NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Cabozantinib for untreated advanced renal cell carcinoma

The Department of Health and Social Care 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?

Issue date: June 2018

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 document.
- Subject to any appeal by consultees, the final appraisal document 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: 26 June 2018

Second appraisal committee meeting: 10 July 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Cabozantinib is not recommended, within its marketing authorisation, for adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria.

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.

Why the committee made these recommendations

Current treatment for untreated advanced renal cell carcinoma is usually pazopanib or sunitinib.

Clinical trial evidence shows that cabozantinib extends the period of time until cancer progresses compared with current treatment. But the evidence on whether cabozantinib increases the overall length of time people live is less certain. It is at least as effective as current treatment, but it is not clear how much further benefit it offers.

Cabozantinib does not meet NICE's end-of-life criteria. The cost-effectiveness estimates are higher than what NICE normally considers acceptable.

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2 Information about cabozantinib

Marketing authorisation indication	Cabozantinib (Cabometyx, Ipsen) is indicated for 'the treatment of advanced renal cell carcinoma in untreated adults with intermediate- or poor-risk' as defined in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria'.
Dosage in the marketing authorisation	Cabozantinib is for oral use. The recommended dose is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefitting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.
Price	£5,143.00 per pack of 30×60 mg tablets (excluding VAT; British National Formulary [BNF] online [accessed May 2018]). The company has a commercial arrangement (simple discount patient access scheme) which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) 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.

New treatment option

People with untreated intermediate- or poor-risk renal cell carcinoma would welcome a new treatment option

3.1 The patient and clinical experts explained that there are no treatments used exclusively for intermediate- or poor-risk advanced renal cell carcinoma. Tyrosine kinase inhibitors, such as sunitinib and pazopanib, are the current standard of care. They can cause adverse effects such as extreme fatigue, hand and foot syndrome, and chronic diarrhoea, which can substantially affect quality of life. The committee concluded that people with intermediate- or poor-risk advanced renal cell carcinoma would welcome a new treatment option.

Clinical management

Prognostic risk scores are not routinely used in UK clinical practice, but there are no barriers to their use

3.2 Cabozantinib is indicated for treating intermediate- and poor-risk advanced renal cell carcinoma. The clinical experts stated that prognostic scores to define intermediate- and poor-risk are not used in clinical practice. They noted that the 2 best known risk scores are the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score and the Memorial Sloan-Kettering Cancer Center (MSKCC) risk score. The clinical experts considered the 2 scores were similar, but would prefer to use the IMDC risk score because it was used in the clinical trial for cabozantinib. They stated that clinicians routinely collect all components of the risk scores, and would be able to start using the risk scores immediately.

Comparators

Sunitinib or pazopanib are appropriate comparators, and can be considered clinically equivalent

3.3 People with newly diagnosed untreated advanced renal cell carcinoma would be offered 1 of 3 tyrosine kinase inhibitors; pazopanib, sunitinib or tivozanib, as recommended in NICE's technology appraisal guidance. Tivozanib was not included in the scope of this appraisal because it was not part of clinical practice at the start of the appraisal. The clinical experts and the Cancer Drugs Fund clinical lead confirmed that most people would be offered pazopanib and the rest sunitinib. The clinical experts stated that in practice, sunitinib and pazopanib are considered clinically equivalent. The committee recalled that in previous appraisals it considered sunitinib and pazopanib to be clinically equivalent, and there was no new evidence to change this conclusion. The committee concluded that pazopanib and sunitinib are the relevant comparators in this appraisal, and can be considered clinically equivalent.

Clinical evidence

The small number of people in the main clinical trial, CABOSUN makes the results uncertain

3.4 The main evidence on the clinical effectiveness of cabozantinib came from CABOSUN. This was a phase 2 clinical trial comparing cabozantinib with sunitinib in 157 patients with untreated, intermediate- or poor-risk (IMDC criteria) advanced renal cell carcinoma. The primary outcome of the trial was progression-free survival; overall survival was a secondary outcome. The company explained that CABOSUN was not designed to be a registration trial, but was submitted to the regulators because the results were thought to be encouraging. The committee concluded that the small number of patients in the trial makes the results uncertain.

