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: 10 May 2017

Third appraisal committee meeting: To be confirmed.

Details of membership of the appraisal committee are given in section 7.

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 recommendation is not intended to affect treatment with cabozantinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements 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 (RCC) 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, 40 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 7) considered evidence submitted by Ipsen and a review of this submission by the evidence review group. 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, despite new treatments recently being recommended by NICE, there remained limited treatment options and an unmet clinical need for some people with advanced renal cell carcinoma. The committee noted that the clinical experts perceived cabozantinib to be more effective than everolimus and axitinib, although it caused more adverse effects. The committee recognised that people with advanced renal cell carcinoma would value any 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 most people in the NHS with newly diagnosed advanced renal cell carcinoma will first be offered 1 of 2 tyrosine kinase inhibitors (TKIs), pazopanib or sunitinib, as recommended in NICE guidance. If the disease progresses and they are fit enough to have further treatment, most people are then offered axitinib (a different TKI), nivolumab (a programmed cell death protein 1 [PD-1]), or everolimus (a mammalian target of rapamycin [mTOR] inhibitor), again as recommended in NICE guidance. If the disease progresses again, people who previously had axitinib may have nivolumab or everolimus as a third-line treatment; people who had nivolumab may have axitinib or everolimus; and people who had everolimus may have axitinib or nivolumab. The committee concluded that the current treatment pathway offered options for patients.

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, axitinib, nivolumab and everolimus are also treatment options (sections 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 a small group of people who are not fit

enough and who will instead have best supportive care. The committee appreciated that, after positive NICE guidance on nivolumab, this group was even smaller, and unlikely to reflect those who would be offered cabozantinib. The committee concluded that cabozantinib would be used in people who have had 1 or 2 previous treatments, and that the relevant comparators were axitinib, nivolumab and everolimus.

4.4 The committee discussed the use of everolimus in clinical practice. At the first committee meeting, it heard from the clinical experts that everolimus could be used after 1 previous treatment (second line), although they would prefer to use it after 2 or 3 previous treatments (third or fourth line). At that time, everolimus was available only through the Cancer Drugs Fund, as a second-line treatment, after 1 TKI for people who cannot have axitinib. So, clinicians could not use everolimus beyond the second-line setting in the NHS. NICE published guidance following the Cancer Drugs Fund reconsideration of everolimus in February 2017, recommending everolimus, with a new patient access scheme (lower price), for routine commissioning. The Cancer Drugs Fund reconsideration of everolimus broadened the population eligible for treatment. It means that everolimus is now recommended after 1 or more lines of vascular endothelial growth factor (VEGF) targeted therapy (which includes TKIs), rather than after only 1 TKI in those who cannot take axitinib. Given the recent changes in the recommendations for everolimus, and the clinicians' preference to use everolimus later in treatment, the committee appreciated that everolimus might be used after 1, but also after 2 or 3 previous treatments. The committee would welcome comments on the likely positioning of everolimus in the treatment pathway, following recent NICE guidance. The committee concluded that everolimus was a relevant option after 1 or 2 previous treatments alongside axitinib and nivolumab.

4.5 The committee discussed whether there was merit in considering separately people who have had 1 or had 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. In addition, the clinical experts stated that cabozantinib would be expected to work similarly after 1 previous treatment as it would after 2 previous treatments, and that it would also work after other TKIs had failed. The committee concluded that it would consider cabozantinib for the population comprising people who have had either 1 or 2 previous treatments as a whole.

Clinical effectiveness

4.6 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 everolimus to cabozantinib at disease progression. The committee agreed that METEOR was well conducted and relevant to the decision problem.

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

- The primary end point intention-to-treat population: the first 375 patients randomised (n=375).
- The intention-to-treat population: all patients randomised at baseline (n=658).

The committee noted that more events occurred in the intention-to-treat population than in the primary intention-to-treat population, which resulted in more 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 for its decision-making.

Clinical trial results

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

- Progression-free survival 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 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.

4.9 The committee noted the updated survival data from METEOR, presented by the company during consultation. These data were based on a cut-off date of October 2016 compared with December 2015 for the original data cut. The committee welcomed the availability of new, more mature data.

Generalisability of the results of METEOR

4.10 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%). This reflected a fitter population than would generally exist in the NHS, and the committee was aware that clinical trials normally include relatively fit patients who may not represent clinical practice. The committee heard from the clinical experts that they did not consider that this would affect the generalisability to patients seen in the NHS. The committee concluded that the results of METEOR were generalisable to the NHS.

