NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Cabozantinib for previously treated advanced renal cell carcinoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using cabozantinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using cabozantinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 14 March 2017

Second appraisal committee meeting: 23 March 2017

Details of membership of the appraisal committee are given in section 8.

1 Recommendations

1.1 Cabozantinib is not recommended within its marketing authorisation for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF)-targeted therapy.

1.2 This guidance is not intended to affect the position of patients whose treatment with cabozantinib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Cabozantinib (Cabometyx, Ipsen) is a small molecule that inhibits multiple receptor tyrosine kinases.
Marketing authorisation	Cabozantinib is indicated for the treatment of advanced renal cell carcinoma in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.
Adverse reactions	The most common serious adverse reactions associated with cabozantinib are abdominal pain, pleural effusion, diarrhoea and nausea (occurring in more than 10% of people). For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Administered orally, 60 mg once daily.
Price	The list price is £5,143.00 per 30-tab pack applicable to all dosages (20 mg, 30 mg and 60 mg). The company has agreed a patient access scheme with the Department of Health. If cabozantinib had been recommended, this scheme would provide a simple discount to the list price of cabozantinib 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 would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 8) considered evidence submitted by Ipsen and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of cabozantinib, having considered evidence on the nature of renal cell carcinoma and the value placed on the benefits of cabozantinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee was aware that advanced renal cell carcinoma is a relatively rare and severe cancer. It was also aware that, despite new treatments recently being recommended by NICE, there remained limited treatment options and an unmet clinical need for some people with the disease. The committee noted that the clinical experts perceived cabozantinib to be more effective than axitinib and nivolumab, although it was associated with more adverse events. The committee recognised that people with advanced renal cell carcinoma valued the increased life expectancy offered by cabozantinib and may be prepared to tolerate the adverse effects of treatment.

Treatment pathway

4.2 The committee heard from the clinical experts that, as recommended in NICE's technology appraisal guidance, most people in the NHS with newly diagnosed advanced renal cell carcinoma would first be offered 1 of 2 tyrosine kinase inhibitors (TKIs), pazopanib or sunitinib. If the disease progresses and they are fit enough to have further treatment, most people are then offered axitinib (a different TKI), or nivolumab (a programmed cell death protein 1 [PD-1]), as recommended in NICE's technology appraisal guidance. If the disease progresses further, people who previously had axitinib may have nivolumab as a third-line treatment, and vice versa. The committee understood that everolimus (a mammalian target of rapamycin [mTOR] inhibitor) was previously available through the Cancer Drugs Fund for people who have had only 1 TKI and who cannot have axitinib; however, final draft guidance issued by NICE following the Cancer Drugs Fund reconsideration recommends everolimus for advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy, which includes TKIs. The clinical experts advised that everolimus could be used after 1 or more previous treatments, and would generally be used later in treatment. The committee recognised that treating advanced renal cell carcinoma in clinical practice followed NICE guidance.

Population and comparators

4.3 The clinical experts explained that they would offer cabozantinib to patients who have had 1 or 2 previous treatments. At this point in the pathway, axitinib, nivolumab and everolimus are also treatment options (section 4.2). The committee was aware that the final scope of this appraisal included best supportive care as a comparator. It heard from the clinical experts that active treatment is unsuitable for some people who are not fit enough and who will instead have best supportive care, but the committee understood that this represents a small group unlikely to reflect those who would be offered cabozantinib. The committee agreed that cabozantinib should not be compared with best supportive care. It concluded that cabozantinib would be used in people who have had 1 or 2 previous treatments, and so the relevant comparators were axitinib, nivolumab and everolimus.

4.4 The committee discussed whether there was merit in considering separately people who have had 1 or 2 previous treatments. It heard from the clinical experts that there was no biological reason for axitinib and everolimus to work any differently based on people having 1 or 2 previous treatments. The clinical experts also noted that cabozantinib acts on more targets than currently available treatments including TKIs. Because of this, they expected that cabozantinib would work similarly after 1 previous treatment as it would after 2 previous treatments, and also that it would also work after other TKIs had failed. The committee also noted that data from the clinical trial METEOR suggested that there was no statistically significant difference between the survival of people who had 1 or 2 previous treatments, and the overall population. The committee concluded that it would consider cabozantinib for the population comprising people who have had 1 or 2 previous treatments as a whole.

