NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendations

1.1 Cabozantinib should not be used to treat unresectable or metastatic well-differentiated extra-pancreatic neuroendocrine tumours (epNETs) and pancreatic neuroendocrine tumours (pNETs) that have progressed in adults 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.

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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 for most people.

The company asked for cabozantinib to be considered for 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. The extent of clinical benefit is also unclear.

Because of the uncertainties in the clinical evidence, it is difficult to determine cost-effectiveness estimates for cabozantinib. But, the most likely cost-effectiveness estimates are above the range normally considered an acceptable use of NHS resources. So, cabozantinib should not be used.

2 Information about cabozantinib

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.

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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.

Sustainability

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]), or the lungs or digestive system (extra-pancreatic NETs [epNETs]). NETs may be 'functional', when cells produce and release higher than normal levels of hormones or non-site-specific hormones, or 'non-functioning', when level of hormone release is too low to cause symptoms. 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

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that can change from day to day and affect many aspects of daily life, including employment, confidence, diet and independence. There are many different types of sub-populations of NETs. 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 based on the specific tumour site, such as hypoglycaemia or symptoms that impact cognitive function. They also explained that living with advanced NETs can be intensely challenging and emotionally exhausting for the person with the condition, and 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 eligibility (see section 3.3). The patient experts explained that symptoms associated with some hormone-related functional NETs, such as hypoglycaemia, can be made worse by some treatments. 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, and their families and carers, would welcome an additional treatment option.

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Clinical management

Treatment options

3.3 The clinical and patient 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
- dihydropyrimidine dehydrogenase (DPYD) status
- overall health
- other health conditions
- 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 the somatostatin analogues (SSAs) lanreotide or octreotide. Some people with pNETs are also offered cytotoxic chemotherapy, an off-label treatment, after SSAs. 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 tumour's primary 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
- peptide receptor radionuclide therapy (PRRT) for treating SSTR-positive progressive gastroenteropancreatic NETs (see the NICE

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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. At the second committee meeting, the clinical experts reiterated the complexity of the different subgroups of NETs and the heterogeneity in the treatment options between subgroups. They explained that individualised treatment is needed. This reaffirmed the committee's conclusions around the complexity in the treatment pathway.

Positioning and comparators

3.4 The marketing authorisation for cabozantinib includes adults 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), had heavy pretreatment, 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. 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. For pNETs, 44% of people who had cabozantinib and 48% of people who had placebo had only 1 previous

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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 or 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 there are more treatments available for pNETs than for epNETs (including lung NETs). So, cabozantinib could be used as an earlier-line treatment after at least 1 previous 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 in the NHS. 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 has some clinical uncertainty, especially when used after at least 1 previous 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, for pNETs in people who had cytotoxic chemotherapy 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

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pathway. The committee was aware that the trial population in CABINET (see section 3.7) included people who were at a later stage of the treatment pathway. Because they were randomised to cabozantinib and best supportive care, they must not have had any further systemic treatment options. At the second committee meeting, clinical experts noted that a small proportion of people with specific types of NETs may have off-label chemotherapy as a subsequent treatment. The committee questioned whether chemotherapy should have been included as a potential comparator for some groups of NETs. But it concluded that, given the extensive heterogeneity and the small numbers of people, it was appropriate to evaluate cabozantinib against a single comparator, that is best supportive care. 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 or compared with other treatments, such as chemotherapy. 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-effectiveness 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

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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 the clarification stage, the company presented a separate analysis for lung NETs and epNETs without lung NETs (see section 3.8). 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. For epNETs (without lung NETs), the results suggested a numerical advantage for 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 compared with 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 questioned the validity 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.

In response to draft guidance consultation, the company provided scenario analyses including only lung NETs. The company also provided clinical expert feedback on the suitability of considering the lung NET population separately. The opinions of the clinical experts diverged on the biological distinctiveness of lung NETs, but there was some consensus

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that lung NETs may be more aggressive than other NET subtypes. Despite this, the company reported there was consensus from all 4 clinical experts that separate consideration for lung NETs would be justified. At the second committee meeting, clinical experts expressed how tumour site, tumour functionality and SSTR status can impact the available treatment. So, there are some subgroups with limited treatment options that may benefit more from cabozantinib, specifically those with non-pancreatic or functional NETs. The EAG noted that, in a post-hoc analysis of the CABINET trial, lung NETs as a subgroup showed a statistically significant improvement in overall survival . But the clinical experts reiterated that the amount of data available was small and therefore this should be interpreted cautiously. Clinical experts noted that, in some cases, chemotherapy would be used as an off-label treatment instead of best supportive care. The committee concluded that, because of the small amount of data and based on clinical expert opinion, it would not be appropriate to consider a recommendation for the lung NETs population alone. The committee acknowledged that there could be an argument for a subgroup with functional NETs, but it noted the company had not provided clinical- or cost-effectiveness evidence for the functional NETs subgroup. The committee understood that it could only consider the populations based upon the available evidence presented by the company. This reaffirmed the committee's conclusion from the first committee meeting that the grouping approach should be pNETs and epNETs.