The results of CABOSUN are generalisable to clinical practice in England

3.5 CABOSUN was carried out in the US, where clinical practice and the characteristics of people who have renal cell carcinoma treatment are potentially different to England. The clinical experts stated that the patients in the trial generally reflected people who are expected to have cabozantinib in clinical practice. However, they noted that people recruited to clinical trials sometimes are younger, in better health and able to tolerate a short wait before treatment begins. The clinical experts would therefore expect people in clinical practice to have poorer health and a poorer prognosis than those in CABOSUN. The Cancer Drugs Fund clinical lead stated that the proportion of people with intermediate- and poor-risk disease who will have treatment in clinical practice was uncertain, but there was no evidence to suggest that the proportion was different in CABOSUN. Also, he advised that because most patients in CABOSUN had relatively good performance status, clinicians may preferentially select people with intermediate-risk disease who tend to be in better health than those with poor-risk disease. Although the committee considered that it was possible that people in clinical practice have poorer health and a poorer prognosis than the trial population, it had not seen

robust evidence to support this. Therefore, the committee concluded that the results of CABOSUN were generalisable to clinical practice in England.

Progression-free survival

Cabozantinib increases progression-free survival compared with sunitinib

3.6 Cabozantinib increased median progression-free survival assessed by investigators (primary outcome), compared with sunitinib, from 5.4 months to 8.3 months (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.37 to 0.83, p=0.0042). The company did a retrospective analysis of progression-free survival assessed by independent review committee to support regulatory submissions. This analysis used a 2-sided test for significance rather than the 1-sided test used in the investigator analysis. It also included additional censoring of patients who had non-protocol systemic anticancer therapy or whose disease progressed after missing 2 or more assessments. The results of the retrospective analysis showed that cabozantinib increased median progression-free survival compared with sunitinib, from 5.3 months to 8.6 months (HR 0.48, 95% CI 0.31 to 0.74, p=0.0008). The committee concluded that cabozantinib increased progression-free survival compared with sunitinib.

Overall survival

There is no strong evidence that people taking cabozantinib live longer than people taking sunitinib

3.7 The company had presented results for overall survival from 2 different data cuts; January 2017 and July 2017. The committee preferred to use the more recent data to assess clinical effectiveness and did not consider the January 2017 data cut further. The results from the July 2017 data cut showed a median overall survival of 26.6 months with cabozantinib compared with 21.2 months with sunitinib (HR 0.80, 95% CI 0.53 to 1.21, p=0.29). The committee was aware that the trial was not powered to show a difference in overall survival between treatments. It noted that the

Kaplan–Meier curves converged at around 14 months before separating again at around 21 months. The clinical experts advised that there was no clinical explanation for this, but it may be explained by random chance given the small numbers in the trial (157 patients). The committee concluded that there was no strong evidence to demonstrate that people taking cabozantinib live longer than those taking sunitinib.

There is no robust evidence to demonstrate that the effectiveness of cabozantinib is different in the poor and intermediate-risk groups

3.8 The company provided data on overall survival in the poor- and intermediate-risk groups in response to a clarification request from the ERG. The committee noted that these results were uncertain, particularly for the poor-risk group, because the patient numbers in each group were small: 127 patients in the intermediate-risk group and 30 patients in the poor-risk group. It concluded that no firm conclusion could be drawn about the effectiveness of cabozantinib in one particular subgroup.

