National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cabozantinib 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
Appropriateness	Exelixis International	Yes	Comments noted. No action required.
	Novartis Pharmaceuticals	NA	Comments noted. No action required.
	Pfizer Ltd	Yes, it is appropriate to refer this topic to NICE for appraisal.	Comments noted. No action required.
	Royal College of Physicians	Yes highly appropriate	Comments noted. No action required.
Wording	Exelixis International	The proposed indication in the MAA under evaluation is: the treatment of advanced (incorrectly stated as “metastatic” on the May 2015 Horizon Scanning Document) RCC in patients who have received one prior therapy.	Comments noted. Cabozantinib received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in July 2016 for ‘the

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			treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy'. The wording of the remit has been updated.
	Novartis Pharmaceuticals	NA	Comments noted. No action required.
	Pfizer Ltd	No comments	Comments noted. No action required.
	Royal College of Physicians	Yes	Comments noted. No action required.
Timing Issues	Exelixis International	There remains a clear unmet medical need in advanced RCC, and therapies that can prolong progression-free survival as well as overall survival (as cabozantinib has demonstrated in a randomized Phase 3 study) convey an important benefit. Insight into the biology and pathogenesis of RCC played a pivotal role in the development of agents targeting pathways affected by the von Hippel-Lindau (VHL) tumor suppressor protein and hypoxia-inducible factors (HIFs), including sunitinib, pazopanib, and axitinib. Despite these advances, the vast majority of patients with advanced RCC will experience disease progression due to acquired or a priori resistance to	Comments noted. An appraisal of cabozantinib has been scheduled into NICE's technology appraisal work programme.

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		VEGFR- or mTOR-targeted therapy. Of note, the median PFS with current second-line VEGFR or mTOR targeting agents or immune checkpoint inhibitors after initial VEGFR-targeted therapy (the current standard of care) is a relatively modest 3 to 5 months. Only the immune checkpoint inhibitor nivolumab (positive opinion from CHMP) has demonstrated an improvement in survival. The proposed appraisal should be completed in time to align with European Marketing Authorization.	
	Novartis Pharmaceuticals	NA	Comments noted. No action required.
	Pfizer Ltd	No comments	Comments noted. No action required.
	Royal College of Physicians	Significant patient need so as soon as possible.	Comments noted. An appraisal of cabozantinib has been scheduled into NICE's technology appraisal work programme.
Additional comments on the draft remit	Novartis Pharmaceuticals	NA	Comments noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Exelixis International	Yes	Comments noted. No action required.
	Novartis Pharmaceuticals	"This recommendation will be reviewed within the ongoing multiple technology appraisal of 'axitinib, everolimus, nivolumab, sorafenib and sunitinib for previously treated advanced or metastatic RCC'.)" : Nivolumab is not part of the MTA anymore, and it is possible that the MTA is stopped.	Comments noted. Following a series of changes to the technologies due to be appraised in the MTA, NICE considered there was limited value to the NHS in conducting an MTA of the remaining second line renal cell carcinoma therapies (axitinib, sorafenib and sunitinib). NICE has decided to remove this appraisal from its current work programme. The background section of the scope has been updated.
	Pfizer Ltd	Pfizer suggests that NICE removes text in the background information making reference to the cancelled multiple technology appraisal of 'axitinib, everolimus, nivolumab, sorafenib and sunitinib of previously treated advanced or metastatic renal cell carcinoma (RCC).	Comments noted. Following a series of changes to the technologies due to be

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			appraised in the MTA, NICE considered there was limited value to the NHS in conducting an MTA of the remaining second line renal cell carcinoma therapies (axitinib, sorafenib and sunitinib). NICE has decided to remove this appraisal from its current work programme. The background section of the scope has been updated.
	Royal College of Physicians	Accurate	Comments noted. No action required.
The technology/ intervention	Exelixis International	Yes	Comments noted. No action required.
	Novartis Pharmaceuticals	NA	Comments noted. No action required.
	Pfizer Ltd	No comments	Comments noted. No action required.
	Royal College of Physicians	Accurate	Comments noted. No action required.

