committee heard from the assessment group that the companies' crossover adjustment method was appropriate. The committee concluded that despite the non-significant overall survival results and high levels of crossover, both everolimus and sunitinib are clinically effective for treating pancreatic NETs.

Everolimus is effective for treating gastrointestinal and lung NETs

3.4 For gastrointestinal and lung NETs, the evidence came from a double-blind, randomised controlled trial of everolimus plus best supportive care compared with placebo plus best supportive care (RADIANT-4). For gastrointestinal and lung NETs combined, the progression-free survival hazard ratio for everolimus compared with best supportive care was 0.48 (95% CI 0.35 to 0.67); the overall survival hazard ratio was 0.73 (95% CI 0.48 to 1.11). The company also provided separate analyses by tumour site, which showed significant reductions in the risk of progression or death with everolimus compared with placebo for both gastrointestinal NETs (hazard ratio 0.56, 95% CI 0.37 to 0.84) and lung NETs (hazard ratio 0.50, 95% CI 0.28 to 0.88). The overall survival results by tumour site are considered confidential by the company and cannot be reported here. The committee concluded that everolimus is a clinically effective treatment for both gastrointestinal and lung NETs.

Indirect treatment comparison

The indirect treatment comparison is appropriate for decision-making

3.5 The assessment group did an indirect treatment comparison of everolimus and sunitinib for pancreatic NETs using data from RADIANT-3 and

A6181111. Based on the evidence presented, the committee considered that the 2 trials were generally comparable. However, it was concerned that the Bucher method used by the assessment group is a fixed-effects model, meaning that any heterogeneity between the trials was not accounted for. It was aware that using a different method that accounted for heterogeneity is likely to have led to wider confidence intervals than those reported. The assessment group explained that it had accounted for this by using the confidence intervals to inform the distributions that it applied to the estimates in the probabilistic cost-effectiveness sensitivity analyses. The committee concluded that although there was uncertainty associated with the indirect treatment comparison, it was appropriate for decision-making.

Everolimus and sunitinib have similar benefits for treating pancreatic NETs

3.6 The committee noted that the hazard ratio for progression-free survival for everolimus compared with sunitinib was 1.06 (95% CI 0.57 to 1.97). When adjusted for crossover, the hazard ratio for overall survival was 1.76 (95% CI 0.20 to 15.78). The committee noted that the confidence intervals were wide, and suggested that there may be no statistically significant difference between sunitinib and everolimus. The clinical experts explained that based on the progression-free survival data from the trials, they would consider the clinical benefit of everolimus and sunitinib to be similar. They noted that a recent crossover study of both treatments for renal cell carcinoma had reported similar effectiveness, providing further evidence for this assumption. However, the experts emphasised that although both treatments are comparable in clinical effectiveness, they are not considered interchangeable because of their different mechanisms of action and safety profiles. Having heard from the clinical experts and with no robust evidence of a difference in effectiveness, the committee concluded that everolimus and sunitinib have similar clinical benefits for treating pancreatic NETs.

Economic models

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

3.7 The committee discussed the economic models presented by Novartis and the assessment group. These were all partitioned survival models with health states corresponding to pre-progression, post-progression and death. The models for pancreatic NETs were driven by the indirect treatment comparisons of everolimus and sunitinib and head-to-head data from the respective trials, whereas the models for gastrointestinal and lung NETs were based solely on data from RADIANT-4. The committee noted that the assessment group identified some flaws with the company's model including:

- no comparison with best supportive care for pancreatic NETs
- using indirect treatment comparison results based on outdated trial data
- utility data for everolimus estimated from a vignette in the absence of trial data
- incorrect treatment duration for sunitinib
- no separate analysis for gastrointestinal NETs and lung NETs and
- limitations with the implementation of costs of subsequent treatments.

The assessment group also noted that the lack of resource use data collected in RADIANT-4 limited the company model. The committee agreed with the assessment group that best supportive care should be included as a comparator for pancreatic NETs and that the most current trial data should be incorporated in the analyses for all tumour sites. Therefore, it concluded that the assessment group's economic model was the most appropriate for decision-making.

Health-related quality of life

The assessment group's estimates are the most appropriate

3.8 The committee considered the different approaches used to estimate utilities in the models. It noted that the main difference lay in the source of utility values for pancreatic NETs. Novartis used condition-specific valuations that were assigned to treatment arms using a time-trade off utility study (Swinburn et al. 2012), whereas the assessment group used EQ-5D valuations from A6181111 and assumed that the utilities for stable disease for everolimus and sunitinib were equal. The clinical experts explained that because both everolimus and sunitinib are offered at the same point in the treatment pathway, and because they have similar clinical effectiveness and safety profiles, it is reasonable to assume that health-related quality of life would be similar. In addition, the committee noted that the assessment group's values for pancreatic NETs were consistently lower than those for gastrointestinal and lung NETs from RADIANT-4. The clinical experts explained that pancreatic NETs are associated with more comorbidities (such as diabetes and pancreatic obstruction) than gastrointestinal NETs, so a lower utility value is plausible. The committee concluded that the assessment group's estimates had superior methodological and clinical validity and were, therefore, the most appropriate.

Cost-effectiveness results

3.9 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.

The ICERs for everolimus and sunitinib for pancreatic NETs are less than £30,000 per QALY gained

3.10 The committee considered 3 cost-effectiveness analyses for pancreatic NETs:

- everolimus compared with best supportive care
- sunitinib compared with best supportive care

- sunitinib compared with everolimus.