Network meta-analysis

4.11 Because there were no head-to-head trials comparing cabozantinib with axitinib or nivolumab, the company did a network meta-analysis to compare the treatments indirectly. The original network linked 6 trials, including TARGET, which compared sorafenib with placebo. Although sorafenib was not a comparator for cabozantinib in this appraisal, the company included TARGET to link together treatments. The committee

was concerned about including this trial for 2 reasons. First, none of the patients had previously had VEGF-targeted therapies. Second, the company used immature data from the trial, which censored patients who switched from placebo to sorafenib. This was likely to have underestimated the effect of sorafenib because the placebo data reflected patients whose disease responded relatively well (who were therefore not censored), and this would in turn have underestimated the effect of axitinib. In response to consultation, and in line with the committee's preference, the company submitted a revised network that excluded TARGET. This assumed that axitinib was as effective as everolimus in terms of overall and progression-free survival. The committee concluded that the company's simplified network reduced the potential bias associated with using immature data from TARGET.

Methodology of the network meta-analysis

4.12 The committee understood that, to estimate long-term outcomes, the company used a 'family' of related survival curves for cabozantinib and for all of the comparator treatments. The company chose the curves based on how well, on average, they fitted the data on overall or progression-free survival for all the treatments in the network. The committee noted that, because of this simplification, the parametric distribution chosen by the company for both progression-free and overall survival (log-normal for both end points) did not fit the data for each individual treatment well. In response to consultation, the company used fractional polynomial modelling, as described by Janssen et al. (2011), to fit survival curves. The new method also used a family of related survival curves for all the treatments. However, the committee agreed that it was a more flexible family, which improved the curve fits to the Kaplan–Meier data on overall and progression-free survival for all treatments in the network compared with the original parametric modelling using the log-normal distribution. The committee appreciated that the fractional polynomial modelling did not fit data in the extrapolation period. The committee noted that the ERG

considered that estimating survival based on the 'average fit' across the network (as opposed to the fit for each individual treatment) was less of an issue with fractional polynomial models than with parametric curve fitting. The committee was satisfied that the company's revised modelling of overall and progression-free survival was more appropriate than the original parametric modelling.

Cost effectiveness

4.13 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, and costs and health-related quality of life associated with cabozantinib and its comparators by forecasting beyond the end of the trials.

4.14 In its original submission, 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 recognised that the trial data were more robust than those estimated from the network meta-analysis because they reflected a direct comparison between 2 treatments. The committee noted that it could have confidence that the model was suitable for decision-making with respect to comparators other than everolimus, if the model based on the network meta-analysis produced plausible estimates for cabozantinib compared with everolimus, which aligned with the analysis based on observed data from METEOR. It concluded that it was appropriate to use the trial-based

analyses to check the internal validity of the model. The committee noted that, in response to consultation, the company did not present a trial-based analysis, although the ERG provided this to the committee.

Survival modelling

4.15 The committee considered the company's revised modelling in response to consultation. It noted that, to estimate overall and progression-free survival for cabozantinib and its comparator treatments, the company extrapolated the curves based on fitting fractional polynomial models (see section 4.12) up to the end of the time horizon. As such, to estimate overall and progression-free survival for cabozantinib and its comparator treatments, the company used fractional polynomial modelling during both the trial follow-up and extrapolation. Hereafter, this analysis will be referred to as 'the company's revised base case'.

Comparison of survival predictions in the company's revised base case with observational data on everolimus (the natural history of the disease)

4.16 In its revised base case (see section 4.15), the company predicted that 5% of people in the everolimus arm would be alive 5 years after starting treatment. The committee compared this estimate with 2 sources of observational data submitted during consultation:

- Registry-based pharmaco-epidemiological data from a publication by Ruiz-Morales et al. (2016) submitted by the company. These data came from the International Metastatic renal cell carcinoma Database Consortium (IMDC) reflecting people initially treated with either pazopanib or sunitinib. Some people then had second-line treatment. The company presented data for people who had second-line treatment after sunitinib (n=2,667) because this group was larger than those who had second-line treatment after pazopanib (n=260). It noted that, in that group, about 10% were alive 5 years after starting treatment.
- Audit data from the Christie Hospital (Manchester, UK) submitted by a clinical expert. These data showed that, among people who had axitinib

or everolimus as a second-line treatment (n=282), around 6% were alive 5 years after starting treatment.