Indirect treatment comparison

An indirect treatment comparison is not needed because pazopanib and sunitinib are considered clinically equivalent

3.9 The company did an indirect treatment comparison to compare the clinical effectiveness of cabozantinib and pazopanib. The committee was aware that indirect comparisons are inherently uncertain, and more so in this appraisal because the evidence on pazopanib came from the COMPARZ trial which included patients with favourable-risk disease who have a different prognosis to people with intermediate- or poor-risk disease. The committee recalled that pazopanib and sunitinib can be considered equally clinically effective (see section 3.3). Therefore, it concluded that an indirect treatment comparison was not needed, and did not consider it further.

The company's economic model

The structure of the company's model is appropriate for decision-making

3.10 The company used a partitioned-survival economic model that included 3 states: pre-progression, post-progression and death. The committee concluded that the structure of the model was appropriate and consistent with the approach used in other appraisals for renal cell carcinoma.

Treatment effects in the economic model

The committee prefers the model that includes pazopanib and assumes that it is as effective as sunitinib

3.11 The company's analysis compared cabozantinib and sunitinib based on data from CABOSUN. The ERG's base case included pazopanib in the analysis, and assumed that it was equally effective to sunitinib, which the committee agreed was a reasonable assumption (see section 3.3). The committee concluded that it was more appropriate to include pazopanib in the analysis and assume that it was clinically equivalent to sunitinib (as per the ERG's analyses) than to consider pazopanib based on an indirect treatment comparison (as per the company's analyses).

Basing the modelling on independent review committee-assessed progression-free survival is acceptable

3.12 The company and ERG both based their modelling of progression-free survival on the retrospective assessement by independent review committee. The committee generally preferred using the primary end point of the trial in the model, which was investigator-assessed progression-free survival. However, it noted that the results using either assessment were similar, and unlikely to have a large effect on cost effectiveness. Also, because CABOSUN was a small phase 2 trial, it may be acceptable in this appraisal to use independently-assessed progression-free survival to minimise bias and reduce the uncertainty resulting from small patient

numbers. The committee therefore accepted the approach used by the company and ERG.

There is a high degree of uncertainty in the extrapolation of overall survival

3.13 The committee recognised that the immaturity of the data and the small size of the trial meant that projecting survival outcomes beyond the trial follow-up would be challenging and inherently uncertain. Also, because the Kaplan–Meier curves for overall survival crossed, no parametric curve fitted the data well. The committee considered whether piecewise modelling would be suitable (that is, using the Kaplan–Meier curves for the duration of follow-up and parametric extrapolation fitted to the end of the curve thereafter), but it agreed that such modelling needs larger patient numbers. The committee noted that both the company and the ERG preferred the exponential distribution, which the clinical experts advised produced plausible predictions of overall survival at 5 and 10 years after starting treatment. The ERG assumed proportional hazards despite the log-cumulative hazard plots violating this because it considered that the Kaplan–Meier curves should not be 'over-interpreted' given the uncertainty in the data. The committee agreed that whether proportional hazards holds was unclear. It concluded that the chosen distributions fitted the data poorly and that the overall survival extrapolation was a source of uncertainty in the economic model, which would need exploring in sensitivity analyses.

It is not appropriate to assume that cabozantinib has a relative survival benefit compared with sunitinib after 5 years

3.14 The company assumed that the relative effect of cabozantinib compared with sunitinib continued beyond the trial follow-up (that is, the hazard ratio remained below 1), even after the disease progressed or patients stopped treatment, but there was no evidence to support this. The clinical experts considered that it was not clear whether a survival benefit would continue after stopping treatment. The ERG's base case assumed that treatment benefit with cabozantinib compared with sunitinib did not persist after

5 years (that is, the hazard ratio became 1 after 5 years). The committee agreed that assuming the treatment benefit of cabozantinib compared with sunitinib continued for up to 20 years or even for 10 years, based on a trial with a median follow-up of under 3 years, was not plausible. The committee agreed that the modelling should assume that there is no treatment effect beyond the observed survival data, which covered a duration of less than 4 years, and so concluded that the ERG's assumption was preferable.