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Population	Exelixis International	Yes, the population is defined appropriately. The patients studied in the Phase 3 study are representative of NHS covered patients. Based on the prospectively defined subgroup analyses in the Phase 3 study (which demonstrated a high level of consistency across endpoints), there are no groups within the indicated patient population which should be considered separately. (Subgroups further described on the following page.) Cabozantinib is likely to meet the NICE End of Life Criteria. Patients with advanced RCC (particularly after receiving prior therapy) have a life expectancy <24 months (the EoL criteria defined by NICE). Median overall survival in the placebo arm (control arm, representing an untreated patient population) of the Phase 3 everolimus study was 14.4 months. Neither axitinib nor everolimus have demonstrated a meaningful improvement in survival in their respective Phase 3 studies, and similarly, OS was <24 months. The increase in median overall survival in the cabozantinib Phase 3 study also meets the EoL criteria defined by NICE (>3 months) compared to everolimus.	Comments noted. The population has been amended to 'people who have received previous VEGF-targeted therapy for advanced renal cell carcinoma'. This is to reflect the population specified in the positive opinion from the Committee for Medicinal Products for Human Use (CHMP).
	Novartis Pharmaceuticals	NA	Comments noted. No action required.
	Pfizer Ltd	Pfizer proposes that the population is defined such that the second- and third-line populations reflected in cabozantanib's METEOR clinical trial are explicitly considered separately. This would align both the approach taken in previous NICE appraisals of RCC treatments, and with the evidence base which will underpin it's license application. Previous NICE appraisals of medicines indicated for the treatment of RCC	Comments noted. If the evidence allows, subgroups defined by 'previous lines of treatment' will be considered.

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		have been undertaken by treatment line. These include: • Sunitinib in first- and second-line (TA169 & TA178) • Sorafenib in first- and second-line (TA178) • Bevacizumab and temsiolimus in first-line (TA178) • Pazopanib in first-line (TA215) • Everolimus in second-line (TA219) • Axitinib in second-line (TA333) The METEOR randomised controlled trial (RCT), assessed the safety and efficacy of cabozantinib vs. everolimus, included a substantial proportion of participants (27-30%) who had previously received two or more vascular endothelial growth factor receptors (VEGFR), including sunitinib, pazopanib, axitinib, sorafenib, bevacizumab (Choueiri et al. 2015). Consequently, this evidence permits NICE to separately assess the clinical and cost-effectiveness of cabozantanib in second-line alongside existing treatments (e.g., axitinib, everolimus, and best supportive care [BSC]) and also in third-line. References Chouieri et al. 2015. The New England Journal of Medicine. 373(19):1814-23 (PubMed link)	
	Royal College of Physicians	Appropriate	Comments noted. No action required.
Comparators	Exelixis International	Based on our understanding of the NHS system, axitinib is the current standard of care for second line treatment for advanced RCC (based on the NICE pathway for Renal Cancer), although having demonstrated a modest	Comments noted. The comparators in the scope have been

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		improvement in PFS and no OS benefit in randomized Phase 3 studies. Indirect comparisons between cabozantinib and axitinib will be provided at the time of appraisal. Everolimus was chosen as the comparator in the cabozantinib Phase 3 study, as it was considered the standard of care across the regions included in the study (North America, Europe, Australia, Asia, and Latin America). Nivolumab received a positive opinion from CHMP 26 February 2016 (pending EC decision) for previously treated advanced RCC and would be a relevant comparator for cabozantinib. Nivolumab is the only other drug (aside from cabozantinib) that has demonstrated an OS benefit in advanced RCC, and assuming inclusion in the NICE pathway, is likely to be considered as the most relevant comparator. Indirect comparisons between cabozantinib and nivolumab will be provided at the time of appraisal.	updated to include nivolumab and everolimus.
	Novartis Pharmaceuticals	Nivolumab, sorafenib, and sunitinib should also be comparators, in addition to everolimus, axitinib, and best supportive care. Some of these treatments are undergoing NICE assessment and may be future standards of care.	Comments noted. The comparators in the scope have been updated to include nivolumab and everolimus. Sorafenib and sunitinib are not recommended after initial therapies have failed in NICE guidance (NICE technology appraisal guidance 178) and are not funded via the Cancer Drugs Fund

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			(CDF). These technologies were due to be appraised in a MTA OF 'axitinib, everolimus, nivolumab, sorafenib and sunitinib of previously treated advanced or metastatic renal cell carcinoma'. However following a series of changes to the technologies due to be appraised in the MTA, NICE considered there was limited value to the NHS in conducting an MTA of the remaining second line renal cell carcinoma therapies (axitinib, sorafenib and sunitinib). NICE has decided to remove this appraisal from its current work programme.
	Pfizer Ltd	To reflect the suggested amendments to the Population (above), Pfizer suggests that the following comparators be considered for each treatment line: Second-line:	Comments noted. Cabozantinib will be appraised within its marketing authorisation

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		• Axitinib • Everolimus • Best supportive care (BSC) Third or subsequent line: • Everolimus • BSC	for treating advanced renal cell carcinoma. Cabozantinib received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in July 2016 for 'the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy'. The comparators in the scope have been updated to include nivolumab and everolimus. In the 'other considerations' section of the scope, it states that "If the evidence allows the following subgroups will be considered. These include previous lines of treatment.

