National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Ipsen	Yes, it is appropriate that NICE reviews cabozantinib via the single technology appraisal route.	Thank you for your comment. No action required.
	Neuroendocrine Cancer UK	Appropriate for evaluation through route proposed.	Thank you for your comment. No action required.
Wording	Ipsen	The remit is appropriate.	Thank you for your comment. No action required.
	Neuroendrocrine Cancer UK	Yes	Thank you for your comment. No action required.

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Timing Issues	Ipsen	Despite the availability of options in the NET indication, cabozantinib can offer a further option where other treatments are inappropriate, ineffective or cannot be used because of specificities in their licensed indication e.g. only for certain types of NETs or characteristics (see comparator section below). With its broad licensed indication, cabozantinib may address unmet needs by being applicable to a wider range of NETs. Therefore, timely assessment of cabozantinib in line with its marketing authorisation timelines is necessary.	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required.
	Neuroendrocrine Cancer UK	N/A	Thank you for your comment. No action required.
Additional comments on the draft remit	Ipsen	No comments	Thank you for your comment. No action required.
	Neuroendrocrine Cancer UK	N/A	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Ipsen	We would suggest NICE to add an explanation for the terms “well/moderately differentiated”, “Somatostatin Receptor (SSTR) status” and “Ki-67 index9” within the background section of the scope. This is because they are discussed later in relation to the licensed therapies and NICE TA’s.	Thank you for your comment and suggested changes. The background section has been

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		All other information is deemed to be complete and accurate.	updated to reflect the suggested changes.
	Neuroendocrine Cancer UK	Has some slight inaccuracies and is incomplete in giving a view of real burden of disease for both the individual and health services – suggest: Neuroendocrine cancers are a heterogeneous group of rare malignancies which develop from neuroendocrine cells: they are 2 key classifications: • Neuroendocrine Tumours (NETs) characterised histologically as well-differentiated tumours (graded 1-3 according to proliferation and growth rate): This group also includes Typical and Atypical Carcinoids (a term usually applied specifically to those of lung origin). • Neuroendocrine Carcinomas (NECs) characterised histologically as poorly-differentiated carcinomas (small or large cell type Pancreatic NETs are found in pancreas. Extra-pancreatic NETs refers to NETs which are found outside the pancreas, including in the stomach, lungs, thyroid, small and large bowel, amongst other sites. NETs (or Carcinoids) may be further characterised as either functioning or non-functioning: referring to the abnormal or normal production/release of site-specific hormones. Functional tumours release higher than normal levels of site-specific or ectopic (non-site specific) hormones. For those with functioning tumours, uncontrolled hormone excess may be the life-limiting factor rather than the tumour itself. Specific symptoms vary by tumour location and whether the tumours are functioning or non-functioning. The incidence of NETs in England was 8.8 per 100,000 of the population per year in 2018, but the incidence is increasing over time.1 The prevalence of NETs is also rising according to both NDRS and global data, with neuroendocrine cancers (as a collective group) identified as the 15th most	Thank you for your comment and suggested changes. The background is intended to give a brief overview of the condition and treatment options in the disease area. Further details can be included in all submissions for this evaluation.

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		prevalent of 24 cancers affecting women and the 14th most prevalent of 21 cancers affecting men in England. (reference: https://nhsd-ndrs.shinyapps.io/prevalence/ accessed 5/12/24) Approximately 50% of NETs occur in the digestive system, including the stomach, small and large bowel, pancreas and rectum, and 20% occur in the lungs.1 and 2 Surgery is the only potentially curative treatment for NETs, if undertaken at early stage of disease (<20% reference 1). For people who are unable to have surgery, where surgery has been unsuccessful, or where curative surgery is not an option because of the position of the tumour or advanced stage of the disease, the choice of treatment depends on site, symptoms, stage of disease, functionality, grading (histological features of the tumour) and patient specific characteristics including co-morbidities, informed choice and accessibility (geographical e.g. travel requirements: time/distance/cost). Somatostatin analogues (SSAs) are usually the first or second-line (post-surgery - if residual or recurrent/metastatic disease seen post-surgery) therapy. However, SSAs do not offer cure, and many patients will eventually progress or have recurrent disease despite them. Therefore, other options and modalities of treatment are required, and understanding of prevalence as well as incidence is essential in decision-making. Other options for treating neuroendocrine tumour include; radiation therapies (see below - 3 & 4), interventional radiology procedures (ablation - has site, position, size and number restrictions , embolisation - may have vascular and/or biliary anatomy restrictions: and neither treat systemic disease), molecular medical therapies (eg Everolimus or Sunitinib: see below 1 & 2), chemotherapy regimens (as monotherapies or combination regimens:	Thank you for your comment and suggested changes. The background is intended to give a brief overview of the condition and treatment options.

