National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cabozantinib for treating advanced hepatocellular carcinoma after prior therapy ID1243

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	British Association for the Study of the Liver (BASL)/HCC UK-LTD	I would add in the word 'systemic' to describe the prior therapies that need to have been received. Hence; To appraise the clinical and cost effectiveness of cabozantinib within its marketing authorisation for treating advanced hepatocellular carcinoma after prior systemic therapy.	Thank you for your comment. The technology will be appraised within its marketing authorisation.
	Ipsen	The wording of the remit is appropriate.	Thank you for your comment.
Timing Issues	British Association for the Study of the Liver (BASL)/HCC UK-LTD	Data from the phase III trial comparing cabozantinib with BSC after sorafenib failure/intolerance has just reported in abstract form at ASCO-GI (Jan 2018), showing significant OS and PFS benefits. Hence the appraisal is timely.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/

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			guidance/indevelopment/gid-ta10287. No action required.
	Ipsen	The timing for NICE appraisal is relevant as there are limited treatment options in this disease area, indicating a clear unmet medical need for this group of people.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10287. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Association for the Study of the Liver (BASL)/HCC UK-LTD	Accurate and complete.	Thank you for your comment. No action required.
	Ipsen	The background section is accurate.	Thank you for your comment. No action required.

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	Royal College of Pathologists	Consideration should be given to the requirement for tissue confirmation of HCC prior to commencing treatment with cabozantinib.	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. No action required.
The technology/ intervention	British Association for the Study of the Liver (BASL)/HCC UK-LTD	Yes. Although the trial referred to has now been published in abstract form (as mentioned above), showing significant OS/PFS benefits compared to BSC.	Thank you for your comment. No action required.
	Ipsen	The description of the technology should read: 'Cabozantinib (Cabometyx, Ipsen) is a small molecule tyrosine kinase inhibitor which inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling and metastatic progression of cancer. It is orally administered'	Thank you for your comment. The scope has been amended.

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Population	British Association for the Study of the Liver (BASL)/HCC UK-LTD	Patients should have received at least one prior *systemic* therapy. Hence; Adults with advanced hepatocellular carcinoma (HCC) after prior systemic therapy	Thank you for your comment. The technology will be appraised within its marketing authorisation.
	Ipsen	The population is appropriately defined as 'adults with advanced hepatocellular carcinoma (HCC) after prior therapy'. There are no groups that should be considered separately.	Thank you for your comment. The technology will be appraised within its marketing authorisation.
Comparators	British Association for the Study of the Liver (BASL)/HCC UK-LTD	Comparators are appropriate.	Thank you for your comment. No action required.
	Ipsen	The comparators are accurate for this patient population. People with advanced hepatocellular carcinoma have very few treatment options. Regorafenib is currently the only licensed treatment option at second line for people with advanced hepatocellular carcinoma, but is currently subject to a NICE technology appraisal.	Thank you for your comment. No action required.
Outcomes	British Association for the Study of the Liver	Yes, appropriate outcomes.	Thank you for your comment. No action required.

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	(BASL)/HCC UK-LTD		
	Ipsen	The outcome measures to be considered are appropriate.	Thank you for your comment. No action required.
	Ipsen	The economic analysis is appropriate and consistent with the NICE reference case. The analysis will include an appropriate time horizon to capture all relevant costs and QALYs.	Thank you for your comment. No action required.
Equality and Diversity	British Association for the Study of the Liver (BASL)/HCC UK-LTD	No concerns.	Thank you for your comment. No action required.
	Ipsen	There are no equality issues to raise at this stage.	Thank you for your comment. No action required.
Innovation	British Association for the Study of the Liver (BASL)/HCC UK-LTD	Yes, this technology is innovative as it targets novel cellular pathways known to be dysregulated in HCC. It is a step change as it provides a second-line therapy option for patients who have not tolerated sorafenib in first-line systemic therapy (unlike regorafenib which has evidence of benefit only for those who tolerated sorafenib well), and also improves survival for those that tolerated sorafenib but have developed sorafenib-resistance.	Thank you for your comment. No action required.

