NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment

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 evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: September 2025

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using cabozantinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 23 October 2025
- Second evaluation committee meeting: TBC
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Cabozantinib should not be used to treat unresectable or metastatic well-differentiated extra-pancreatic neuroendocrine tumours (epNET) and pancreatic neuroendocrine tumours (pNET) that have progressed after at least 1 systemic treatment other than somatostatin analogues (SSAs).

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 healthcare professional consider it appropriate to stop.

What this means in practice

Cabozantinib is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that cabozantinib is value for money in this population.

Why the committee made these recommendations

Unresectable or metastatic well-differentiated epNETs and pNETs are usually treated with SSAs, which are systemic treatments. After this, other systemic treatments can be used, including everolimus, sunitinib and peptide receptor radionuclide therapy (PRRT). After systemic treatments, best supportive care is the only treatment option.

The company asked for cabozantinib to be considered in a population for whom best supportive care is the only treatment option, to reflect the population in the clinical trial. This evidence does not include everyone cabozantinib is licensed for.

Evidence from a clinical trial shows that, compared with placebo, cabozantinib increases how long people have before their condition gets worse. But it is not clear whether people live longer if they have cabozantinib.

There are also uncertainties in the economic evidence. This is because of the way the economic model:

- predicts long-term survival
- includes treatments used at the same time and after cabozantinib.

Because of the uncertainties in the economic and clinical evidence, it is not possible to determine the most likely cost-effectiveness estimates for cabozantinib. So, it should not be used.

2 Information about cabozantinib

Anticipated marketing authorisation indication

2.1 Cabozantinib (Cabometyx, Ipsen) is indicated 'for the treatment of adult patients with unresectable or metastatic well-differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cabozantinib.

Price

2.3 The list price of cabozantinib is £5,143 for a 30-day pack of 60-mg capsules

2.4 The company has a commercial arrangement. This makes cabozantinib available to the NHS with a discount and it would have also applied to this

indication if cabozantinib had been recommended. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Ipsen will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Ispen, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Neuroendocrine tumours (NETs) are a heterogeneous group of rare tumours that arise from neuroendocrine cells. They can develop throughout the body but mainly occur in the pancreas (pancreatic NETs [pNETs]), lungs and digestive system (extra-pancreatic NETs [epNETs]). NETs may be 'functional', where cells produce and release higher than normal levels of hormones or non-site-specific hormones, or 'non-functioning', where normal levels of hormones are released. The patient experts explained that for many it is a debilitating and life-changing condition. They explained that they face ongoing challenges from having frequent medical appointments, invasive tests and complicated treatment regimens. People with NETs experience symptoms that can change from day to day and affect many aspects of daily life, including employment, confidence, diet and independence. Because of the heterogeneous nature of NETs, symptoms can vary and may include pain, fatigue, diarrhoea, nausea, rectal bleeding, shortness of breath and weight loss. The patient experts clarified that people with functional NETs can have hormone-related symptoms such as hypoglycaemia, or may experience symptoms

that impact cognitive function. The patient experts explained that living with advanced NETs can be intensely challenging and emotionally exhausting for the person with the condition, their family and carers. The committee concluded that advanced NETs can have a negative impact on the person with the condition, and on their family and carers

Unmet need

3.2 The patient and clinical experts explained that the main aim of treatment is to control symptoms and delay tumour progression, while providing a good quality of life. They explained that several treatment options are available, but they are not suitable for everyone and often have unpleasant side effects. The clinical experts explained that for epNETS, particularly functional lung NETs, there are limited treatment options after progression on 1 or 2 systemic treatments. They explained that having different options is particularly important because treatment choice is often based on a person's eligibility (see section 3.3). The patient and clinical experts agreed that, because cabozantinib is an oral treatment, it may be more convenient than other treatments, which may support adherence. The committee concluded that there is an unmet need for effective treatments and that people with the condition, their families and carers, would welcome an additional treatment option.