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	Royal College of Physicians	Yes	Comments noted. No action required.
Outcomes	Exelixis International	Yes. Within the pivotal study, healthcare resource utilization data were collected, including data from UK study subjects. This data will be provided at the time of appraisal.	Comments noted. No action required.
	Novartis Pharmaceuticals	Particular focus should be placed on percentage of patients experiencing adverse events, particularly grade 3 / 4 events.	Comments noted. No action required.
	Pfizer Ltd	No comments	Comments noted. No action required.
	Royal College of Physicians	Yes	Comments noted. No action required.
Economic analysis	Exelixis International	Cabozantinib is likely to meet the NICE End of Life Criteria. Exelixis requests that meeting the EoL criteria is explicitly considered when assessing the cost effectiveness case for cabozantinib in advanced RCC. A full cost effectiveness analysis will be submitted in accordance with NICE guidance at the time of appraisal.	Comments noted. In the case of a 'life-extending treatment at the end of life', the appraisal committee will satisfy itself that all of the following criteria have been met: • the treatment is indicated for patients with a short life expectancy, normally less than 24 months and

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			• there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. For more details, please see sections 6.2.9–6.2.12 of NICE's guide to the methods of technology appraisal (2013).
	Novartis Pharmaceuticals	Due to the nature of the adverse events, the economic analysis should capture their costs and disutilities.	Comments noted. Submissions to NICE should include an analysis of results generated using NICE's reference case methods. For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. Please

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			see NICE's guide to the methods of technology appraisal (2013).
	Pfizer Ltd	No comments	Comments noted. No action required.
	Royal College of Physicians	Appropriate	Comments noted. No action required.
Equality and Diversity	Exelixis International	The proposed remit and scope do not require any changes to promote equality of opportunity.	Comments noted. No action required.
	Novartis Pharmaceuticals	NA	Comments noted. No action required.
	Pfizer Ltd	No comments	Comments noted. No action required.
Other considerations	Exelixis International	Yes, the listed subgroups (previous treatment and prognostic score) are appropriate. Additional prospectively-defined subgroups were analyzed in the cabozantinib Phase 3 study: risk score (Memorial Sloan-Kettering Cancer Center prognostic criteria for previously treated patients with RCC [Motzer et al 2004] and International mRCC Database Consortium (IMDC) criteria [Heng et al 2009]), various demographics, extent of tumor burden (number of organs with metastases, presence of visceral metastases, sum of lesion diameters at baseline) and location of metastases, and tumor MET status. Based on the outcomes of subgroup analyses, there are no subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective.	Comments noted. No action required.
	Novartis	As well as just focussing on previous treatment, attention should be paid to all	Comments noted. In the

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	Pharmaceuticals	prior therapies received, and how many prior therapies have been received.	'other considerations' section of the scope, it states that "If the evidence allows the following subgroups will be considered. These include: • previous lines of treatment • prognostic score No action required.
	Pfizer Ltd	No comments	Comments noted. No action required.
	Royal College of Physicians	None	Comments noted. No action required.
Innovation	Exelixis International	Yes. In a randomized Phase 3 study, treatment with cabozantinib was associated with statistically significant clinical benefit in PFS, OS, and ORR compared with everolimus in previously treated subjects with advanced RCC. None of the other therapies for previously treated advanced RCC have demonstrated a significant benefit across these three efficacy parameters. Both axitinib and everolimus have demonstrated a modest (≈ 2 month) improvement in PFS (primary endpoint) but no OS benefit in randomized Phase 3 studies. Nivolumab demonstrated superior OS (primary endpoint) but no PFS benefit	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.