4.17 The committee discussed whether the Ruiz-Morales et al. (2016) data on were generalisable to patients who would be offered everolimus in the UK. It observed that:

- Ruiz-Morales et al. did not include patients from the UK, and acknowledged that the company considered that the study included people with similar characteristics at baseline to patients in METEOR, and that the countries from which these people were included had similar socio-economic profiles and health systems to the UK
- As second-line treatment, only 45% of people had everolimus, and some had treatments that were not available in the NHS
- Ruiz-Morales et al. did not report information on the third-line treatments; these treatments may not be available in the NHS, and may have biased the effect of second-line treatment.

For these reasons, the committee suspected that the survival estimates from Ruiz-Morales et al. were likely to overestimate the survival of patients who have everolimus in the NHS. The committee considered the 5-year survival estimate from the Christie Hospital audit to be unreliable because the numbers were small and there were no observations beyond 3 years 3 months after starting treatment. The committee concluded that survival in the UK was likely to have been overestimated in Ruiz-Morales et al., but did provide useful data with which to compare the survival prediction of the company's model.

4.18 The committee noted that the company presented a scenario analysis to align the revised base-case predictions (see section 4.16) and the data from Ruiz-Morales et al. (2016). In this, the company did not change the modelling of progression-free survival, that is, it continued to use fractional polynomial modelling across the entire time horizon. For overall survival, it used fractional polynomial modelling during the trial follow-up period (as

per the revised base case), but used parametric modelling choosing the log-normal distribution during the extrapolation period. The committee noted that this scenario aligned the model's predictions of survival with data from Ruiz-Morales et al., but did not consider that it was appropriate to base the extrapolation on meeting the 5-year death rate observed in the study. The committee recalled survival among people having everolimus was likely to have been overestimated in Ruiz-Morales et al. The committee concluded that it preferred the company's revised based case, which used fractional polynomial modelling across the entire time horizon for both overall and progression-free survival.

Duration of cabozantinib's treatment effect

4.19 The committee noted that both the company and the ERG assumed that the effect of cabozantinib continued beyond the trial follow-up, even after the disease progressed or patients stopped treatment, but the committee was not presented with evidence to support this. 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 have stable disease for 2 to 3 years after stopping treatment, whereas the disease progresses more quickly in others. Also, some patients have a prolonged response after a short length of treatment and others do not. The committee concluded that assuming the effect of cabozantinib continues for up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival, was highly uncertain.

Modelling of nivolumab

4.20 The committee noted that, for nivolumab, the company's revised base case (see section 4.16) estimated a longer progression-free survival than overall survival. The committee understood that, in the model, disease progression could occur until the point where overall and progression-free survival curves cross (around 5 years after starting treatment), after which people whose disease had not progressed followed the overall survival

curve. This meant that the company assumed at that point that the disease would never progress, instead people would die of causes other than their cancer. It also meant that they would accrue the utility associated with pre-progressed disease during their remaining time in the model. The committee was not presented with any evidence that people who are alive and on treatment 5 years after starting treatment remain progression-free until they die. The company did not consider it plausible that progression-free survival would be longer than overall survival, and conducted a scenario analysis. In this, it continued to use fractional polynomial modelling for overall survival across the entire time horizon as in the revised base case. For progression-free survival, it used parametric modelling using the log-normal distribution during both the trial follow-up and extrapolation periods. The committee recalled that the log-normal distribution did not fit the data for the individual treatments well (see section 4.12). Because of this, the committee did not consider this analysis further. The committee recognised the uncertainties in the company's revised base case with respect to the modelling of nivolumab, but concluded it could use it for decision-making.

4.21 The committee noted that the company presented a further scenario analysis that, as in the previous scenario (see section 4.20), used the log-normal distribution to model progression-free survival across the entire time horizon. However, it differed in that of those who were alive 5 years after starting treatment and still having nivolumab, the company assumed that half had the same mortality as the age-matched general population. The committee recalled that using the log-normal distribution to model progression-free survival did not produce robust estimates (see section 4.20). Furthermore, the committee noted that this scenario had little impact on the mean overall survival associated with nivolumab, which it did not expect. The company suggested that this may have been because the risk of death estimated by the log-normal curve was similar to that of the general population. The committee recalled from the NICE

technology appraisal on nivolumab that the committee preferred to base its decision on a mixed model that relied 50% on a single generalised gamma model and 50% on a model that assumed a greater long-term survival benefit than in the single generalised gamma model for nivolumab. Although the committee would have liked to explore predictions of better survival for nivolumab, in line with the NICE technology appraisal of nivolumab, it concluded that the estimates from the company's scenario analysis were unrealistic.