Clinical management

Treatment options

3.3 The clinical experts explained that the treatment options for advanced NETs depend on several factors. These include:

- the site, stage and grade of the tumour
- functionality and performance of the tumour
- somatostatin receptor (SSTR) status
- overall health
- other health conditions and

- eligibility.

The clinical experts stated that managing NETs in the NHS follows the European Neuroendocrine Tumour Society's (ENETS) guidelines. They explained that most people with advanced NETs are first offered somatostatin analogues (SSAs), either lanreotide or octreotide. Some people with pNETs are also offered cytotoxic chemotherapy as first-line systemic treatment after SSAs as an off-label treatment. They explained that in clinical practice, the sequence of the treatments is also taken into account to manage the toxicity. Targeted systemic treatments are then offered based on the primary tumour site, grade, functional status and SSTR expression status. These include:

- everolimus for treating progressive pNETs and non-functional progressive gastrointestinal or lung NETs (see the NICE technology appraisal guidance on everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease)
- sunitinib for treating progressive pNETs (see the NICE technology appraisal guidance on everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease)
- peptide receptor radionuclide therapy (PRRT) for treating SSTR-positive progressive gastroenteropancreatic NETs (see the NICE technology appraisal guidance on lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours).

The company clarified that off-label chemotherapy may also be used for functional lung NETs and functional STTR-negative gastrointestinal NETs. The committee concluded that managing advanced NETs is highly complex, heterogeneous and individualised based on the specific characteristics of the person with the condition. It noted that the treatment

decision is based on several factors and that some off-label treatments can also be used earlier in the treatment pathway.

Positioning and comparators

3.4 The anticipated marketing authorisation for cabozantinib includes people with pNETs or epNETs whose condition has progressed after 1 systemic treatment other than SSAs. The company has positioned cabozantinib for treating advanced NETs at a later stage in the treatment pathway, when best supportive care is the only treatment option. The committee noted that the population included in the company's main clinical trial, CABINET (see section 3.7) was heavily pretreated, representing people who are at a later stage in the treatment pathway. The EAG explained that in CABINET, people with pNETs had a mean number of 3 previous systemic treatments, excluding SSAs. While people with epNETs had a mean number of 2 systemic treatments, excluding SSAs. It noted that for pNETs, 27% of people who had cabozantinib and 32% of people who had placebo had only 1 previous systemic treatment. While for pNETs, 44% of people who had cabozantinib and 48% of those who had placebo had only 1 previous systemic treatment. So, the EAG felt that 2 populations were relevant for the evaluation:

- CABINET population: people who have had heavy pretreatment, for whom best supportive care is the only available treatment option
- Marketing authorisation population: people who have had lighter pretreatment and still have treatment options other than best supportive care, for whom everolimus, sunitinib and PRRT may be offered.

The clinical experts explained that for some people, they would prefer to offer cabozantinib as an earlier rather than later line of treatment. They explained that for pNETs there are more treatments available than for epNETs (including lung NETs). So, cabozantinib could be used as an earlier-line treatment after at least 1 prior treatment other than SSAs, in line with its marketing authorisation. The NHS England Cancer Drugs Fund

clinical lead mentioned that 86 people with pNETs had either everolimus or sunitinib. While for epNETs, 115 people had everolimus and 323 people with STTR-positive neuroendocrine carcinoma of the gastrointestinal tract or pancreas had PRRT. The committee was aware that CABINET mainly represented a population with NETs at a later point in the treatment pathway when best supportive care is the main treatment option. The committee noted that the indication for cabozantinib involves some clinical uncertainty, especially when used after at least 1 prior systemic treatment other than SSAs. The committee heard that there would be some scenarios in which cabozantinib could be used as an earlier treatment. For example, people with pNETs who had cytotoxic chemotherapy as first-line treatment after SSAs or when off-label treatments are used to treat some NETs after SSAs. The committee thought that this may introduce challenges in clearly identifying the population who should be eligible for cabozantinib and at which stage. The committee acknowledged that cabozantinib could be used as an earlier-line treatment, and healthcare professionals and people with NETs would like to have additional treatment options earlier in the treatment pathway. The committee was aware that the trial population in CABINET (see section 3.7) had people who were at a later stage of the treatment pathway. Because they had been randomised to cabozantinib and best supportive, they must not have any further systemic treatment options. The committee clarified that it could only make a decision based on the evidence presented to it. It noted that no evidence was provided for using cabozantinib as an earlier-line treatment. The committee concluded that the company's positioning of cabozantinib as a later-line treatment and its choice of comparator (that is, best supportive care) was appropriate.

