National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma [ID1089]

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	No, the wording of the remit should reflect the proposed marketing authorisation wording for lenvatinib. Please see below proposed alternative wording: "To appraise the clinical and cost effectiveness of lenvatinib within its marketing authorisation for hepatocellular carcinoma."	Thank you for your comment, the wording has been updated.
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	**To appraise the clinical and cost effectiveness of lenvatinib within its marketing authorisation for advanced, unresectable, hepatocellular carcinoma not previously treated with systemic therapy.** Note, patient may have received prior therapies for earlier stage disease and then experienced disease progression to advanced stage, at which treatment with systemic therapies (such as lenvatinib) would be considered. Hence suggested change in wording as above.	Thank you for your comment, the wording has been updated.

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Timing Issues	Eisai Limited	There is currently only one treatment option that has marketing authorisation and NICE approval for these patients and therefore this appraisal should be prioritised to address an area of unmet need. Furthermore, priority scheduling of this appraisal will facilitate NICE's aim to publish guidance within 90 days of marketing authorisation.	Thank you for your comment, no changes are needed.
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	Moderate urgency. There is a currently available systemic therapy option for patients fitting these criteria (sorafenib) with similar efficacy.	Thank you for your comment, no changes are needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eisai Limited	Most of the background information is accurate. The ONS dataset for 2015 is now available; as such the statement "there were 2,374 people diagnosed with HCC in England in 2014" could be updated to "there were 2,456 people diagnosed with HCC in England in 2015"	Thank you for your comments, the background section has been updated.

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		The information on sorafenib needs to be updated to reflect that final NICE guidance recommending sorafenib was published on the 6th September 2017.	
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	Treatment for HCC depends on the location and stage of the cancer, and how well the liver function is preserved. Early stage hepatocellular carcinoma may be treated with potentially curative surgery (hepatic resection) or percutaneous radiofrequency/thermal ablation in patients with well-preserved liver function, or liver transplantation for those with impaired liver function. However, for patients presenting with more advanced disease, treatment is given with non-curative intent. Treatment options for patients with disease confined to the liver include interventional procedures such as transarterial chemoembolisation (using doxorubicin or cisplatin) or selective internal radiation therapy, and external beam radiotherapy. For patients unsuitable for these treatments, or for those with metastatic disease, the only available systemic therapy is the oral multi-kinase inhibitor sorafenib, which has recently been recommended by a NICE technology appraisal (TA189). Additional comments; • SIRT is not funded for NHS patients, hence it may need to be removed from the treatment options. • Cytotoxic chemotherapy (doxorubicin/cisplatin) is not routinely used for HCC due to lack of efficacy, hence I have removed it. Sorafenib can be considered ‘chemotherapy’ but may be better termed ‘systemic’ therapy to avoid confusion with cytotoxic chemotherapy. • I think a recent update to TA189 has recommended use of sorafenib.	Thank you for your comments, the background section has been updated.

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	The Royal College of Pathologists	As the proposed study involves the assessment of a novel treatment for HCC, the final study design should consider histological confirmation of HCC as an entry criterion	Thank you for your comment, no changes are needed.
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 Eisai have now filed a marketing authorisation application for this indication.	Thank you for your comments, no changes are needed.
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	Yes	Thank you for your comment.
Population	Eisai Limited	Yes, the population is defined appropriately.	Thank you for your comment.
	HCC-UK, Association of Cancer Physicians, British Association of	There is a typographical error in the description of the population; 'Adults with unresectable hepatocellular carcinoma who have not ~~been~~ previously received systemic treatment'	Thank you for your comment, the error has been corrected.

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	the Study of the Liver (BASL)		
Comparators	Eisai Limited	Yes, the population is defined appropriately. As highlighted above, sorafenib was recommended by NICE in this indication in September 2017, but it has been routinely used on the NHS since 2010 via the Cancer Drugs Fund. Therefore, sorafenib is recognised in the UK as the standard of care for patients with advanced/unresectable hepatocellular carcinoma and has been defined as such in international guidelines agreed in Europe by the European Association for the Study of the Liver (EASL) . Furthermore, it is important to note that the EASL guidelines recommend best supportive care only following sorafenib in cases of intolerance or failure to the treatment.	Thank you for your comments, the background section now includes information about TA474, the sorafenib Cancer Drugs Fund reconsideration of TA189.
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	Yes	Thank you for your comment.
Outcomes	Eisai Limited	The outcome measures listed are appropriate.	Thank you for your comment, time to

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		As time to progression (TTP) was a specified secondary outcome measure in the phase III trial in the relevant patient population, Eisai propose that this outcome is also included in the scope.	progression was added to the list of outcomes.
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	Yes	Thank you for your comment.
Economic analysis	Eisai Limited	No comments.	Thank you for your comment.
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	Appropriate time horizon would be 2 years since very few patients would be expected to take either lenvatinib of the comparator (sorafenib) for longer than this period (although there will be exceptions).	Thank you for your comment.
Equality and Diversity	Eisai Limited	No comments.	Thank you for your comment.