Crossover

3.6 CABINET was a multicentre, randomised, phase 3 clinical trial comparing cabozantinib with placebo. People in the placebo arm were allowed to cross over 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

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from the 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 cross over. 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 effects, 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. The committee noted that the company clarified that the 2-stage estimation method had been analysed, so it requested to see the results.

At draft guidance consultation the company provided justification for determining that the 2-stage estimation method was unfeasible. The EAG agreed with this and agreed that there was some justification for the IPCW assumptions to have been met, but stated that it is not

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possible to test. The EAG explained that neither method was ideal. It explained that, for the epNETs subgroup, IPCW numerically favours cabozantinib and RPSFTM numerically favours placebo. At the second committee meeting, the committee acknowledged the benefits and limitations of both methods. It noted both methods were associated with considerable uncertainty and for the epNETs subgroup, neither method resulted in a statistically significant difference. It concluded that neither method could be considered better than the other but that both suggested a hazard ratio (HR) of 1 for overall survival is plausible (see section 3.8).

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 people had placebo. The results from the August 2023 data cut-off showed a statistically significant improvement in progression-free survival for cabozantinib compared with placebo in the pNETs group (HR 0.23, 95% confidence interval [CI] 0.12 to 0.42) and the epNETs group (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 cut-off provided an additional 12 months of overall-survival data. In response to draft guidance consultation, the company updated its base case to use the August 2024 data cut-off. The results of the August 2024 data cut-off 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 did not show a statistically significant benefit for cabozantinib.

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The committee sought a possible explanation for 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 cut-off was from after the trial was stopped. 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.

HR for overall survival

3.8 The company preferred to use an overall-survival HR below 1 for cabozantinib, while the EAG used a HR of 1 (except for lung NETs when considered separately, see section 3.12). After the first meeting the committee concluded it would consider an overall-survival HR of 1 in its decision making. But it acknowledged the progression-free survival benefit and therefore requested 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. After draft guidance consultation, the company used a HR of 1 for pNETs. It maintained the IPCW-adjusted HR for epNETs which was less than 1 and stated that using a HR of 1 would be implausible. It explained this was based on clinical expert feedback and that previous literature indicated an association between progression-free survival and overall survival. This implied that it was possible to infer that if progression-free survival is

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improved with cabozantinib then overall survival would be too. The company also noted that the expert elicitation exercise used to validate the overall-survival extrapolations supported a survival benefit of cabozantinib over the comparator. The committee noted that the expert elicitation exercise produced a wide range of responses. For pNETs, 5-year overall survival ranged from 11.0% to 27.8% for best supportive care, and 24.1% to 44.0% for cabozantinib. For epNETS, the overall-survival estimates were between 5.8% and 15% for best supportive care and between 12.3% and 24.0% for cabozantinib. The clinical expert at the second committee meeting noted that while these outputs were extremely varied, this was to be expected. This is because of the heterogeneity within NETs and within the subgroup of NETs each healthcare professional may regularly encounter based on their expertise and their centre's expertise. The company explained that in the previous evaluation of everolimus and sunitinib, the committee had accepted a clinical-effectiveness benefit with non-significant overall-survival results and high levels of crossover. The EAG noted that while the previous literature showed an association between progression-free survival and overall survival, it lacked statistical power, used an exploratory analysis, included a wider population (Imaoka et al, 2017) or did not show a significant result (Singh et al. 2014; Ter-Minassian et al. 2017). This introduces uncertainty to conclusions around progression-free survival and overall survival association. The EAG noted previous NICE appraisals in which a clinical benefit had been assumed showed numerical advantage to the technology of interest rather than disadvantage, as in this evaluation. The EAG also expressed concern that the expert elicitation results were not robust because they were not informed by an appropriate elicitation approach. The company explained that overall-survival benefit would be difficult to demonstrate because of confounding with crossover, subsequent treatment variation, small sample size and long post-progression survival.