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	Ipsen	Cabozantinib is an innovative therapy in a disease area of high unmet medical need. It offers an alternative treatment option for an underserved patient population with poor prognoses.	Thank you for your comment. No action required.
Other considerations	British Association for the Study of the Liver (BASL)/HCC UK-LTD	Recent abstract publication of phase III trial data needs to be considered by the appraisal.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10287. No action required.
Questions for consultation	British Association for the Study of the Liver (BASL)/HCC UK-LTD	*Have all relevant comparators for cabozantinib been included in the scope?* Yes, all relevant comparators have been included. *Is best supportive care a comparator for the populations described above? If so, how should best supportive care be defined?* Yes, BSC would be defined as management of symptoms related to cancer, generally managed by local team (GP/Macmillan nurse) with referral back to the oncology centre for management of complex symptoms control issues. *Which treatments are considered to be established clinical practice in the NHS for hepatocellular carcinoma?* Established treatments for advanced HCC in the NHS include TACE, radioembolisation (SIRT), sorafenib and supportive care. Patients will also be considered for clinical trials wherever possible. *Are the outcomes listed appropriate?* Yes.	Thank you for your comments. No action required.

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		Are there any subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? It is possible that patients whose tumours are MET-high on immunohistochemistry may preferentially benefit from cabozantinib, but this hypothesis needs to be supported by molecular subgroup analyses from the phase III trial. *Where do you consider cabozantinib will fit into the existing NICE pathway, liver cancers?* Cabozantinib will fit into the existing pathway as a second-line systemic therapy after sorafenib failure/intolernace. If sorafenib is replaced by nivolumab as the standard-of-care first-line systemic therapy in the future, then it is possible that cabozantinib might be used as second-line systemic therapy after nivolumab failure. *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 cabozantinib 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;* No.	

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		• *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.* *Do you consider cabozantinib 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 in 'innovation' section. *Do you consider that the use of cabozantinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* The outcomes for patients with advanced HCC after sorafenib failure are poor and there are no current NHS funded therapy options. Hence cabozantinib represents the only potential therapeutic strategy for these patients. *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Recently published phase III trial abstract. *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* No.	

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	Ipsen	*Have all relevant comparators for cabozantinib been included in the scope?* Yes *Is best supportive care a comparator for the populations described above? If so, how should best supportive care be defined?* Examples of BSC include herbs, acupuncture, vitamins and mineral supplements, antibiotics, bisphosphonates for bone metastases, chronic erythropoietin, analgesics, radiation therapy for pain control (limited to bone metastases), nutritional support, corticosteroids, transfusions, psychotherapy, and palliative surgery. *Which treatments are considered to be established clinical practice in the NHS for hepatocellular carcinoma?* There are few licensed systemic therapies for people with advanced hepatocellular carcinoma. The only first-line systemic treatment currently approved for use is sorafenib, and is considered standard of care but is highly toxic. However, patients who fail sorafenib have no other treatment options other than best supportive care. Regorafenib has a license for 'monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib', but have yet to receive positive NICE recommendation. *Are the outcomes listed appropriate?* Yes.	Thank you for your comments. No action required.

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		Are there any subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? No. *Where do you consider cabozantinib will fit into the existing NICE pathway, liver cancers?* Cabozantinib will be a second-line treatment option after patients have received prior therapy. *Do you consider cabozantinib 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)?* Cabozantinib is an innovative therapy associated with a statistically significant overall survival gain compared with placebo. *Do you consider that the use of cabozantinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* No *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Not applicable	

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		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. No *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)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-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.* *Would it be appropriate to use the cost comparison methodology for this topic?* No *Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?* No *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 was the primary endpoint in the CELESTIAL pivotal trial underpinning the marketing authorisation).	

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		Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? No	
	Ipsen	Small addition of 'untreated': under 'Related NICE recommendations and NICE Pathways', the lenvatinib wording should read: 'Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma. NICE technology appraisal guidance [ID1089] Publication expected October 2018'	Thank you for your comment. The related appraisal title has been amended.

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

Department of Health & Social Care