Clinical effectiveness

4.5 The committee noted that the main evidence for cabozantinib came from METEOR, an open-label randomised controlled trial comparing cabozantinib with everolimus. The committee appreciated that the trial did not allow patients to switch from placebo to cabozantinib at disease progression. The committee agreed that METEOR was well conducted and relevant to the decision problem.

4.6 The committee noted that METEOR measured progression-free survival in 2 populations:

- The primary intention-to-treat analysis (primary end point): when 259 patients had progressed among the first 375 patients randomised (n=375).
- The intention-to-treat analysis: all patient randomised at baseline (n= 658).

The company explained that METEOR used the 'primary intention-to-treat population' to detect a difference between treatments sooner than had it used the intention-to-treat population. The company argued that using a larger sample size would over-represent patients whose disease progressed early, or under-represent those whose disease progressed late. The committee noted that fewer events occurred in the primary intention-to-treat population than in the intention-to-treat population, which resulted in less mature data. It also noted that the intention-to-treat population reflected a longer follow-up than the primary intention-to-treat population. Because of this, the committee concluded that it would use the intention-to-treat analysis in its decision-making to best make use of all available data, and the longest follow-up of patients.

Clinical trial results

4.7 In the intention-to-treat population of METEOR (as of December 2015 data cut-off):

- Progression-free survival was significantly improved with cabozantinib compared with everolimus (median 7.4 and 3.9 months respectively; hazard ratio 0.51; 95% confidence interval [CI] 0.41 to 0.62; p<0.0001).
- Overall survival was improved with cabozantinib compared with everolimus (median 21.4 and 16.5 months respectively; hazard ratio 0.66; 95% CI 0.53 to 0.83; p=0.00026).

The committee concluded that cabozantinib was more effective than everolimus in METEOR.

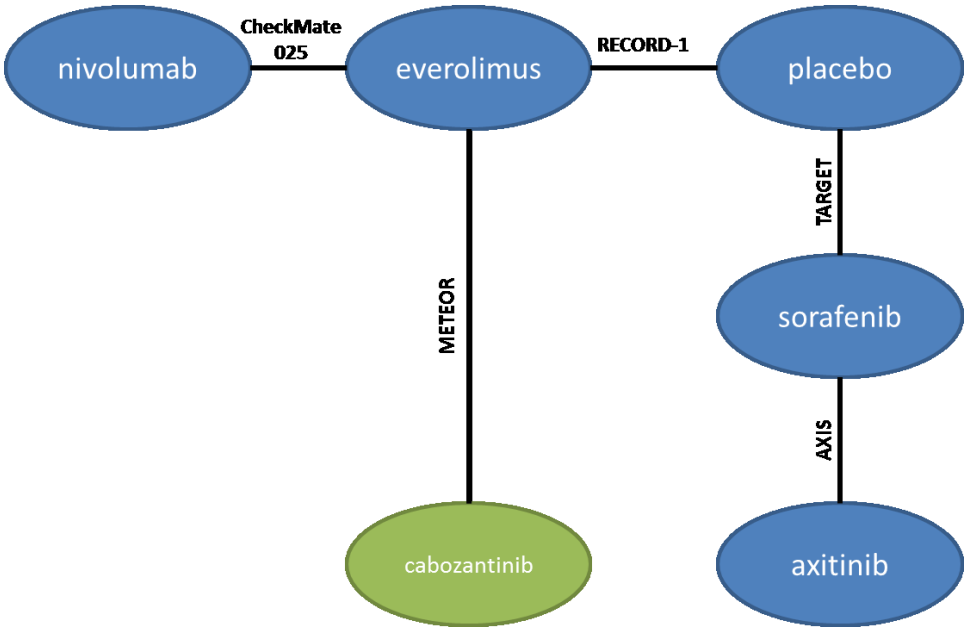
Generalisability of the results of METEOR

4.8 The committee noted the evidence review group's (ERG's) comment that 67% of patients in METEOR had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (67%), which is a higher proportion than would generally be seen in the NHS. The committee was aware that clinical trials normally include relatively fit patients who may not fully represent clinical practice. The committee heard from the clinical experts that measuring ECOG performance status is somewhat subjective, and they did not consider that this would affect the generalisability of the results to patients seen in the NHS. The committee concluded that the results of METEOR were generalisable to the NHS.

Network meta-analysis

4.9 Because there were no head-to-head trials comparing cabozantinib with axitinib, nivolumab or best supportive care, the company did a network meta-analysis to compare the treatments indirectly (Figure 1).