Utility values in the economic model

The source of utility values used in the economic model is appropriate

3.15 Quality-of-life data were not collected in CABOSUN. Therefore, the company and ERG used utility values from NICE's technology appraisal guidance on tivozanib in their base cases. The committee concluded that this source of utility values was appropriate.

Costs in the economic model

Subsequent treatment proportions from CABOSUN should be used

3.16 The company's and ERG's base case both included a distribution of subsequent therapies based on CABOSUN for cabozantinib and sunitinib, and based on COMPARZ for pazopanib (see table 1). The committee agreed that given the assumption that pazopanib and sunitinib are equivalent (see sections 3.3 and 3.11) the same source of data for therapies after sunitinib and pazopanib should be used. The committee preferred to use CABOSUN because CABOSUN is more recent than COMPARZ and therefore more closely reflects clinical practice. However, CABOSUN and COMPARZ included subsequent treatments that are not recommended in the NHS. The committee noted that both the company and the ERG presented scenario analyses of second-line NHS drug use based on clinical expert opinion. The clinical experts at the committee meeting indicated that the ERG's scenario analysis more closely reflected the expected second-line therapy use in the NHS. However, it reflected

only the cost, but not the benefits, of subsequent therapies and the committee preferred both costs and benefits of subsequent therapies to be included. Therefore, it concluded that the base case assumptions based on clinical trial data were acceptable but should have included an equivalent distribution for pazopanib and sunitinib. It also concluded that it was appropriate to consider the ERG's scenario analysis when making its decision.

Table 1 Subsequent therapy distributions – ERG base case and scenario analysis

First therapy:	**Cabozantinib (%)**		**Sunitinib (%)**		**Pazopanib (%)**	
	Base case	ERG scenario	Base case	ERG scenario	Base case	ERG scenario
NHS recommended subsequent therapies:						
Axitinib	23	0	19	0	6	0
Cabozantinib	1	0	6	30	0	30
Everolimus	8	0	19	0	31	0
Nivolumab	13	45	15	30	0	30
Lenvatinib plus everolimus	0	45	0	30	0	30
Best supportive care	16	10	3	10	10	10
Other therapies:	40	–	38	–	53	–
Company and ERG base case both based on CABOSUN for cabozantinib and sunitinib and COMPARZ for pazopanib.						

Cost-effectiveness estimates

The assumptions in the ERG's base case are more appropriate than the company's

3.17 The committee noted that the ERG's base-case model was more closely aligned with several of its preferred assumptions:

- Including pazopanib in the analysis and assuming it to be clinically equivalent to sunitinib (see sections 3.3 and 3.11).

- Overall survival extrapolation based on the most recent data cut (see section 3.7).
- Duration of treatment benefit for cabozantinib compared with sunitinib persists only up to 5 years (see section 3.14).
- Distribution of subsequent treatment reflecting both costs and benefits of treatment (see section 3.16).

The committee concluded that the ERG's base case was more appropriate for decision-making than the company's base case.

The plausible ICERs are above those usually considered a cost-effective use of NHS resources

3.18 In the ERG's base case, the gains in quality-adjusted life years (QALYs) for pazopanib and sunitinib were almost identical and the cost of pazopanib was lower than sunitinib. Pazopanib therefore 'dominated' sunitinib. The incremental cost-effectiveness ratio (ICER) reflecting the cost effectiveness of cabozantinib compared with pazopanib was more than £50,000 per QALY gained. Because the subsequent therapies included in the model have confidential patient access schemes, the exact ICER cannot be reported here. The committee also considered several scenarios exploring the main areas of uncertainty in the model:

- Assuming no overall survival benefit (see sections 3.7 and 3.13): The ERG's base-case ICER compared with pazopanib increased by over £280,000 per QALY gained when a scenario assumed no relative survival benefit over alternative treatments.
- Distributions of second-line treatment (see section 3.16): The ERG's base-case ICER compared with pazopanib decreased by approximately £7,000 per QALY gained when considering the scenario reflecting second-line treatment use in the NHS.