Utility values

4.22 The committee was aware that METEOR collected health-related quality-of-life data using the EQ-5D-5L measure, which the company adjusted for age, as requested by the committee, and used in its revised base case. The committee considered these data, together with data from other studies, including those used in previous appraisals of renal cell carcinoma. It 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 clinicians would expect to see in clinical practice and, notably, the utility value before disease progression was higher than that of the age-matched general population. Because of this, the ERG explored using utility values from the AXIS trial. The committee accepted that the new, more detailed version of the EQ-5D (EQ-5D-5L) used in METEOR could explain the relatively high utility values reported in this trial. Another possible explanation was greater attrition bias in METEOR, in which unhealthy people were less likely to continue filling in quality-of-life questionnaires. The committee was also aware that AXIS and METEOR differed in whether they allowed patients to switch between treatment arms, the number and type of therapies that patients took before enrolling in the trial or after the disease progressed during the trial, and the prognostic scores at baseline of the study populations. The committee generally preferred sourcing utility and effectiveness from the same trial.

However, it agreed that some of the utility values from METEOR appeared high, particularly the utility value before disease progression. The committee concluded that it would take into account both sets of utility values.

Analyses used for decision-making

4.23 The committee noted that the company had addressed its request from the first meeting, that is, to:

- exclude best supportive care from the comparison with cabozantinib
- use methods that allow for better-fitting distributions to model progression-free and overall survival
- assume that axitinib is as effective as everolimus in terms of overall survival
- use evidence on the natural history of the disease to guide the modelling of overall survival with cabozantinib, adjusted as necessary for confounders
- account for wastage for nivolumab using the ERG's assumptions
- exclude the costs and any survival benefit of subsequent treatments not available in the NHS, such as sorafenib
- assume that patients are monitored by consultant oncologists for an average of 4 weeks before disease progression
- use age-adjusted utility values from METEOR
- explore, in scenario analyses, predictions of better survival for nivolumab
- derive the results from incremental cost-effectiveness analyses
- reflect incremental probabilistic cost-effectiveness analyses.

4.24 The committee considered the cost-effectiveness results incorporating the revisions to the models in response to consultation, the new data from METEOR (cut-off of October 2016), and the confidential discounts for all technologies applied by the ERG. In its consideration of the cost-effectiveness estimates, the committee took into account:

- the company's revised base case (see section 4.12)
- the company's scenario analysis using fractional polynomial modelling during the trial follow-up period, and parametric modelling using the log-normal distribution during the extrapolation period (see section 4.18)
- the ERG's revised base case (which reflected minor changes with minimal impact on the results compared with the company's revised base case)
- the ERG's scenario analysis exploring utility values from AXIS.

End-of-life considerations

4.25 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.

4.26 The committee considered the life expectancy of people with previously treated advanced renal cell carcinoma having each of the 3 comparator treatments. Across the analyses listed in section 4.24, the committee noted that the mean life expectancy, based on the revised model in response to consultation, and the updated dataset from METEOR, was about 24 months among people with advanced renal cell carcinoma having axitinib and everolimus, but not among those having nivolumab.

4.27 The committee discussed whether cabozantinib extended life by at least 3 months. The committee agreed that the results of the cost-effectiveness analyses (see section 4.24) suggested that cabozantinib was likely to extend mean overall survival by more than 3 months compared with everolimus and axitinib, but not compared with nivolumab. The committee therefore concluded that cabozantinib met the end-of-life criteria when compared with axitinib and everolimus, but did not meet the end-of-life criteria when compared with nivolumab.

Results of cost-effectiveness analyses

4.28 The committee noted that, in all the analyses, the incremental analysis showed that cabozantinib was associated with an incremental cost-effectiveness ratio (ICER) than exceeded £60,000 per quality-adjusted life year (QALY) gained compared with everolimus. It also noted that, in the incremental analyses, cabozantinib dominated nivolumab, and everolimus, dominated axitinib. The ICER for cabozantinib compared with everolimus from the trial-based analysis was comparable to the estimated ICER in the incremental analysis including all comparator treatments based on the network meta-analysis.