Clinical effectiveness

Grouping approach for epNETs

3.5 The company presented the clinical and cost-effective evidence for pNETs and epNETs separately. The committee was aware that CABINET

included people with tumours of the pancreas, gastrointestinal tract, lungs or thymus, or other or unknown primary sites. People with gastrointestinal, lung, thymus, other, and unknown primary NETs were enrolled in the epNET cohort of the study. The committee noted that the company grouped gastrointestinal NETs, lung NETs and other types of epNETs together. For lung NETs, 33 people were included in the cabozantinib arm and 16 people were included in placebo arm. The committee noted the differences in baseline characteristics. The EAG explained that lung NETs have a worse prognosis and have fewer treatment options than other epNETs. It explained that grouping lung NETs with other epNETs may be inappropriate and could conceal differences in treatment responses. At clarification, the company presented a separate analysis for lung NETs and epNETs without lung NETs (see section 3.8). The committee questioned the validity of the EAG's approach of separating lung NETs from other epNETs. The clinical experts explained that there is no clinical justification or biological reasoning for separating and analysing lung NETs independently. They explained that the observed benefit (see section 3.8) in lung NETs compared with other epNETS was based on a very small number of events. The committee noted the low number of people with lung NETs and that the decision to separate lung NETs lacks a strong clinical justification. It concluded that the grouping of lung NETs with other epNETs was appropriate, unless stronger justification is provided for analysing lung NETs separately.

Crossover

3.6 CABINET is a multicentre, randomised, phase 3 clinical trial comparing cabozantinib with placebo. People in the placebo arm were allowed to crossover to have cabozantinib on disease progression. The committee noted that a considerable proportion of people in the placebo arm had crossed over to have cabozantinib (39% in the pNET cohort and 29% in the epNET cohort using the August 2023 data cut-off). Crossover data from August 2024 data cut-off is considered confidential, so cannot be

reported here. The company clarified that it had explored formal methods for adjusting treatment switching, such as:

- rank-preserving structure failure time models (RPSFTM)
- simplified 2-stage estimation
- inverse probability of censoring weighting (IPCW).

The company thought the 2-stage method was not feasible because of the small sample sizes and the small number of overall-survival events for people who were eligible to crossover. It explained that it preferred to use IPCW over RPSFTM. This was because IPCW could account for prognostic factors in the estimation of weights and treatment effect and more reliably adjusted the intent-to-treat hazard ratios closer to 1. The EAG explained that the company did not provide sufficient justification of the 'no unmeasured confounder' assumption necessary for the IPCW method. It explained that IPCW weights were unstable because of small numbers and a high percentage of people crossing over, leading to considerable uncertainty in the results. Despite the limitations of each crossover adjustment method, the EAG felt that the RPSFTM approach was more appropriate. This was because although the total number of people crossing over was small, the percentage of the population that crossed over was large. The committee noted that the choice of adjustment method had an impact on the overall-survival results (see section 3.7). The committee noted that the company clarified that the 2-stage estimation method had been analysed, so it requested to see the results. It agreed with the EAG's reasoning and concluded that the RPSFTM method for adjusting for crossover was more appropriate than the IPCW.