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The committee recalled that neither IPCW nor RPSFTM resulted in a statistically significant overall-survival benefit for cabozantinib for epNETs. It noted substantial uncertainty remained regarding the progression-free survival and overall-survival surrogacy relationship and the wide variation between overall-survival estimates from expert elicitation. It acknowledged that assuming a HR of 1 for overall survival reflects the results observed in CABINET with the August 2024 data cut-off, which do not show a statistically significant overall-survival benefit for cabozantinib.The committee concluded that there was no strong reason to select either IPCW or RPTSM and that assuming an overall-survival HR of 1 for epNETs was the most reasonable method because:

- The overall-survival HR confidence intervals had a wide range and crossed 1 for both IPCW and RPSFTM methods, meaning both methods showed no significant difference between cabozantinib and best supportive care.
- In previous NICE evaluations in which clinical effectiveness and a positive association between progression-free survival and overall survival was assumed, the data available showed a non-significant numerically positive association favouring the evaluated technology in the preferred base case. In this evaluation, at least some of the possible HRs numerically favoured best supportive care.
- The company base case included an overall-survival HR of 1 in the pNETs population, despite there being a progression-free survival benefit in the trial. It was unclear to the committee why a progression-free survival benefit would translate to an overall-survival benefit in the epNETs group but not the pNETs group.
- There was no reason to place more weight on the expert elicitation exercise than what the trial data showed when adjusted using appropriate methods. This was especially the case given the wide variation in clinical expert estimates and the issues identified by the EAG with the expert elicitation methodology.

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- While there could be an association between progression-free survival and overall survival, there was not enough evidence to determine the magnitude of overall-survival benefit.

Indirect treatment comparisons

3.9 The company thought best supportive care was 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 thought that cabozantinib may be appropriate for a less heavily pretreated population for whom 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 were exploratory and associated with substantial limitations, such as differences in populations and the number of previous 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.

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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 pNETs and epNETs cabozantinib progression-free survival Kaplan–Meier data. It then applied the trial-stratified HR (derived with a Cox proportional hazards 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 EAG noted that the company's proportional hazards assumption did not hold because cabozantinib was less effective earlier than later for pNETs and vice versa for epNETs. 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 curves for both pNETs and epNETs for cabozantinib and a log-normal curve for best supportive care in its base case. The committee noted that the choice of the progression-free survival model for cabozantinib had a minor impact on results. It was aware that, unless

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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. The company updated their model to reflect this after draft guidance consultation.

Overall-survival extrapolation

3.12 In response to draft guidance consultation, the company updated its base case to use August 2024 overall-survival data from CABINET (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. The company selected log-logistic curves for pNETs and epNETs based on the AIC and BIC values and curves matching clinician landmark survival estimates for overall survival with 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 curves for pNETs and epNETs. The EAG and company acknowledged there were minimal differences in statistical fit between log-logistic and Weibull curves. The committee was aware that the EAG preferred to use the RPSFTM method to adjust for crossover using the August 2024 data cut-off and, based on that result, assume a HR 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 HR approach, but it concluded that it would prefer Weibull curves for both treatment arms for both pNETs and epNETs. The committee noted its preference for an overall-survival

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HR of 1. This results in the best supportive care overall-survival curve being equivalent to the cabozantinib curve, meaning the choice of curve has no impact on the survival benefit estimated.

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) after 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. The EAG suggested that the company provide further details of its regression analysis of the CABINET data, together with additional analysis of the raw

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data.

At draft guidance consultation, the company provided the further analysis requested by the EAG. But, given the uncertainty at the first committee meeting, the company updated its base case to use utility values from Swinburn et al. for pNETs and from the phase 3 trial of everolimus (RADIANT-4) for epNETs. The EAG stated that the additional analysis provided by the company resolved most of the original concerns and that there was now sufficient information to justify using the CABINET data to inform the utility value in the progression-free health state. The EAG therefore adopted the company approach from the first committee meeting that used CABINET data for the progression-free utility values and decrements from Swinburn et al for pNETs and RADIANT-4 for epNETs to generate progressed-disease utility values. The committee noted it would prefer to use utility values from the relevant clinical trial when possible. It also noted that the majority of the EAG's initial concerns had been resolved by the company response to draft guidance. So, the committee concluded that CABINET data should be used for the progression-free health state utility values and decrements from Swinburn et al. for pNETs and RADIANT-4 for epNETs should be applied to produce progressed-disease utility values.

Concomitant treatments

3.14 At the first committee meeting, 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

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that there was no rationale why concomitant SSAs would be stopped at the point that another 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 when starting another systemic treatment. So, the EAG preferred to model that people having concomitant SSAs would continue from baseline until death. It 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. It further explained that SSAs are continued after progression, especially for functional NETs for which 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.