4.29 The committee discussed how the remaining uncertainties in the model could affect the results. It recalled that the cost-effectiveness of cabozantinib would:

- improve (that is, cabozantinib's ICER could decrease) if:
  - the long-term survival rate were higher than predicted by the model
  - everolimus were used later in treatment than cabozantinib
- worsen (that is, cabozantinib's ICER could increase) if:
  - cabozantinib had no effect, or a diminishing effect over time
  - nivolumab were associated with better long-term survival
  - the utility values from AXIS better represented the quality of life of people in the NHS (the ICER could increase by as much as £17,000 per QALY).

The committee agreed that uncertainty remained high in the model.

Innovation

4.30 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 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 consider cabozantinib to reflect a 'step change' in treatment nor did it identify a benefit to utility that was not otherwise accounted for in the modelling.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.31 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 Drugs Fund

4.32 The committee considered whether cabozantinib for advanced renal cell carcinoma should be included in the Cancer Drugs Fund. The committee agreed that the Cancer Drugs Fund would not address the areas of uncertainty identified, and that there was not plausible potential for cost effectiveness. 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). The committee noted that the company's simplified network reduced the potential bias associated with using immature data from TARGET.	4.8, 4.11
The committee concluded that cabozantinib met the end-of-life criteria when compared with axitinib and everolimus, but did not meet the end-of-life criteria when compared with nivolumab.	4.26**Error! Reference source not found.**
The committee noted that, in all the analyses, the incremental analysis showed that cabozantinib was associated with an incremental cost-effectiveness ratio (ICER) than exceeded £60,000 per quality-adjusted life year (QALY) gained compared with everolimus. It also noted that, in the incremental analyses, cabozantinib dominated nivolumab, and everolimus, dominated axitinib. The committee agreed that uncertainty remained high in the model.	4.29, 4.29
Current practice	

Clinical need of patients, including the availability of alternative treatments	The committee was aware that there remained limited treatment options and an unmet clinical need for some people with advanced renal cell carcinoma. Most people fit enough for second-line treatment are offered axitinib, nivolumab or everolimus. If the disease progresses further, people who previously had axitinib may have nivolumab or everolimus as a third-line treatment; people who had nivolumab may have axitinib or everolimus; and people who had everolimus may have axitinib or nivolumab.	4.1 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 clinical experts perceived cabozantinib to be more effective than everolimus and axitinib, although it caused more adverse effects. The committee heard from the clinical experts that, because of its multi-targeted approach, cabozantinib 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.	4.1 4.30

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.	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. The company presented updated survival data from the METEOR trial during consultation (based on a cut-off date of October 2016 compared with December 2015 for the original data cut).	4.6 4.9
Relevance to general clinical practice in the NHS	The committee concluded that the results of METEOR were generalisable to the NHS.	4.10
Uncertainties generated by the evidence	The committee noted that the company used fractional polynomial modelling to fit survival curves. The new method used a family of related survival curves for all the treatments. However, it was a more flexible family, which improved the curve fits to the Kaplan–Meier data on overall and progression-free survival for all treatments in the network compared with the original network meta-analysis.	4.12

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, progression-free and overall survival was significantly improved with cabozantinib compared with everolimus.	4.8
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.	4.13

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee concluded that assuming that the effect of cabozantinib continues for up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival, was highly uncertain. The committee suspected that the survival estimates from Ruiz-Morales et al. were likely to overestimate the survival of patients who have everolimus in the NHS. The committee recognised the uncertainties in the company's revised base case with respect to the modelling of nivolumab, but concluded it could use it for decision-making.	4.19 4.18 4.20, 4.21
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 ERG explained that the utility values collected from METEOR were higher than those clinicians would expect to see in clinical practice and, notably, the utility value before disease progression was higher than that of the age-matched general population. The committee concluded that it would also take into account utility values from the AXIS trial. The committee did not identify a benefit to utility that was not otherwise accounted for in the modelling.	4.22 4.30

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 positioning of everolimus in the treatment pathway, choice of utility values, duration of the effect of cabozantinib, and prediction of long-term survival rate with the disease.	4.29
Most likely cost-effectiveness estimate (given as an ICER)	The committee noted that, in all the analyses, the incremental analysis showed that cabozantinib was associated with an ICER than exceeded £60,000 per QALY gained compared with everolimus.	4.28
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 discounts for all technologies.	
End-of-life considerations	The committee concluded that cabozantinib met the end-of-life criteria when compared with axitinib and everolimus, but did not meet the end-of-life criteria when compared with nivolumab.	4.27**Error! Reference source not found.**

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
April 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

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