CABINET results

3.7 The primary outcome of CABINET was progression-free survival. Key secondary outcomes included overall survival, objective response rate and safety and tolerability. CABINET enrolled 298 people with pNETs or epNETs whose disease had progressed after systemic treatment. A total

of 198 people had cabozantinib and 100 had a placebo. The results from the August 2023 data cutoff showed a statistically significant improvement in progression-free survival for cabozantinib compared with placebo in pNETs (hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.12 to 0.42) and epNETs (HR 0.38, 95% [CI] 0.25 to 0.58). The results did not show a statistically significant difference in overall survival between cabozantinib and placebo for pNETs (HR 0.95, 95% CI 0.45 to 2.00) or epNETs (HR 0.86, 95% CI 0.56 to 1.31). The committee noted that the August 2024 data cutoff provided an additional 12 months of overall survival, but the company preferred to use the August 2023 data cutoff for its base case. The results of the August 2024 data cutoff are considered confidential by the company and cannot be reported here. The committee was aware that the overall survival results with the August 2024 data cut also do not show a statistically significant benefit for cabozantinib. The committee recalled that the choice of adjustment method had an impact on the overall-survival results (see section 3.6). It noted that the results suggested a numerical advantage for cabozantinib compared with placebo when using IPCW for epNETs. While using RPSFTM, the results suggest a numerical advantage for placebo. The committee sought a possible explanation of the conflicting progression-free survival and overall-survival results. It considered whether they were influenced by trial design or by the possibility that improvements in progression-free survival may not necessarily translate into improvements in overall survival. The clinical experts explained that this may be because of the small sample sizes for the relevant populations, high percentage of people crossing over to cabozantinib, treatment sequences used and short trial follow up. They explained that the lack of an overall-survival benefit does not indicate a lack of clinical benefit. They clarified that they would normally use progression-free survival as a clinically relevant endpoint instead of overall survival. The committee was aware that the trial was stopped earlier than planned for efficacy reasons and the August 2024 data cutoff was from after the trial was stopped. The committee was aware that the

company preferred to use an overall-survival HR below 1 for cabozantinib, while the EAG used a HR of 1 in its base case (except for lung NETs when considered separately; see section 3.11). The committee noted the uncertainty in the overall-survival results. It concluded that the August 2024 data was more mature and should be used in decision making. The committee would like to see more robust evidence of a surrogacy relationship between progression-free survival and overall survival to support an assumption of an overall-survival benefit for cabozantinib. The committee agreed that it would consider an overall-survival hazard ratio of 1 in its decision making.

CABINET post-hoc results

3.8 Following clarification, the company presented overall-survival results for lung NETs and epNETs (without lung NETs) separately, using both the August 2023 and August 2024 data cutoffs. The results are confidential and cannot be reported here. The committee noted that the results suggested a statistically significant difference between cabozantinib and placebo for lung NETs. While for epNETs (without lung NETs), the results suggested a numerical advantage for the placebo compared with cabozantinib. The committee noted the considerable difference in the effect of cabozantinib on overall survival between lung NETs and epNETs (without lung NETs). The clinical experts explained that there is no obvious biological rationale for a large difference in effectiveness of cabozantinib for lung NETs versus epNETs. The committee was aware of the small sample size and imbalances in baseline characteristics in the lung NET cohort, which were likely to favour cabozantinib. The committee concluded that the results of the post-hoc analysis were uncertain, and it would consider lung NETs and epNETs as a single cohort in its decision making (see section 3.5).

Indirect treatment comparisons

3.9 The company considered best supportive care to be the most appropriate comparator for cabozantinib, with direct evidence from CABINET (see section 3.4). So, it did not present any indirect treatment comparisons (ITCs) for other comparators in the NICE scope (everolimus, sunitinib and PRRT). The company clarified that it had performed an ITC feasibility assessment. This suggested that the small sample sizes in CABINET, along with differences in populations and treatment effect modifiers between trials, meant that robust ITCs could not be done. The EAG considered that cabozantinib may be appropriate for a less heavily pretreated population where best supportive care is not the only option (see section 3.4). So, it presented simple Bucher exploratory ITCs between cabozantinib, everolimus and sunitinib for progression-free survival and overall survival. The evidence on PRRT was excluded because it only included people with midgut NETs and did not include best supportive care as a common comparator. The committee was aware that the EAG's ITCs are exploratory and associated with substantial limitations, such as differences in populations and the number of prior treatments. It noted that the EAG's ITCs suggested that cabozantinib has a numerical benefit for progression-free survival compared with everolimus and sunitinib. For overall survival, the results numerically favoured the comparators for both pNETs and epNETs. The committee acknowledged that the results of the ITCs were very uncertain. It recalled that it had previously concluded that the company's positioning of cabozantinib and its choice of comparator was appropriate (see section 3.4). The committee concluded the EAG's exploratory ITCs would not be considered further.