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	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	No concerns.	Thank you for your comment.
Other considerations	Eisai Limited	Under “Related NICE recommendations and NICE pathways” the information on sorafenib needs to be updated to reflect that final NICE guidance recommending sorafenib was published on the 6th September 2017	Thank you for your comment, the background section now includes information about TA474, the sorafenib Cancer Drugs Fund reconsideration of TA189.
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	None.	Thank you for your comment.

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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. As indicated, sorafenib is currently the only treatment option available in England and Wales for these patients with hepatocellular carcinoma and therefore, there is an unmet need for new treatments which delay progression and improve survival without negatively impacting patient's quality of life. In the ITT analysis of a large phase III trial , lenvatinib demonstrated non-inferiority in comparison to sorafenib with respect to overall survival (OS). In addition, lenvatinib achieved statistically significant and clinically meaningful improvements in progression-free survival (PFS), time to progression (TTP) and overall response rates (ORR). Importantly, results from the EORTC QLQ-C30 show that there was no decrease in health related quality of life (HRQoL) for those patients treated with lenvatinib.	Thank you for your comments, no changes are needed.
	HCC-UK, Association of Cancer Physicians, British Association of	The technology is innovative since it exhibits significantly greater inhibitory action on the target kinase enzymes in comparison to sorafenib. I do not consider the technology to be a 'step-change' in the management of this condition.	Thank you for your comments, no changes are needed.

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	the Study of the Liver (BASL)	The QALY calculation may not account for data which appears to indicate that lenvatinib is better tolerated than sorafenib, for example leading to less diarrhoea. Data on the treatment related adverse events and quality of life data from the phase III trial comparing lenvatinib vs sorafenib was recently presented at the ESMO 2017 meeting (abstract	
Questions for consultation	Eisai Limited	*Where do you consider lenvatinib will fit into the existing NICE pathway?* Eisai consider that lenvatinib will be used as an alternative to sorafenib in those patients with unresectable hepatocellular carcinoma who have not previously received systemic treatment.	Thank you for your comment.
	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	See responses to questions below.	Thank you for your comment.
Additional comments on the draft scope	HCC-UK, Association of Cancer Physicians, British Association of the Study of the Liver (BASL)	Any additional comments on the draft scope Have all relevant comparators for lenvatinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for advanced, unresectable, untreated, hepatocellular carcinoma? *Yes, all the relevant comparators have been included in the scope.* How should best supportive care be defined?	Thank you for your comments, no changes are needed.

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		Control of symptoms with use of systemic anti-cancer therapy. For example; analgesia, ascetic drainage, dexamethasone. Are the outcomes listed appropriate? *Yes.* Are there any subgroups of people in whom lenvatinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? *No*. Where do you consider lenvatinib will fit into the existing NICE pathway? *Lenvatinib will sit where sorafenib currently sits (ie it would replace sorafenib). In particular, patients who receive lenvatinib and experience disease progression would not be expected to subsequently receive sorafenib.* NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which levatinib will be licensed; *No.* • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;	

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		No • could have any adverse impact on people with a particular disability or disabilities. *No* Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. *I am not aware of any such evidence.* Do you consider lenvatinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *See comment above*. Do you consider that the use of lenvatinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *See comment above.* Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. *Data presented at recent ESMO 2017 conference; Vogel A. et al. Health related quality of life and disease symptoms in patients with unresectable HCC treated with lenvatinib or sorafenib. abstract 6180; annals oncology 2017; vol 28 supplement 5, p210*. NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-	

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		do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. We welcome comments on the appropriateness and suitability of the cost comparison methodology to this topic. • Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? *Lenvatinib is likely to be similar in terms of resource use as sorafenib.* • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? *Yes, overall survival end point is still relevant.* • Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year? *A phase III trial comparing nivolumab with sorafenib for patients with advanced HCC previously untreated with systemic therapy has completed recruitment and is likely to report within the nest 12months.*	

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

- Department of Heath