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		when compared with everolimus in the randomized Phase 3 study. Indirect comparisons will be completed to demonstrate the incremental clinical benefit compared to current SOC in the NHS (axitinib) and to nivolumab. Cabozantinib presents a unique approach to treatment due to its mechanism of action. Cabozantinib inhibits several receptor tyrosine kinases known to influence tumor growth, metastasis, and angiogenesis including MET, VEGFRs, and AXL. Several approved drugs for RCC are known VEGFR-targeting therapies, confirming the role of this signaling pathway in RCC. Emerging preclinical and clinical data suggest that acquired resistance to VEGF pathway inhibition is associated with upregulation of alternative proangiogenic and proinvasive signaling pathways, including the MET pathway (Shojaei et al 2010, Ebos et al 2011, Sennino and McDonald 2012). This concept has been demonstrated in a clear cell RCC patient-derived xenograft tumor model with acquired resistance to the VEGFR-TKI sunitinib associated with MET overexpression, where combined VEGFR and MET inhibition significantly improved efficacy over VEGFR inhibition alone (Ciamporcero et al 2015). AXL has also been implicated in the development of acquired resistance to sunitinib in clear cell RCC tumors and cell lines (Zhou et al 2015). Thus, targeting multiple signaling pathways simultaneously, including MET, VEGFRs, and AXL, may provide advantages over targeting the VEGF signaling pathway alone in advanced RCC.	
	Novartis Pharmaceuticals	Do not consider the technology to be a step-change in the management of this this condition.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.

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	Pfizer Ltd	No comments	Comments noted. No action required.
	Royal College of Physicians	Yes innovative in that it results in a significant improvement for previously treated patients compared to a current standard of care.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.
NICE Pathways	Exelixis International	Cabozantinib would be a second-line treatment for advanced renal cancer, according to the existing NICE pathway.	Comments noted. No action required.
	Pfizer Ltd	Please see our response to population.	Comments noted. No action required.
	Royal College of Physicians	Likely 2nd and 3rd line treatment – will be influenced by outcome of nivolumab appraisal.	Comments noted. No action required.
Questions for consultation	Exelixis International	***2.*** *Provide a definition of best supportive care for patients with advanced RCC.* In advanced RCC, supportive care is used in conjunction with systemic therapy (eg, axitinib, the standard of care for second line treatment for advanced RCC based on the NICE pathway for Renal Cancer) and not used alone, given the availability of therapy and progressive nature of the disease. Supportive care in RCC can include symptom-based treatment including pharmacologic management of pain and paraneoplastic syndromes, transfusions, palliative radiotherapy, metastasectomy, and bone-stabilizing drugs. It is our understanding that these are standard for supportive care,	Comments noted. No action required.

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		were included (as needed) in the cabozantinib Phase 3 study, and would be used by NHS.	
	Novartis Pharmaceuticals	NA	Comments noted. No action required.
	Pfizer Ltd	How should best supportive care be defined? BSC (defined as the provision of drug and non-drug therapy for the relief of symptoms and general patient management (TA333). Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Please see our response to population. 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)? Please see our response to population.	Comments noted. If the evidence allows, a subgroup defined by 'previous treatment' will be considered. The potential innovative nature of the technology will be considered by the appraisal committee.
	Royal College of Physicians	1. Have all relevant comparators for cabozantinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for previously treated metastatic renal cell carcinoma? Yes – axitinib and everolimus are the appropriate comparators – both are	Comments noted. No action required.

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		established clinical practice for previously treated RCC 2. How should best supportive care be defined? Presumably this has been addressed in previous appraisals? 3. Are the outcomes listed appropriate? Yes 4. Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? They are appropriate.	
Additional comments on the draft scope	Exelixis International	Data on all outcomes, including overall survival, have been submitted to EMA and FDA in supported of the submitted marketing applications. Therefore, this data will be available at the time of NICE submission. Cited references: Ciamporcero E, Miles KM, Adelaiye R, Ramakrishnan S, Shen L, Ku S, Pizzimenti S, et al. Combination strategy targeting VEGF and HGF/c-met in human renal cell carcinoma models. Mol Cancer Ther. 2015;14(1):101-10. Ebos JM, Kerbel RS. Antiangiogenic therapy: impact on invasion, disease progression, and metastasis. Nat Rev Clin Oncol. 2011;8:210–221. Erratum in: Nat Rev Clin Oncol 2011;8:316. Heng DY, Xie W, Regan MM, Warren MA, Golshavan AR, Sahi C et al. Prognostic factors for overall survival in patients with metastatic renal cell	Comments noted. No action required.

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		carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27(34):5794-9. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, et al. Prognostic Factors for Survival in Previously Treated Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol. 2004;22:454-463. Sennino B, McDonald DM. Controlling escape from angiogenesis inhibitors. Nat Rev Cancer. 2012;12(10):699-709. Shojaei F, Lee JH, Simmons BH et al. HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. Cancer Res 2010;70:10090–10100. Zhou L, Liu XD, Sun M, Zhang X, German P, Bai S, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. 2015 Sep 14. doi: 10.1038/onc.2015.343.	
	Novartis Pharmaceuticals	NA	Comments noted. No action required.

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

- Department of Health
- Royal College of Nursing