Economic model

Company's modelling approach

3.10 The company presented a partitioned survival model. The model comprises 3 mutually exclusive health states: progression-free, progressed disease and death. The model had a lifetime horizon of 40 years and a 4-week cycle. The company's model structure was similar to that used in previous NET appraisals. The EAG broadly agreed with the company's model structure and noted that the company had captured all relevant health states. The committee concluded that the company's model was appropriate for its decision making.

Progression-free survival extrapolations

3.11 To estimate progression-free survival beyond the observed CABINET data, the company used a log-normal curve for both pNET and epNET cabozantinib progression-free survival Kaplan–Meier data. It then applied the trial stratified HR (derived with a Cox proportional hazard model) to derive progression-free survival for the best supportive care arm. It explained that it had selected log-normal curves based on low Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values. The company clarified that all curves provided a similar fit to Kaplan–Meier data except for the exponential, which also aligned with 10-year progression-free survival data reported by Fröss-Baron et al. (2021). The EAG noted that the company's proportional hazard assumption did not hold because cabozantinib was less effective earlier than later for pNETs and vice versa for epNETs. It explained that using the Cox model from the trial was not appropriate or justified by the company. It noted that the HRs should be derived from the same parametric model used to estimate the respective survival curves to maintain internal validity. The EAG explained that a log-normal curve was not appropriate to use with a fixed HR. It also noted that it overpredicts progression-free survival with cabozantinib by 18 months for pNETS and 28 months for epNETs. So, the

EAG preferred to use Weibull for both pNETs and epNETs for cabozantinib and log-normal for best supportive care in its base case. The committee noted that the choice of the progression-free survival model for cabozantinib has a minor impact on results. It was aware that, unless strong justification is provided, the same curves should be used for both treatment arms, in line with the NICE Decision Support Unit Technical Support Document 14. It concluded that it would prefer to see Weibull curves for both treatment arms for both pNETs and epNETs.

Overall-survival extrapolations

3.12 The company's base case used August 2023 overall-survival data, but it also provided a scenario using August 2024 overall-survival data (see section 3.7). The company used the IPCW method to adjust the overall-survival data for crossover (see section 3.6). The IPCW crossover-adjusted HR was applied to the cabozantinib arm to derive the best supportive care overall-survival curve, so only the cabozantinib arm required the process of survival-curve selection. For its scenario using the August 2024 data cutoff, the company selected log-logistic curves for pNETs and epNETs based on AIC and BIC values and curves matching clinician landmark survival estimates for overall survival in cabozantinib. The EAG noted that log-logistic curves were not compatible with using fixed HRs because they indicate time-varying hazards. It explained that because of minimal differences in AIC and BIC values, it preferred to use Weibull for pNETs and epNETs. This is because it showed the best fitting curves and was compatible with the hazard ratio in the model. The committee was aware that the EAG preferred to use the RPSFTM method to adjust for crossover (see section 3.6) using the August 2024 data cutoff and based on that result, assume a hazard ratio of 1 (see section 3.7). The committee acknowledged that there was a very high level of uncertainty with overall-survival extrapolations, so assuming equal overall survival for cabozantinib and best supportive care in the model was appropriate. The committee was unclear why the company chose to use

the hazard ratio approach, but it concluded that it would prefer to see Weibull curves for both treatment arms for both pNETs and epNETs and further data to support a surrogacy assumption between progression-free survival and overall survival.