Figure 1 Network of trials used by the company for progression-free survival and overall survival



The ERG considered the results of the network meta-analysis to be unreliable and advised caution when interpreting them. This was because the trials included in the network differed substantially in whether they allowed patients to switch between treatment arms, the number and type of therapies taken before enrolling in the trial and after the disease progressed during the trial, and the prognostic scores at baseline. The ERG was particularly concerned about TARGET having been included in the network, which compared sorafenib with best supportive care; TARGET allowed patients to switch treatment after their disease progressed, but the data that the company used from the trial censored patients who switched treatment. Excluding these patients reduced the number of events, and thus the maturity of the dataset. The ERG explained that if sorafenib was more effective than placebo, then using censored data from TARGET was likely to underestimate the effect of sorafenib. Because AXIS showed that axitinib and sorafenib are similarly effective, underestimating the relative effect of sorafenib would in turn underestimate the effect of axitinib. The committee was aware that

TARGET was done before VEGF-targeted therapies were available for renal cell carcinoma, so none of the patients in this study had previously had VEGF-targeted therapies. The committee acknowledged the caveats about TARGET but agreed that TARGET needed to be included in the network to link to axitinib. The committee concluded that it would take into account any potential biases in the network when making decisions.

Methodology of the network meta-analysis

4.10 The committee noted that the company modelled parametric survival curves separately for each treatment, rather than generating a curve for one treatment from a curve of another treatment using hazard ratios from clinical trials. The company did this because the proportional hazard assumption (which is required of hazard ratios generated from proportional hazards models) did not hold for progression-free and overall survival in some of the studies included in the network meta-analysis. The committee understood from the ERG that modelling separate parametric curves meant that the company used the same parametric distribution for all the treatments, which was chosen based on how well, on average, it fitted the progression-free or overall survival curves for all the treatments in the network. The ERG considered this simplification to be a serious limitation of the company's network meta-analysis, leading to potentially unreliable results. This was because the distribution chosen by the company for either progression-free or overall survival may not fit the curve for each individual treatment. For example, the ERG noted that the log-normal distribution that the company used for overall survival did not fit the overall survival curve for sorafenib. This resulted in the relative effectiveness of cabozantinib compared with axitinib being uncertain because sorafenib is linked to axitinib in the network. The committee also noted that none of the distributions that the company tested for progression-free survival fitted the data well. The committee agreed that the company should have tested more flexible distributions. The committee noted that the company used the methods described by

Ouwens et al. (2010), whereas other publications describe methods using models that can fit the data more flexibly (for example, the publication by Janssen et al. 2011). The committee concluded that the company's current network meta-analysis was highly uncertain, and that it should use better-fitting distributions. In addition, the committee considered that it was important to see the estimated survival benefit of the alternative treatments both before and after disease progression, using modelling approach, to assess the plausibility of the estimates.

4.11 Because of the limitations in the company's methods, the ERG estimated the relative effect of axitinib by assuming that it is as effective as everolimus for overall survival (Table 1). The ERG noted that the proportional hazard assumption for overall survival did not hold in TARGET and the first 6 weeks of CheckMate 025. By assuming that axitinib and everolimus are clinically equivalent (thereby dropping TARGET from the network), and assuming that the first 6 weeks of CheckMate 025 do not have an important impact on overall survival, the ERG accepted that the proportional hazard assumption holds for overall survival. The committee was aware that the committee had accepted clinical equivalence between axitinib and everolimus in the technology appraisal of nivolumab, and it heard from the clinical experts that this was clinically reasonable. The committee preferred the ERG's approach because it simplified the evidence network and reduced the potential bias associated with using censored data from TARGET, but the committee remained concerned about the methodology underpinning the network meta-analysis (section 4.10).

Table 1 Estimated median overall and progression-free survival: company's base case and ERG's approach

Treatment	Median OS (months)		Median PFS (months)	
	Company's NMA	ERG's amended NMA	Company's NMA	ERG's amended NMA
Cabozantinib	22.9	22.0	7.8	7.8
Axitinib	15.7	16.3	4.9	4.7
Everolimus	16.3	16.3	4.4	4.7
Placebo	11.5	10.1	2.4	1.9
Nivolumab	20.8	20.4	5.1	5.2
Abbreviations: NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.				

