

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final appraisal document**

**Cabozantinib for untreated advanced renal cell  
carcinoma**

**1 Recommendations**

- 1.1 Cabozantinib is 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. It is recommended only if the company provides cabozantinib according to the commercial arrangement (see section 2).

**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 time until cancer progresses compared with current treatment. But the evidence on whether cabozantinib increases how long people live is less certain. It appears to be at least as effective as current treatment, but it's not clear how much extra benefit it offers.

Cost-effectiveness estimates for cabozantinib compared with current treatment are uncertain. This is because there is not much evidence available to estimate how long people live, and the costs and benefits of treatments after cabozantinib do not fully reflect those in the NHS. The cost-effectiveness estimates are within the range that NICE usually considers a cost-effective use of NHS resources, taking into account the uncertain estimates. Therefore, cabozantinib is recommended as an option for treating advanced renal cell carcinoma in the NHS.

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## 2 Information about cabozantinib

<b>Marketing authorisation indication</b>	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’.
<b>Dosage in the marketing authorisation</b>	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.
<b>Price</b>	£5,143 per pack of 30×60 mg tablets (excluding VAT; British National Formulary online, accessed August 2018).  The company has a commercial arrangement (simple discount patient access scheme). This makes cabozantinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company’s responsibility to let relevant NHS organisations know details of the discount.

## 3 Committee discussion

The appraisal committee (section 6) 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 tyrosine kinase inhibitors, such as sunitinib and pazopanib, are the current standard of care for people with untreated advanced renal cell carcinoma. They can cause adverse effects such as extreme fatigue, hand and foot syndrome, and chronic diarrhoea, which can 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 using them**

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 groups 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 that 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 were the relevant comparators in this appraisal, and could 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 'encouraging'. The committee concluded that the small number of patients in the trial made 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 different to those in England. The clinical experts stated that the patients in the trial generally reflect people who are expected to have cabozantinib in NHS clinical practice. However, they noted that people recruited to clinical trials are sometimes younger, in better health and able to tolerate a short wait before treatment begins. The clinical experts therefore expected people in NHS 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 to that in CABOSUN. Although the committee considered that it was possible that people in NHS clinical practice have poorer health and a poorer prognosis than the trial population, it had not seen robust evidence

to support this. Therefore, it concluded that the results of CABOSUN are 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 retrospectively analysed progression-free survival assessed by an independent review committee to support its 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 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 between treatments in overall survival, a secondary outcome. 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 that it may be explained by chance given the small numbers in the trial (157 patients). The committee concluded

that there was no strong evidence to show that people who are offered cabozantinib live longer than those who are offered sunitinib.

**There is no robust evidence to show 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 any 1 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. This was because the evidence on pazopanib came from the COMPARZ trial, which also included patients in the favourable-risk category who have a better prognosis than those 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 model that includes the assumption that pazopanib is as effective as sunitinib is preferable**

3.11 The company's original analysis modelled the treatment effectiveness of pazopanib based on an indirect treatment comparison. The ERG's base case did not include pazopanib separately, but assumed that it was equally effective to sunitinib, which the committee agreed was reasonable (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 include an indirect treatment comparison (as per the company's analyses). The company used this approach in their revised analysis.

#### **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 assessment by independent review committee. The committee generally prefers using the primary end point of the trial in the model, which for CABOSUN was investigator-assessed progression-free survival. However, it noted that the results using either assessment were similar, and unlikely to have had a large effect on cost effectiveness. 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 (for example, 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 years and 10 years after starting treatment. The ERG assumed proportional hazards (despite the log-cumulative hazard plots violating proportional hazards) because it considered that the Kaplan–Meier curves should not be ‘over-interpreted’ given the small numbers of patients. The committee agreed that it was unclear whether proportional hazards holds. It concluded that the chosen distributions fitted the data poorly and that the curve was a source of uncertainty in the economic model.

**Scenario analyses of the choice of curve for overall survival extrapolation are appropriate to consider in decision-making**

3.14 The company conducted scenario analyses to examine the sensitivity of the model to the choice of overall survival extrapolation. It provided analyses using Weibull and Gompertz distributions fitted separately (assuming the proportional hazards assumption did not hold) and jointly (assuming the proportional hazards assumption did hold). The ERG also included scenarios using alternative parametric distributions. The committee noted that the incremental cost-effectiveness ratios (ICERs) generated by the scenario analyses varied by around £6,500 per quality-adjusted life year (QALY) gained, depending on whether curves were fitted separately or jointly, and depending on which distribution was used. It concluded that it would take into account the uncertainty in the choice of curve for extrapolating overall survival in its decision-making.

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

3.15 The company’s original base case 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. It therefore concluded that the ERG's assumption was preferable and the company used this assumption in its revised base case.