Utility values

3.13 In the company's model, health-related quality of life for the progression-free health state was accounted for by deriving utility values from European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30) data. This data was collected in the health-related quality of life sub-study of CABINET. Individual patient data was mapped to the EQ-5D and then fitted to a regression analysis to derive a utility value for use in the economic model. This was done separately for pNETs and epNETs. The company explained that its sub-study data was limited to inform the progression-free disease health state. So, it calculated utility values for the progressed-disease health state by multiplying the progression-free utility values by the proportional decrease in utility value seen in Swinburn et al. (2012) following disease progression. The utility values are confidential and cannot be reported here. The EAG explained that the company's approach to deriving the utility values may not be appropriate. It explained that enrolment in the sub-study was optional. This resulted in some patient characteristics not being balanced across study arms. Data on the reasons for sub-study dropout was also not available. It noted that the company also provided a limited justification for using the mixed models for repeated measures structure. It explained that the company did not provide utility values resulting from using the full model and fitted coefficients for either the simplified or the full model, or p-value estimates for the coefficients. It noted that there was no evidence that a systematic approach was used to select the fixed effect terms for inclusion in either model, and there was no rationale for drop-outs and missing data. So, given its concerns with the company's approach, the EAG preferred to

use progression-free utility values from Swinburn et al. and progressed-disease utility values from RADIANT-4. So that the trial utility values could be used in future analysis, the EAG suggests that the company provide further details of its regression analysis of the CABINET data, together with additional analysis of the raw data. The committee concluded that it would like to see the information requested by the EAG.

Concomitant treatments

3.14 The company's model assumed that concomitant SSA treatment would stop at the same time as cabozantinib. The duration of SSA treatment in the best supportive care arm was aligned with the time to discontinuation for placebo in CABINET. The acquisition and administration costs of SSAs were applied until the time to discontinuation for each subgroup. The company separately applied costs for subsequent treatment with SSAs when people entered the progressed-disease health state. The EAG considered the company's approach was inconsistent because it does not align with clinical opinion. It explained that there was no rationale why concomitant SSAs would be stopped at the point that systemic treatment is stopped because SSAs are used for continued symptom management. It explained that using the time to discontinuation data for placebo from CABINET is inappropriate to cost the use of concomitant SSAs in the best supportive care arm. This is because most people having systemic SSAs would stop on starting another systemic treatment. So, the EAG preferred to model that people having concomitant SSAs would continue from baseline until death. The clinical experts explained that the concomitant use of SSAs is uncertain in clinical practice. They clarified that there is no strong evidence of stopping or continuing SSAs, and there may be some variability based on the functional status of the disease. They further explained that SSAs are continued after progression, especially for functional NETs where SSAs help to control symptoms. The committee thought that the use of concomitant SSAs may be uncertain but noted that the clinical expert broadly agreed that concomitant SSAs do not stop with

treatment discontinuation. The committee concluded that the EAG's approach of modelling concomitant SSAs from baseline until death was more appropriate.

Subsequent treatments

3.15 In the company's model, subsequent treatment costs were applied as a one-off cost when entering the progressed-disease health state based on how many people had subsequent treatments in CABINET. This was then rescaled to sum to 100% assuming people could only have 1 subsequent treatment. The EAG noted that the proportions of people having each individual subsequent treatment in the company's model were informed by clinical expert opinion. It was concerned that the values were not robust because they were not informed by an appropriate elicitation approach. It highlighted that the distributions used in the model were not reflective of UK clinical practice. It explained that in clinical practice, some people would have multiple lines of subsequent treatments. So it considered it was inappropriate to scale individual proportions of people having each subsequent treatment to 100%. It noted that this does not account for people leaving the progressed-disease health state to the death health state each cycle, which could underestimate subsequent treatment costs. So, the EAG preferred to implement subsequent treatment costs to people leaving the progression-free state. For people moving from progression-free to the death state, proportions of people having subsequent treatments were taken as proportions of the whole population, rather than proportions of people surviving to progression. The clinical experts explained that people who have heavy pretreatment will have fewer treatment options available than those who have less heavy pretreatment. They explained that for the company's target population, the subsequent treatment options are limited but mainly include SSAs and palliative care. The committee concluded that, given cabozantinib's positioning in the heavy pretreatment population, where best supportive care is considered

to be the only available treatment option, it was unclear why the model included subsequent treatments.