All of the pairwise deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) were either less than £20,000 per quality-adjusted life year (QALY) gained or between £20,000 and £30,000 per QALY gained. The committee noted that most of the scenario analyses (including using alternative curves to model survival) also produced ICERs between £20,000 and £30,000 per QALY gained for both treatments.

Separate cost-effectiveness analyses for gastrointestinal and lung NETs are appropriate for decision-making

3.11 For gastrointestinal and lung NETs, the committee also considered 3 sets of cost-effectiveness analyses: an analysis with gastrointestinal and lung NETs combined and separate analyses for each tumour site (based on subgroup data from RADIANT-4 provided by the company). The committee understood that prognosis and quality of life can differ by tumour site and agreed that these factors are likely to affect the cost-effectiveness estimates. The committee concluded that the analyses specific to each tumour site were more appropriate for decision-making.

The ICERs for everolimus for gastrointestinal NETs are less than £20,000 per QALY gained

3.12 For gastrointestinal NETs, the committee considered everolimus compared with best supportive care. The deterministic and probabilistic ICERs as well as the ICERs for most of the scenario analyses were less than £20,000 per QALY gained.

The ICERs for everolimus for lung NETs are less than £30,000 per QALY gained

3.13 For lung NETs, the committee considered everolimus compared with best supportive care. The deterministic and probabilistic ICERs as well as the

ICERs for most of the scenario analyses were either less than £20,000 per QALY gained or between £20,000 and £30,000 per QALY gained.

Innovation

All significant health-related benefits were captured in the analyses

3.14 The committee discussed whether sunitinib and everolimus were innovative. It heard from the clinical experts that there are limited alternative treatment options available for NETs, especially for lung NETs. It noted the comment from the companies that both treatments are tolerable options which provide meaningful improvements in life expectancy and health-related quality of life. However, the committee concluded that there were no additional health-related quality-of-life benefits that had not been captured in the QALY calculations.

End-of-life considerations

3.15 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.

Everolimus and sunitinib for pancreatic NETs meet the end-of-life criteria

3.16 For pancreatic NETs, the committee noted that the extrapolated survival of the best supportive care group was 20.5 months from A6181111 and 41.6 months from RADIANT-3. The assessment group explained that the choice of parametric extrapolation could have led to different results, so the estimates were very uncertain. The clinical experts stated that they would expect survival to be similar, given that the technologies are indicated for people at the same point in the treatment pathway. They further explained that in clinical practice they would expect survival to be closer to 20.5 months than 41.6 months for this group of people, meaning that they would have a life expectancy of less than 24 months (the first end-of-life criterion). For both everolimus and sunitinib, the extrapolated survival benefit compared with best supportive care was over 3 months

(14.7 and 38.5 months respectively), meaning that the second end-of-life criterion, of extending life by at least 3 months, was met. The committee accepted the clinical experts' views about life expectancy and concluded that both everolimus and sunitinib met the end-of-life criteria for pancreatic NETs in people with progressive disease.

Everolimus for gastrointestinal NETs does not meet the end-of-life criteria

3.17 For gastrointestinal NETs, the committee noted that the extrapolated survival from the best supportive care arm was 51.4 months. It heard from the clinical experts that life expectancy for people with advanced gastrointestinal NETs was around 5 to 6 years and survival of less than 24 months, as would be necessary to meet the first end-of-life criterion, is not seen in practice. Therefore, although everolimus met the second criterion (it gave an extension to life compared with best supportive care of 26.6 months based on the survival extrapolation), the committee concluded that the end-of-life criteria were not met for gastrointestinal NETs.

Everolimus for lung NETs does not meet the end-of-life criteria

3.18 For lung NETs, the committee noted that the extrapolated survival from the best supportive care arm was 35.5 months (so the first end-of-life criterion was not met). Everolimus met the second end-of-life criterion (it gave extension to life compared with best supportive care of 25.9 months) but the committee concluded that the end-of-life criteria were not met for lung NETs because the life expectancy was shown to be greater than 24 months.

Summary of recommendations

Everolimus and sunitinib are recommended for treating pancreatic NETS

3.19 For pancreatic NETs, given that everolimus and sunitinib met the end-of-life criteria (see section 3.16) and all the ICERs were either below £20,000

per QALY gained or between £20,000 and £30,000 per QALY gained (see section 3.10), the committee concluded that it could recommend both everolimus and sunitinib as a cost-effective use of NHS resources for treating pancreatic NETs in people with progressive disease.

Everolimus is recommended for treating gastrointestinal and lung NETs

3.20 The committee had concluded that everolimus did not meet the end-of-life criteria for gastrointestinal NETs and lung NETs (see sections 3.17 and 3.18). However, the ICERs for gastrointestinal NETs were below £20,000 per QALY gained (see section 3.12), which is normally considered cost effective. Although some of the ICERs for everolimus compared with best supportive care for lung NETs were above £20,000 per QALY gained, the committee noted that they were all below £30,000 per QALY gained. It also considered the comments from the clinical experts that there is a high unmet need for treatment for lung NETs because there are limited treatment options available for this group of people (see section 3.1). Based on the ICER estimates for the 2 populations and the limited treatment options for lung NETs, the committee concluded that it could recommend everolimus as a cost-effective use of NHS resources for treating gastrointestinal NETs and lung NETs in people with progressive disease.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology

appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has unresectable or metastatic neuroendocrine tumours and the doctor responsible for their care thinks that everolimus or sunitinib are the right treatments, they should be available for use, in line with NICE's recommendations.

4.4 The Department of Health and Novartis have agreed that everolimus will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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
May 2017

6 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

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Technical Adviser

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Project Manager

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