### ***Utility values in the economic model***

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

3.16 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***

#### **The costs and benefits of subsequent therapies (treatments second line and beyond) are a key source of uncertainty in the cost-effectiveness model**

3.17 Both the company's and ERG's base cases included a distribution of subsequent therapies (that is, therapies for renal cell cancer second line and beyond) based on CABOSUN for cabozantinib and sunitinib, and based on COMPARZ for pazopanib. 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. It preferred using CABOSUN because

CABOSUN is more recent than COMPARZ, so 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. Clinical experts indicated that the ERG's scenario analysis more closely reflected the expected second-line therapy use in the NHS. However, the company modelled therapies by reflecting only their cost, but not their benefits, and the committee preferred including both costs and benefits of subsequent therapies. Therefore, the committee agreed that the base-case assumptions using clinical trial data to depict subsequent treatment were acceptable, but should be based on CABOSUN for both pazopanib and sunitinib. In response to consultation, the company revised its analyses to assume the same subsequent therapies after pazopanib and sunitinib (see table 1). Because the ERG's scenario analysis more closely reflected the cost of subsequent therapies used in the NHS, the committee also considered this scenario when making its decision. The ERG's scenario increased the revised base-case ICER by around £10,500 per QALY gained. However, this difference would likely be smaller when adjusting the benefits as well as the costs of subsequent therapy to reflect NHS practice. Because of this, the committee concluded that the costs and benefits of subsequent therapies were a key source of uncertainty in the cost-effectiveness model.

**Table 1 Distributions of subsequent therapies – ERG base case and scenario analysis**

First therapy	Cabozantinib (%)		Sunitinib (%)	
	Revised company base case	ERG scenario	Revised company base case	ERG scenario
<b>NHS recommended subsequent therapies</b>				
Axitinib	23	0	23	0
Cabozantinib	1	0	1	30
Everolimus	8	0	8	0
Nivolumab	13	45	13	30
Lenvatinib plus everolimus	0	45	0	30
Best supportive care	16	10	16	10
<b>Other therapies:</b>	39	–	39	–
<b>Total</b>	100%	100%	100%	100%
Abbreviation: ERG, evidence review group.				

### **Cost-effectiveness estimates**

#### **The company’s revised base case reflects the committee’s preferred assumptions**

3.18 In response to the appraisal consultation document, the company updated its economic model to include the committee’s preferred assumptions, which were:

- including pazopanib in the analysis and assuming it is clinically equivalent to sunitinib (see sections 3.3 and 3.11)
- basing overall survival extrapolation on the most recent data cut (see section 3.7)
- including a duration of treatment benefit for cabozantinib compared with sunitinib persisting only up to 5 years (see section 3.15)
- reflecting both costs and benefits of subsequent treatments (see section 3.17).

The company also updated its model to incorporate an increase to the confidential patient access scheme discount. The committee concluded that the company's revised model reflected its preferred assumptions.

### ***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 were 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 24.0 months in the sunitinib arm.

The committee preferred mean estimates when considering the end-of-life criteria. It was aware that survival estimates were also available from the ongoing CheckMate 214 clinical trial of nivolumab with ipilimumab in the same population. The median overall survival in the sunitinib arm of

CheckMate 214 was 25.9 months, but the mix of patients with intermediate- or poor-risk disease differed from the CABOSUN trial. For the combined poor- and intermediate-risk group, there was no robust evidence that average life expectancy was less than 24 months. Therefore, the committee 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 CABOSUN trial did not show that cabozantinib extends life, 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 around 6 months on average in the company's revised base case. 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.

### **The plausible ICERs are consistent with those usually considered a cost-effective use of NHS resources**

3.22 In incremental analyses using the company's revised base case, cabozantinib and sunitinib 'extendedly dominated' pazopanib (that is, pazopanib was more expensive and more costly than having the options of cabozantinib and sunitinib) leaving the relevant comparison between cabozantinib and sunitinib. The ICER reflecting the cost effectiveness of cabozantinib compared with sunitinib was less than £20,000 per QALY gained. Because the subsequent therapies included in the model were priced based on confidential patient access schemes, the estimated ICER taking these into account cannot be included here. In addition to the base case, the committee considered several scenarios exploring the key areas of uncertainty in the model, including:

- The choice of curve used to estimate overall survival: the ICERs generated from these scenario analyses changed by about £6,500 per QALY gained (see section 3.14).
- The costs and benefits of treatments second-line and beyond: when considering the ERG's scenario reflecting the costs (but not benefits) of second-line treatment use in the NHS, the company's revised base-case ICER compared with sunitinib increased by about £10,500 per QALY gained (see section 3.17). The committee agreed that the impact of this change on the most plausible ICER was likely to be lower when including the benefits of life-extending, second-line treatments used in the NHS.

The committee concluded that, taking into account the degree of uncertainty associated with the evidence base, the estimated ICERs reflected a cost-effective use of NHS resources for people with untreated intermediate- and poor-risk advanced renal cell carcinoma.

## **4 Implementation**

- 4.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated intermediate- or poor-risk advanced renal cell carcinoma and the doctor responsible for their care thinks that cabozantinib is the right treatment, it should be available for use, in line with NICE's recommendations.

## 5 Review of guidance

5.1 The guidance for this technology will be 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  
August 2018

## 6 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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