Severity

3.16 The committee may apply a greater weight to quality-adjusted life years (QALYs), known as a severity modifier, if technologies are indicated for conditions with a high degree of severity. So, the committee considered the severity of NETs, that is, the future health lost by people living with the condition and having standard care in the NHS. The company provided absolute and proportional QALY shortfall estimates in line with the NICE's health technology evaluations manual. In both the company and EAG's analyses, the proportional QALY shortfall was below 0.85 for pNETs. But for epNETs it was 0.90. So a severity weight of 1.2 was applicable for epNETs. The committee noted that both the company and EAG's analyses were subject to a high degree of uncertainty because of the underlying assumptions adopted in their base cases. The committee concluded that severity may need to be reconsidered following its request for additional information on utilities and survival modelling.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.17 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty, specifically in:

- overall survival and the method to adjust for crossing over
- progression-free and overall survival were modelled.

But the committee also noted:

- the unmet need in the heavily pretreated advanced NETs population because of the lack of treatment options
- the rarity of NETs and the unavoidable heterogeneity that this introduces into the clinical evidence.

So, the committee concluded that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). But that it would reconsider this once further analyses have been provided.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.18 The committee noted that the company's base case gave ICERs below £30,000 per QALY gained for cabozantinib compared with best supportive care. The EAG made several changes to the company's base case, which increased the cost-effectiveness estimates to a level that was above what NICE normally considers an acceptable use of NHS resources. The committee noted that the EAG's probabilistic base case showed that ICERs for cabozantinib compared with best supportive care were over £100,000 per QALY gained.

Committee's preferred assumptions and request for additional analyses

3.19 The committee would like to see analyses based on:

- company's positioning and best supportive care as the relevant comparator (see section 3.4)
- pNETs and epNETs as the main subgroups (see section 3.5)
- August 2024 data cutoff coupled with the RPSFTM method for adjusting for crossover with data to support a surrogacy assumption, and provide the results of the 2-stage estimation results for crossover (see section 3.6 and section 3.7)

- Weibull curves to extrapolate progression-free survival for both cabozantinib and best supportive care (see section 3.11)
- Weibull curves to extrapolate overall survival for both treatment arms with a hazard of 1 for cabozantinib, and further data to support a surrogacy assumption (see section 3.12)
- further information, as requested by the EAG, on utility values (see section 3.13)
- continue concomitant SSAs from baseline until death and no subsequent treatment modelled (see section 3.14 and section 3.15).

Other factors

Equality

3.20 The committee noted that people from Black ethnic backgrounds have a higher incidence of NETs and can have poorer outcomes. It noted people may experience inequalities linked to age, disability, mobility, financial circumstances, or geographical distance from specialist NET centres. It also noted that differences can arise from language and culture, which may limit understanding of treatment and side-effect management. The committee noted that differences in incidence and prevalence cannot be addressed in a technology appraisal. Because its recommendation does not restrict access to treatment for some people over others, the committee concluded that there were no potential equality issues.

Uncaptured benefits

3.21 The committee considered whether there were any uncaptured benefits of cabozantinib. It noted that the company highlighted that two-thirds of people with NETs require caregivers, which is likely to increase with progressive disease, and this was not captured in the model. The committee noted that it was not presented with evidence to support this. The committee did not identify additional benefits not captured in the

economic modelling. So, the committee concluded that all additional benefits of cabozantinib had already been taken into account

Conclusion

Recommendation

3.22 The committee recognised that cabozantinib is an effective treatment in terms of progression-free survival. But overall survival and its modelling coupled with assumptions used in the model are highly uncertain and the available evidence does not suggest that cabozantinib is value for money. It concluded that further analyses were needed to inform its decision making. So, cabozantinib should not be used to treat unresectable or metastatic well-differentiated epNETs or pNETs that have progressed after at least 1 systemic treatment other than SSAs.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John

Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Harsimran Sarpal
Technical lead

Caron Jones
Technical adviser

Kate Moore
Project manager

Ross Dent
Associate director

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