National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

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
Wording	Eisai Limited	Yes, it reflects the current EMA approved label.	Comment noted. No action required.
	Novartis Pharmaceuticals UK Limited	No, see below alternative wording: 'To appraise the clinical and cost effectiveness of lenvatinib in combination with everolimus within its marketing authorisation for the treatment of adult patients with RCC following one prior VEGF-targeted therapy.'	Comment noted. The full wording of the marketing authorisation in the UK is specified in 'the technology' paragraph and in the 'population' section of the table in the scope. No action required.
	Pfizer Ltd	No comments	Thank you.

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Timing Issues	Eisai Limited	It is urgent as lenvatinib was approved in this indication by the EMA in August 2016 and is yet to be made available on the NHS in England and Wales.	Comments noted. An appraisal of lenvatinib has been scheduled into NICE's technology appraisal work programme.
	Novartis Pharmaceuticals UK Limited	Little urgency	Comment noted. No action required.
	Pfizer Ltd	No comments	Thank you.
Additional comments on the draft remit	Eisai Limited	No	Thank you.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eisai Limited	Most of the background information is accurate. The information on nivolumab needs to be updated to reflect that final positive guidance was published on the 23rd November. In addition, information on the ongoing NICE technology appraisal for cabozantinib for previously treated advanced renal cell carcinoma [ID931] needs to be included.	Comments noted. The background section of the scope has been amended.

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	Novartis Pharmaceuticals UK Limited	Since the draft scope was written nivolumab has been NICE approved and cabozantinib and tivozanib are also undergoing NICE appraisals.	Comments noted. The background section of the scope has been amended.
	Pfizer Ltd	No comments	Thank you.
The technology/ intervention	Eisai Limited	The description of the technology is mostly accurate. However, the scope needs to be updated to reflect the fact that lenvatinib was granted a marketing authorisation for this indication on the 25th August 2016.	Comments noted. The technology section of the scope has been amended.
	Novartis Pharmaceuticals UK Limited	Lenvatinib in combination with everolimus has now been EMA approved.	Comment noted. The technology section of the scope has been amended.
	Pfizer Ltd	No comments	Thank you.
Population	Eisai Limited	Yes, the population is defined appropriately. There are no groups within this population that should be considered separately.	Comments noted. No action required.
	Novartis Pharmaceuticals UK Limited	Trial data relates to clear cell RCC only.	Comment noted. No action required.
	Pfizer Ltd	No comments	Thank you.

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Comparators	Eisai Limited	The list of comparators is not correct. An ongoing NICE technology appraisal is in development for cabozantinib for previously treated advanced renal cell carcinoma [ID931]. Final guidance is expected in June 2017 and therefore cabozantinib should be included as a comparator in this scope. The information on nivolumab needs to be updated to reflect that final positive guidance was published on the 23rd November. Axitinib was recommended by NICE in this indication in February 2015 and has been routinely used on the NHS since then. Therefore, it can be described as the current “best alternative care”.	Comments noted. The ‘comparator’ section of the table in the scope has been amended.
	Novartis Pharmaceuticals UK Limited	Yes.	Comment noted.
	Pfizer Ltd	Pfizer notes that there is an ongoing NICE appraisal of cabozantinib for people with previously treated renal cell carcinoma[1], and therefore, if timelines permit, recommends that cabozantinib is also included as a comparator in this appraisal.	Comment noted. The ‘comparator’ section of the table in the scope has been amended.
Outcomes	Eisai Limited	Yes, the outcome measures listed are appropriate.	Comment noted. No action required.
	Novartis Pharmaceuticals UK Limited	NA	Thank you.
	Pfizer Ltd	No comments	Thank you.

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Economic analysis	Eisai Limited	No comments.	Thank you.
	Novartis Pharmaceuticals UK Limited	NA	Thank you.
	Pfizer Ltd	No comments	Thank you.
Equality and Diversity	Eisai Limited	No comments.	Thank you.
	Novartis Pharmaceuticals UK Limited	NA	Thank you.
	Pfizer Ltd	No comments	Thank you.
Other considerations	Eisai Limited	No comments.	Thank you.
	Pfizer Ltd	No comments	Thank you.
Innovation	Eisai Limited	Eisai do consider lenvatinib to be innovative as it is a multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor [PDGF] receptor PDGFRα; KIT; and RET) involved in tumour proliferation.	Comments noted. The potentially innovative nature of the technology will be considered by the appraisal committee.