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		streptozocin, 5-fluorouracil, capecitabine, temozolomide, etoposide, cisplatin, carboplatin and doxorubicin: are site, stage and grading specific) and, rarely, interferon-alpha. Immunotherapy has yet to prove its place in neuroendocrine tumours (particularly those within Grade 1-2 regardless of primary site). Several of these treatment options are recommended by NICE for treating certain types of unresectable or metastatic NETs in adults with progressive disease, for example: 1. NICE TA449 recommends everolimus and sunitinib for treating well- or moderately differentiated unresectable or metastatic NETs of pancreatic origin in adults with progressive disease. 2. NICE TA449 recommends everolimus for treating well-differentiated (grade 1 or grade 2) non-functional unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease. 3. NICE TA539 recommends lutetium (177Lu) oxodotreotide for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic NETs in adults. 4. NICE IPG786 recommends the use of selective internal radiation therapy (SIRT) as an option for neuroendocrine tumours that have metastasised to the liver, with standard arrangements in place for clinical governance, consent and audit. Best supportive care, including disease-specific dietetic support and palliation of hormone-specific and/or treatment-related symptoms, ideally run alongside all options - transitioning to End-of-Life care where required. While expert consensus clinical guidelines exist, in terms of overall management, sequencing of targeted or systemic therapies is unclear. This is largely due to the number of inherent variables such a heterogenous group of	

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		malignancies possess: considerations and influences therefore include site, stage of disease, grade and pace of growth (which may change over time), functional status, somatostatin-receptor status, performance status, side-effect impact and longer-term consequences of disease and/or previous treatments, and co-morbidities.	
Population	Ipsen	The population is appropriately defined.	Thank you for your comment. No action required.
	Neuroendocrine Cancer UK	Patients with neuroendocrine or carcinoid tumours that may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body (advanced): Grade 1-3, Functioning and non-functioning NETs (including Typical & Atypical Carcinoids) of pancreatic, gastrointestinal (GI), lung, thymus, other, or unknown primary sites included.	Thank you for your comment. This population is already covered, as defined in the scope. No action required.
Subgroups	Ipsen	The cabozantinib trial in NET (CABINET) has results available for the pancreatic NETs (pNETs) and extra-pancreatic NETs (epNETs) populations, which the trial was powered for. Subgroup analysis of the epNETs cohort by tumour location was not pre-specified and is under investigation. Tumour location was not a stratification factor for randomisation within the epNETs cohort.	Thank you for your comment. The scope has been updated to include subgroups based on other characteristics such as functioning status, differentiation, Ki-67 index and somatostatin receptor expression.

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	Neuroendocrine Cancer UK	The scope suggests following the trial protocol of considering 2 subgroups: • Pancreatic NETs • Extra-pancreatic NETs (including by tumour location) It should be noted however that within these subgroups, when interpreting data, not all will have had equivalent access to prior therapies due to licensing or indication restrictions – and that grading (proliferation rate) may also be influential: eg G1-2 v G3 (Typical Carcinoid would equate to G1-low G2, Atypical Carcinoid would equate to high G2-G3).	Thank you for your comment. No action required.
Comparators	Ipsen	We agree with NICE's inclusion of best supportive care (BSC) as a comparator in this indication. Chemotherapy is not a relevant comparator for cabozantinib in this indication for a number of reasons as explained below. NETs is a heterogenous disease with a broad range of characteristics such as whether the NET is functional or non-functional, SSTR positive or negative, whether they are well/moderate or poorly differentiated, the location of primary tumour site and grade of tumour (G1, G2 or G3). This heterogeneity is reflected in the relatively narrow labels of the currently licenced systemic treatment options. Somatostatin analogues, such as lanreotide is licensed for the treatment of grade 1 and a subset of grade 2 (Ki-67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease. In the case of licensed therapies that have been reviewed by NICE, these drive the recommendations in the first line setting (as illustrated in Table 1 below).	Thank you for your comment. The comparator has been updated to established clinical management without cabozantinib.

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<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
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Table 1: Systemic therapies in the first line setting for NET and recommended by NICE in line with their label
<table>
<tr><th></th><th>Pancreatic</th><th>GI</th><th>Lung</th></tr>
<tr><td>Everolimus (TA449)[1]</td><td>✓</td><td>✓ G1 or G2 and non-functional)</td><td>✓ (G1 or G2 and non-functional)</td></tr>
<tr><td>Sunitinib (TA449)[1]</td><td>✓</td><td>x</td><td>x</td></tr>
<tr><td>Lutetium (177Lu) oxodotreotide (TA539)[2]</td><td>✓ (G1 or G2 and SSTR +ve)</td><td>✓ (G1 or G2 and SSTR +ve)</td><td>x</td></tr>
</table>

The wording of the license for these systemic therapies further highlights the heterogeneity of the NET treatment pathway and the differences in treatment options available in the different primary tumour sites.