Cost effectiveness

4.12 The company used a 3-stage, partitioned-survival economic model, which the committee considered appropriate to capture the natural history of the disease. The health states included in the model were pre-progressed disease, progressed disease and death. The company used the model to estimate average delay in time to disease progression, average delay in time to death, costs and health-related quality of life associated with cabozantinib and its comparators by forecasting beyond the end of the trials.

4.13 The company presented 2 separate cost-effectiveness analyses based on the model:

- A trial-based analysis comparing cabozantinib with everolimus using data from METEOR only.
- A network meta-analysis-based analysis comparing cabozantinib with axitinib, everolimus, best supportive care and nivolumab using data from the network meta-analysis.

The committee agreed that the trial-based analysis was useful to check the internal validity of the model; if it produced plausible and robust estimates that aligned with the observed data from METEOR, the

committee could then confirm that the network meta-analysis-based model was suitable for its decision-making for comparators other than everolimus. The committee recognised that the trial data were more robust than those estimated from the network meta-analysis, which was associated with methodological limitations implying that decisions based on it would be highly uncertain (section 4.10). The committee concluded that both analyses presented by the company would inform its decision about the cost effectiveness of cabozantinib.

Modelling progression-free survival and overall survival

4.14 The committee recalled its misgivings about how the company estimated progression-free survival and overall survival in the network meta-analysis (section 4.10), and reiterated its concerns about the resulting estimates. It noted that the model was highly sensitive to distributions chosen for progression-free survival and overall survival. For example, the ERG modelled overall survival in the trial-based analysis using the Weibull distribution, instead of the log-logistic distribution used by the company in its base case. This change alone increased the incremental cost-effectiveness ratio (ICER) by more than £30,000 per quality-adjusted life year (QALY) gained compared with the company's base-case ICER. The log-logistic distribution predicted that around 16% of patients having cabozantinib and 11% of those having everolimus would be alive 5 years after starting treatment. This compares with around 5% and 2% respectively when using the Weibull distribution. The committee heard from the clinical experts that some people have slowly growing cancer, and that these people would be expected to live longer, but they represent only a small proportion of patients with renal cell carcinoma in the NHS. The company stated that recent data showed that 6% of patients would be alive 7 years after starting treatment, but did not present this evidence to the committee. The committee agreed that when modelling overall survival, it was important to choose the parametric distribution based on reliable evidence on the natural history of the disease in current UK

clinical practice. The committee invited the company to submit any such evidence, accounting for differences in population and disease characteristics that may increase or decrease the risk of death.

4.15 The committee considered the treatment effect of cabozantinib during the extrapolation period. It noted that both the company and the ERG assumed that the effect of treatment continued beyond trial follow-up, even after stopping treatment, although the committee was not presented with evidence to support this assumption. The clinical experts considered that it was not clear whether a survival benefit would continue after stopping treatment. They explained that in clinical practice, some patients may have stable disease for 2 to 3 years after stopping treatment, whereas the disease may progress more quickly in others. Also, some patients have a prolonged response after a short length of treatment, and others do not. The committee discussed whether patient survival in METEOR could provide insight into the long-term effect of cabozantinib. It noted that the Kaplan–Meier curves continued to diverge during the trial period for overall survival, but for progression-free survival the 2 arms initially diverged but then converged later into the follow-up period. The committee agreed that it could not preclude the possibility that the overall survival curves for cabozantinib and everolimus could converge over the extrapolation period, similar to the convergence seen with progression-free survival. Given the available evidence, the committee considered the assumption that the treatment effect continues up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival (18.7 months), to be highly uncertain. The committee emphasised the need for evidence on the natural history of the disease in current UK clinical practice to guide the modelling of overall survival (section 4.14), and reiterated the importance of seeing the estimated survival benefit of the alternative treatments, both before and after disease progression, for each modelling approach used to extrapolate survival across the model time horizon (see section 4.10).

4.16 The committee discussed the modelled effect of nivolumab. It recalled from the NICE technology appraisal on nivolumab that the clinical experts who advised the committee at the time felt it was plausible that an overall survival curve with a 'long tail' could be shown for renal cell carcinoma treated with nivolumab because it was an immunotherapy. This committee could not be sure that the long tail would be seen in renal cell carcinoma, but it agreed to consider scenarios with predictions of better survival for nivolumab in its decision-making; for example, the scenario put forward by the company in the technology appraisal of nivolumab suggesting that patients whose disease was treated with nivolumab and who survive for 5 years would have the same risk of death after 5 years as the age-matched general population.