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		To date, several failed studies have investigated a synergistic combination of VEGF RTK inhibitor and mammalian target of rapamycin (mTOR) inhibitor for the treatment of advanced renal cell carcinoma. The lenvatinib plus everolimus combination is the first such combination regimen to be approved for use in second-line metastatic renal cell carcinoma.	
	Novartis Pharmaceuticals UK Limited	The technology is not considered as a 'step-change' in the management of this condition. The use of the technology will not result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.	Comments noted. The potentially innovative nature of the technology will be considered by the appraisal committee.
	Pfizer Ltd	No comments	Thank you.
Questions for consultation	Eisai Limited	**How should best supportive care be defined?** Best supportive care in advanced RCC generally involves symptomatic treatment including pharmacologic management of pain, the use of corticosteroids, palliative radiotherapy and bone-stabilising drugs.[1] [1] Escudier B., et al. Annals of Oncol 2016; 27(Suppl 5): v58-v68 **Where do you consider lenvatinib will fit into the existing NICE pathway for renal cancer**? Lenvatinib would be a second-line treatment for advanced renal cancer, according to the existing NICE pathway.	Comments noted. No action required.
	Novartis Pharmaceuticals UK Limited	Lenvatinib + everolimus will fit as a 2L treatment option based on the data in the Phase II trial. However, phase III data is required to fully warrant the use of this combination in practice.	Comments noted. No action required.

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	Pfizer Ltd	No comments	Thank you.
Additional comments on the draft scope	Eisai Limited	No	Thank you.
	Kidney Cancer Support Network	Lenvatinib in combination with everolimus has been proven to be clinically effective for the treatment of advanced renal cell carcinoma (RCC) following treatment with one prior vascular endothelial growth factor (VEGF) targeted therapy. This has led to the lenvatinib/everolimus combination designated a breakthrough therapy by the FDA as a treatment for advanced or metastatic RCC. As a breakthrough therapy, the lenvatinib/everolimus combination has been fast tracked for approval in a number of countries, including the US and Europe, based on the phase 2 clinical trial data. Lenvatinib is a multiple kinase inhibitor against VEGF kinases, in addition to other tyrosine kinases implicated in pathogenic angiogenesis, tumour growth and cancer progression. It is the first multiple kinase inhibitor to gain marketing authorisation in North America and Europe for advanced RCC, and has proven to be effective in the treatment of certain kinds of thyroid cancer. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America. Clinicians in the UK should have the ability to choose the most effective treatments for individual patients from those available. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not	Thank you for your comments, which are noted. No changes to the scope are required.

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		able to predict which patients will respond to which drug. Therefore, selection of the most effective treatment for individual patients is accomplished by trial and error. Without the lenvatinib/everolimus combination, the clinician's choice of treatment is seriously compromised. Without treatment alternatives in the second-line, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second-line therapy to continue managing their disease, and to maintain quality of life. The current second-line treatment options are not effective for everyone, and can be difficult to access. Axitinib and nivolumab are the only second-line treatments available to patients in England on the NHS, while funding for everolimus as a second-line treatment through the Cancer Drugs Fund is currently undergoing review. Undue restrictions in accessing the lenvatinib/everolimus combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Choice in the second-line, and access to new innovative treatments remains paramount to managing the progression of this disease. Having a choice in second-line treatment would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient. The lenvatinib/everolimus combination is the second drug combination for the treatment of advanced RCC to undergo NICE appraisal (the first being the bevacizumab/interferon combination). Previous drug combinations have proven to be unsuccessful as a result of unacceptable side effects. However, the lenvatinib/everolimus combination seems to be well tolerated, as well as proven to be more effective at extending overall survival compared to single agent therapy with lenvatinib and everolimus. In addition, a number of drug combinations have been shown to be effective in the treatment of non-clear cell RCC, especially papillary RCC. If recommended, the	

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		lenvatinib/everolimus combination could, therefore, be used to address an area of significant unmet need in the treatment of non-clear cell RCC. Clinical trials have been conducted in previously treated advanced/metastatic RCC patients with the lenvatinib/everolimus combination in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of lenvatinib/everolimus on the NHS, we would have to question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE. We appreciate that the lenvatinib/everolimus combination is expensive, and we urge NICE and the manufacturer to negotiate and find a way to make this new and innovative drug combination available to the patients who need it; failure to do so would be seen as professional inadequacy. NICE and the manufacturer need to think outside the box to negotiate an alternative funding scheme, for example, the government could pay for those cases where lenvatinib/everolimus is effective, and the manufacturer reimburse the NHS for those cases who do not respond to treatment. This will require more collaborative working with the manufacturer to negotiate an acceptable patient access scheme. Current treatments have been proven to shrink tumours and delay disease progression in some patients, but adding the lenvatinib/everolimus combination as a choice in the second-line (and beyond) enables patients and clinicians to have individualised treatment plans to better control this disease and maintain a high quality of life. It could also address the massive	

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		unmet need for treatment options for non-clear-cell RCC and treatment in the third-line. Thank you for allowing us to take part in this single technology appraisal. We welcome the opportunity to put forward the views of the Kidney Cancer Support Network patient community for this important health technology appraisal of the lenvatinib/everolimus combination in advanced renal cell carcinoma.	
	Pfizer Ltd	References: 1) Cabozantanib for previously treated advanced renal cell carcinoma [ID931]. Final Scope. Link: https://www.nice.org.uk/guidance/GID-TA10075/documents/final-scope. Accessed: 19/12/2016	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health