The committee concluded that the range of most plausible ICERs is higher than that usually considered a cost-effective use of NHS resources.

Uncaptured benefits

There are no health-related benefits that are not captured in the analysis

3.19 The committee recalled the conclusion from NICE's technology appraisal guidance on cabozantinib for previously treated advanced renal cell carcinoma. This was that cabozantinib did not reflect a 'step-change' in treatment and no benefits were identified which were not otherwise accounted for in the modelling. The committee saw no evidence to change its conclusion for people with untreated advanced renal cell carcinoma. It therefore concluded that there are no additional health-related quality-of-life benefits not already captured in the QALY calculations.

End of life

Life expectancy for people in the combined intermediate- and poor-risk group is likely to be more than 24 months

3.20 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods:

- The median overall survival in the sunitinib arm in CABOSUN was 21.2 months.
- Using the committee's preferred analysis, the model estimated a mean of more than 24 months in the sunitinib arm.

The committee preferred mean estimates when considering the end-of-life criteria. The committee was aware that there was an ongoing NICE technology appraisal of nivolumab with ipilimumab for the same population. The committee considered that it should refer to that appraisal in its discussion about life expectancy in the context of end of life to take into account all available evidence. The median overall survival in the sunitinib arm of the clinical trial was 25.9 months, acknowledging that the

mix of patients with intermediate- or poor-risk disease differed from the CABOSUN trial.

The committee recalled that it was possible that people in clinical practice have poorer health and a poorer prognosis than the trial population (see section 3.5). It noted that the median survival estimates from the literature showed a lower life expectancy for people in the poor-risk group compared to the combined intermediate- and poor-risk group. However, the analyses the committee had seen related to the combined poor- and intermediate-risk group for whom there was no robust evidence that life expectancy was less than 24 months. Therefore, it concluded that cabozantinib did not meet the criterion for short life expectancy.

Cabozantinib meets the criterion for extending life by more than 3 months compared with standard of care

3.21 The committee noted that no overall survival benefit was shown in CABOSUN, but acknowledged that the trial was not powered to show a difference in overall survival (see section 3.7). The economic model estimated that cabozantinib extends life compared with sunitinib by more than 12 months using the company's preferred overall survival extrapolation and by around 6 months using the ERG's preferred extrapolation. Therefore, the committee accepted that cabozantinib extends life by more than 3 months compared with established NHS practice in England for the purposes of the end-of-life considerations.

Conclusion

Cabozantinib is not recommended for people with untreated intermediate- and poor-risk renal cell carcinoma

3.22 Cabozantinib did not meet the end-of-life criteria because people with intermediate- and poor- risk advanced renal cell carcinoma are likely to survive for longer than 24 months. When using the analysis that most closely reflected the committee's preferred assumptions the ICER was higher than would normally be considered a cost-effective use of NHS

resources. Therefore, committee concluded that cabozantinib is not recommended for people with untreated intermediate- and poor-risk renal cell carcinoma.

It is not appropriate to make a separate recommendation for people with untreated poor-risk renal cell carcinoma

3.23 Having concluded that cabozantinib could not be recommended for people with intermediate- or poor-risk untreated renal cell carcinoma the committee then considered the prognostic risk groups separately. It was aware that the median life expectancy for people with poor-risk untreated renal cell carcinoma was likely to be lower than 24 months, and considered that it may meet the end-of-life criteria. However, it had not been presented with mean estimates of life expectancy, nor had the 2 prognostic groups been modelled separately. It recalled that there was no robust estimates of cabozantinib's effectiveness by subgroup based on risk (see section 3.8). Therefore, the committee concluded that it is not appropriate to make a separate recommendation for people with untreated poor-risk renal cell carcinoma.

4 Proposed date for review of guidance

4.1 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.

Dr Amanda Adler

Chair, Appraisal Committee B

June 2018

5 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.

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.

Alan Lamb
Technical Lead

Ahmed Elsada
Technical Adviser

Jeremy Powell
Project Manager

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