Cost of nivolumab

4.17 The company's model did not include any wastage for nivolumab, because the company noted that nivolumab is dosed by body weight. The committee recalled that during the technology appraisal of nivolumab, it had considered that some nivolumab would be wasted. The ERG presented an analysis that included the wastage costs estimated at 8.5% for nivolumab, and obtained using the weight distribution of patients in the METEOR trial (average 80.19 kg). The committee concluded that the model should account for wastage for nivolumab, and that the ERG's assumptions were reasonable.

Cost and effect of subsequent treatments

4.18 The company included the cost of sorafenib as a subsequent treatment in the model, whereas the ERG excluded it because sorafenib it is not available in the NHS. The committee agreed that sorafenib should not be included as a subsequent treatment in the model, but that the model should correct for the effect on overall survival unless sorafenib was assumed not to prolong survival when used at third line or beyond.

Cost of monitoring before disease progression

4.19 The company's model assumed that patients with advanced renal cell carcinoma were monitored by GPs for an average of 4 weeks before disease progression. The committee heard from the ERG that patients were more likely to be monitored by consultant oncologists during this period of time. The committee concluded that the ERG's approach better reflected clinical practice.

Utility values

4.20 The committee was aware that METEOR collected health-related quality-of-life data using the EQ-5D-5L measure. It considered these data, together with data from other studies, including those used in previous appraisals of renal cell carcinoma. The committee noted that the available utility values varied widely, particularly those used for the post-progression state. The ERG explained that the utility values collected from METEOR were higher than those it would expect to see in clinical practice. Because of this, the ERG used utility values from the AXIS trial in its exploratory analyses. The committee noted that METEOR used the new version of the EQ-5D (EQ-5D-5L) which is more detailed than the previous version; the committee accepted that this could explain the relatively high utility values reported in METEOR. Also, the subsequent treatments that patients had after disease progression, which could include continuing study treatment, may have contributed to the higher estimates. Nevertheless, the committee expressed its general preference for trial-based utility values particularly when, as in METEOR, the patients reflected those seen in clinical practice. The committee therefore considered the company's base case, which applied utility values for all comparator treatments from METEOR, to be appropriate. The committee noted, however, that the company had not adjusted the utility values for age, whereas aging would naturally affect health-related quality of life. The committee considered that using utility values from METEOR was appropriate, but that these values should be adjusted for age.

4.21 In its base case, the company considered the utility decrements for adverse events separately from other utility values. The ERG explained that the company had calculated the overall adverse event-related decrement in utility values for each treatment arm from METEOR by weighting the adverse event utility decrement by the proportion of patients experiencing a grade 3 or 4 adverse event. The ERG considered that the initial utility decrement used by the company (−0.055) was too low. The committee acknowledged that adverse events could have a major effect on patients' health-related quality of life, and it recalled hearing from clinical experts that cabozantinib is associated with more adverse events than axitinib and nivolumab (section 4.1). The committee was not persuaded that the utility decrements used by the company represented the best available evidence because alternative data reflecting a larger sample size may be available. It concluded that it would like to see evidence on how adverse events affect health-related quality of life from other published sources, based on a systematic review of the literature.

End-of-life considerations

4.22 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.

4.23 The committee considered the life expectancy of people with previously treated advanced renal cell carcinoma having each of the 4 comparator treatments. It considered that the overall survival estimates were unreliable because of the large amount of uncertainty in the network meta-analysis (section 4.10) and the company's model. The committee was aware from the technology appraisal of nivolumab that people with advanced renal cell carcinoma having axitinib or everolimus had an average life expectancy of less than 24 months. For nivolumab, the committee considered that the evidence from the model was not reliable enough to establish the mean life expectancy of people who have this

treatment, but it was aware that CheckMate 025 reported a median overall survival among patients in the nivolumab treatment arm of 25 months. The committee concluded that, until it considers revised analyses which address the issues in the current evidence base, it could not make an informed decision as to whether cabozantinib meets the end-of-life criteria.

Results of cost-effectiveness analyses

4.24 The committee considered the base-case cost-effectiveness results from both the company's model and ERG's amendments, including confidential discounts for all technologies. The committee recalled its reservations about the analyses presented, particularly the modelling of progression-free survival and overall survival (section 4.10). It noted that the ICER for cabozantinib compared with everolimus in the trial-based model exceeded £30,000 per QALY gained. The ICERs for cabozantinib compared with any comparator from the network meta-analysis model also exceeded £30,000 per QALY gained. The committee concluded that it could not recommend cabozantinib as a cost-effective use of NHS resources.