After draft guidance consultation the company accepted that assuming concomitant SSAs stop on discontinuation of cabozantinib does not reflect clinical practice. However, the company explained that its clinical experts reported that SSA use is not always lifelong and some discontinuation is anticipated. The company updated its base case to include a constant discontinuation rate for concomitant SSAs (1.7% for cabozantinib and 2.4% for best supportive care [epNETs] and 1.1% for cabozantinib and BSC [pNETs]) based on clinical expert opinion on the proportion of people who have concomitant SSAs and the proportion who stop concomitant SSA before death. In the second committee meeting a clinical expert agreed that people with functional NETs would continue SSAs for the purpose of hormone control. In both meetings the clinical experts explained that the concomitant use of SSAs is uncertain and varied in clinical practice. The EAG acknowledged that the expert elicitation estimates suggested that the original assumption of continuing SSAs until death is an oversimplification. The EAG still had concerns with the expert

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elicitation approach and the averages taken from the expert elicitation because of the heterogeneity in responses. The EAG's preferred approach was using the company discontinuation rate but using CABINET data for the proportion of people having concomitant SSAs. The committee noted that assuming concomitant SSAs continue until death may not reflect clinical practice and some people would stop concomitant SSAs. The committee noted that the company discontinuation rates were uncertain. But, in the absence of an alternative source, it concluded the company discontinuation rates with CABINET data for the proportion of people having concomitant SSAs was most appropriate for decision making.

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 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 moving from 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 the progression-free health state to the death health 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

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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 the only available treatment option, it was unclear why the model included subsequent treatments. But, at draft guidance consultation, the company updated its base-case analysis to reflect the EAG's preference for using the CABINET subsequent treatments in the model. The committee noted the company and EAG were aligned on the approach to subsequent treatments and accepted that this was an appropriate approach.

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. The absolute and proportional QALY shortfall was recalculated after the company provided further analysis. The EAG confirmed that the updates to the analysis did not change severity the weightings for epNETs and pNETs discussed at the first committee meeting.

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Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.17 NICE's technology appraisal and highly specialised technologies guidance manual 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 inthe extent of any overall-survival benefit and the method to adjust for crossover. But the committee also noted:

- its preferred assumptions around modelling overall survival which largely mitigate this uncertainty
- 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.

The committee concluded that an acceptable ICER would be towards the higher end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

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 above what NICE normally considers an acceptable use of NHS resources. The committee's preferences aligned with the EAG's base case. It noted that the EAG's probabilistic base case showed that ICERs for cabozantinib compared

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with best supportive care were substantially above the range NICE considers an acceptable use of NHS resources in both the pNETs and epNETs subgroups. Overall, the committee preferred the following modelling assumptions:

- including best supportive care as the only relevant comparator
- grouping populations into pNETs and epNETs
- for epNETs and pNETs, assuming a HR of 1 for overall survival
- using Weibull curves for both pNETs and epNETs progression-free survival and overall-survival extrapolations
- using the August 2024 data cut-off for decision making
- calculating health state utility values using CABINET data for the progression-free health state and applying decrements from Swinburn et al. for pNETs and from RADIANT-4 for epNETs for progressed disease
- using a constant discontinuation rate for concomitant SSAs (1.7% for cabozantinib and 2.4% for best supportive care [epNETs] and 1.1% for cabozantinib and best supportive care [pNETs]) with CABINET data to inform the proportion of people having concomitant SSAs.

Other factors

Equality

3.19 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

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not restrict access to treatment for some people over others, the committee concluded that there were no potential equality issues.

Uncaptured benefits

3.20 The committee considered whether there were any uncaptured benefits of cabozantinib. It noted that the company highlighted that two-thirds of people with NETs need carers, 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 any other benefits not captured in the economic modelling. So, the committee concluded that the benefits of cabozantinib for which there was supporting evidence had been taken into account

Conclusion

Recommendation

3.21 The committee recognised that cabozantinib is an effective treatment in terms of progression-free survival. But based on the available evidence the most likely cost-effectiveness estimates are above the value that NICE considers would represent a good use of NHS resources (see section 3.17). 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.

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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.

Chairs

Megan John

Chair, technology appraisal committee D

Raju Reddy

Vice-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 and Alice Bell

Technical leads

Caron Jones and Nigel Gumbleton

Technical advisers

Kate Moore

Project manager

Ross Dent

Associate director

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