4.25 The committee had concerns about the quality of the cost-effectiveness evidence presented. It would have preferred to have seen analyses that:

- Exclude best supportive care from the comparison with cabozantinib.
- Use methods allowing better-fitting distributions to model progression-free survival and overall survival (section 4.10).
- Assume that axitinib is as effective as everolimus in terms of overall survival (section 4.11).
- Use evidence on the natural history of the disease to guide the modelling of overall survival with cabozantinib, adjusted as necessary for confounders (sections 4.14 and 4.15).
- Present a comparison of the survival benefits of cabozantinib and each of its comparators, before and after disease progression, for each modelling approach used (section 4.15).

- Account for wastage for nivolumab using the ERG's assumptions (section 4.17).
- Exclude the costs and any survival benefit of subsequent treatments not available in the NHS such as sorafenib (section 4.18).
- Assume that patients are monitored by consultant oncologists for an average of 4 weeks before disease progression (section 4.19).
- Use age-adjusted utility values from METEOR (section 4.20).
- Use utility decrements based on a well-conducted systematic review of the literature (section 4.21).
- Explore, in scenario analyses, predictions of better survival for nivolumab (section 4.17).
- Derive the results from incremental cost-effectiveness analyses.
- Reflect probabilistic cost-effectiveness analyses.

Innovation

4.26 The committee considered whether cabozantinib was an innovative treatment. It heard from the clinical experts that, because of its multi-targeted approach, cabozantinib would likely have additional benefits for some patients and so could be considered innovative. The committee also heard that cabozantinib would be highly valued in patients whose disease is resistant to standard TKIs and whose disease may or may not have responded to nivolumab. The committee agreed that cabozantinib could fulfil the unmet need in these patients. However, the committee did not identify a benefit to utility that was not otherwise accounted for in the modelling.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.27 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost

effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Cancer Drug Fund

4.28 The committee considered whether cabozantinib for advanced renal cell carcinoma could be considered for inclusion in the Cancer Drug Fund. The committee agreed that the areas of uncertainty associated with the clinical effectiveness of cabozantinib could not be addressed by the Cancer Drugs Fund arrangements. The company did not express a view as to whether or not there might be a case for using cabozantinib within the Cancer Drugs Fund.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
Cabozantinib is not recommended within its marketing authorisation for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF)-targeted therapy.		1.1
Cabozantinib improved progression-free survival and overall survival compared with everolimus (METEOR), but there was substantial uncertainty about the results of the network meta-analysis.		4.7, 4.10
The committee concluded that, until it considers revised analyses which address the issues in the current evidence base, it could not make an informed decision as to whether cabozantinib meets the end-of-life criteria.		4.23

The committee recalled its reservations about the analyses presented, particularly the modelling of progression-free survival and overall survival. It noted that the ICER for cabozantinib compared with everolimus in the trial-based model and the ICERs for cabozantinib compared with any comparator from the network meta-analysis model exceeded £30,000 per QALY gained. The committee concluded that it could not recommend cabozantinib as a cost-effective use of NHS resources.	4.24
Current practice	

Clinical need of patients, including the availability of alternative treatments	Most people in the NHS with newly diagnosed advanced renal cell carcinoma would first be offered 1 of 2 tyrosine kinase inhibitors (TKIs), pazopanib or sunitinib. If the disease progresses and they are fit enough to have further treatment, most people are then offered axitinib (a different TKI), or nivolumab (a programmed cell death protein 1 [PD-1]), as recommended in NICE's technology appraisal guidance. If the disease progresses further, people who previously had axitinib may have nivolumab as a third-line treatment, and vice versa. The committee understood that everolimus (a mammalian target of rapamycin [mTOR] inhibitor) was previously available through the Cancer Drugs Fund for people who have had only 1 TKI and who cannot have axitinib; however, final draft guidance issued by NICE following the Cancer Drugs Fund reconsideration recommends everolimus for advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy, which includes TKIs. The clinical experts advised that everolimus could be used after 1 or more previous treatments, and would generally be used later in treatment.	4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from the clinical experts that, because of its multi-targeted approach, cabozantinib would likely have additional benefits for some patients and so could be considered innovative. The committee also heard that cabozantinib would be highly valued in patients whose disease is resistant to standard TKIs and whose disease may or may not have responded to nivolumab.	4.26
What is the position of the treatment in the pathway of care for the condition?	Cabozantinib can be used in people who have had 1 or 2 previous treatments, and so the relevant comparators were axitinib, nivolumab and everolimus.	4.3
Adverse reactions	The most common serious adverse reactions associated with cabozantinib are abdominal pain, pleural effusion, diarrhoea and nausea (occurring in more than 10% of people).	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The main evidence came from METEOR, an open-label randomised controlled trial comparing cabozantinib with everolimus. The committee appreciated that the trial did not allow patients to switch from placebo to cabozantinib at disease progression. METEOR measured progression-free survival in 2 populations: • The primary intention-to-treat analysis (primary end point): when 259 patients	4.5 4.6

	had progressed among the first 375 patients randomised (n=375). • The intention-to-treat analysis: all patient randomised at baseline (n= 658). The committee concluded that it would use the intention-to-treat analysis in its decision-making, to best make use of all available data and the longest follow-up of patients.	
Relevance to general clinical practice in the NHS	The committee concluded that the results of METEOR were generalisable to the NHS.	4.8

Uncertainties generated by the evidence	The ERG considered the results of the network meta-analysis to be unreliable and advised caution when interpreting the results. This was because the trials included in the network differed substantially in whether they allowed patients to switch between treatment arms, the number and type of therapies taken before enrolling in the trial and after disease progressed during the trial, the prognostic scores at baseline, and the inclusion of TARGET within the network. The committee concluded that the company's current network meta-analysis was highly uncertain, and that it should use better-fitting distributions. Because of the limitations in the company's methods, the ERG estimated the relative effect of axitinib by assuming that it is as effective as everolimus for overall survival.	4.9 4.10 4.11
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that it would consider cabozantinib for the population comprising people who have had 1 or 2 previous treatments as a whole.	4.4

Estimate of the size of the clinical effectiveness including strength of supporting evidence	In the intention-to-treat population of METEOR (as of December 2015 data cut-off): • Progression-free survival was significantly improved with cabozantinib compared with everolimus. • Overall survival was improved with cabozantinib compared with everolimus.	4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The company used a 3-stage, partitioned-survival economic model, which the committee considered appropriate to capture the natural history of the disease.	4.12

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee recalled its misgivings about how the company estimated progression-free survival and overall survival in the network meta-analysis, and reiterated its concerns about the resulting estimates. It noted that the model was highly sensitive to distributions chosen for progression-free survival and overall survival.	4.14
	Given the available evidence, the committee considered the assumption that the treatment effect continues up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival (18.7 months), to be highly uncertain.	4.15
	This committee could not be sure that the long tail would be seen in renal cell carcinoma, but it agreed to consider scenarios with predictions of better survival for nivolumab in its decision-making.	4.16
	The committee noted, however, that the company had not adjusted the utility values for age, whereas aging would naturally affect health-related quality of life.	4.20

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee was not persuaded that the utility decrements used by the company represented the best available evidence because alternative data reflecting a larger sample size may be available. The committee did not identify a benefit to utility that was not otherwise accounting for in the modelling.	4.21 4.26
Are there specific groups of people for whom the technology is particularly cost effective?	No subgroup analyses were presented.	
What are the key drivers of cost effectiveness?	The choice of distribution for modelling progression-free survival and overall survival	4.10

Most likely cost-effectiveness estimate (given as an ICER)	When the confidential discounts for all technologies were included: • the ICER for cabozantinib compared with everolimus in the trial-based model exceeded £30,000 per QALY gained. • the ICERs for cabozantinib compared with any comparator from the network meta-analysis model also exceeded £30,000 per QALY gained.	4.24
Additional factors taken into account		
Patient access schemes (PPRS)	There are patient access schemes for cabozantinib, axitinib, everolimus and nivolumab. The ERG presented analyses that included the confidential discount for all technologies.	
End-of-life considerations	The committee could not make an informed decision as to whether cabozantinib meets the end-of-life criteria.	4.23
Equalities considerations and social value judgements	No equality issues were identified by consultees or the committee.	

5 Implementation

5.1 The Department of Health and Ipsen have agreed that cabozantinib 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]

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance.NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
February 2017

7 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 B.

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.

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.

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.

Aminata Thiam
Technical lead

Ahmed Elsada
Technical adviser

Jeremy Powell
Project manager

ISBN: [to be added at publication]