However, the patient population in CABINET trial was broad, including patients irrespective of SSTR status, functional status and grade. The inclusion criteria specified patients needed to have had at least one prior systemic therapy such as: everolimus, sunitinib or lutetium (177Lu) oxodotreotide.6

The heterogeneity of the disease and variable patient characteristics make the management of the condition complex. There is therefore no clear treatment
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		pathway and because the CABINET trial included a broad population the only relevant comparator is BSC. Chemotherapy regimens such as CAPTEM are used off-label with the evidence base for their use made up of retrospective or small trials with a diverse patient population with results not often reported for sub-populations. Chemotherapy was excluded as a comparator in both TA491 and TA539 as clinical feedback had suggested that it is typically reserved for higher-grade NETs (e.g., grade 3 tumours with high Ki-67) and is less commonly used for well-differentiated NETs. Given the limited overlap in patient populations and the lack of evidence, chemotherapy is not a relevant comparator. In summary, chemotherapy is not a relevant comparator and given the broad population enrolled in the CABINET trial it is more appropriate to consider BSC/no treatment/placebo as the comparator.	
	Neuroendocrine Cancer UK	The scoping document suggests chemotherapy regimens or best supportive care without Cabozantinib as comparators – without defining which chemotherapy regimens and grade appropriateness. Eg platinum regimens tend to be reserved for high-grade, rapidly progressing disease eg G3, whereas CapTem and Strep/5FU may be used in all Grades in progressive disease.	Thank you for your comment. The comparator has been updated to established clinical management without cabozantinib. It is anticipated that more information regarding the relevant treatments

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			will be included in the submissions.
Outcomes	Ipsen	Yes, the outcomes listed are appropriate.	Thank you for your comment. Comment noted. No action required.
	Neuroendocrine Cancer UK	Yes – however it should be noted that patients (within incurable disease) have been shown to favour PFS, tolerability, QoL and maintenance of physical, emotional and cognitive function above overall survival. HR-QoL as well as PFS & AE data is important.	Thank you for your comment. Comment noted. No action required.
Equality	Ipsen	Cabozantinib does not present any issues to the NICE's commitment of promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.	Thank you for your comment. Comment noted. No action required.
	Neuroendocrine Cancer UK	No change	Thank you for your comment. Comment noted. No action required.
Other considerations	Ipsen	No	Thank you for your comment. No action required.
	Neuroendocrine Cancer UK	NA	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Ipsen	***Where do you consider cabozantinib will fit into the existing care pathway for advanced pancreatic or extra-pancreatic NETs that have progressed after systemic treatment?*** The proposed label for cabozantinib would mean it could be prescribed in pNET and epNET patients who have had a least one line of prior systemic therapy. The CABINET trial has a broad population of patients compared to the other therapies recommended by NICE.[6] As such, the positioning of cabozantinib will differ according to patient characteristics and prior treatment history and therefore clinical experts will be best placed to determine the patients in which cabozantinib is given. ***Would cabozantinib be used after everolimus, sunitinib and lutetium (177Lu) oxodotreotide?*** The proposed label for cabozantinib would mean it could be prescribed in pNET and epNET patients who have had a least one line of prior systemic therapy which means it could be prescribed after everolimus, sunitinib and lutetium (177Lu) oxodotreotide. *Please select from the following, will cabozantinib be:* *A. Prescribed in primary care with routine follow-up in primary care* *B. Prescribed in secondary care with routine follow-up in primary care* *C. Prescribed in secondary care with routine follow-up in secondary care* *D. Other (please give details):* ***For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.***	Thank you for your comment. Comments noted. No action required.

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		For the comparators and subsequent treatments, the prescribing and follow-up pathway should not differ as it will be managed mainly in secondary care. ***Are interferons a relevant comparator for cabozantinib for advanced pancreatic or extra-pancreatic NETs that have progressed after systemic therapy?*** Interferons are not a relevant comparator. The use of Interferons is limited from our discussions with clinical experts and, as noted in the TA539[1] and TA449[2], clinical experts stated that interferons are not routinely used in England due to their toxicity. Interferons were excluded by the committees from both TAs for this reason. ***Should any other comparators for cabozantinib be included in scope?*** No, we do not think there are any other relevant treatments to consider. ***Are there any subgroups of people in whom cabozantinib is expected to more clinically effective or cost effective or other groups that should be examined separately?*** As proposed in the scope the following sub-groups can be examined i.e. pNETs and epNETs. ***Would cabozantinib be a candidate for managed access?*** Cabozantinib is not a candidate for managed access at present. There are no further data-cuts planned from the CABINET trial as far as Ipsen is aware. ***Do you consider that the use of cabozantinib can result in any potential substantial health-related benefits that are unlikely to be included in the***	

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		QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. ***The value of a new, efficacious treatment option and the simplification of treatment paradigm given the wider reimbursement population associated with cabozantinib is likely to be an uncaptured benefit in the QALY calculation.***	
	Neuroendocrine Cancer UK	**Where do you consider cabozantinib will fit into the existing care pathway for advanced pancreatic or extra-pancreatic NETs that have progressed after systemic treatment?** Excepting SSAs: 2nd/3rd line for those who have access to Everolimus/Sunitinib/PRRT or as alternative given current guideline options 2nd line for those who don't currently have access to Everolimus/Sunitinib/PRRT **Would cabozantinib be used after everolimus, sunitinib and lutetium (177Lu) oxodotreotide? Possibly pending appropriate expert clinical assessment.** Please select from the following, will cabozantinib be: A.Prescribed in primary care with routine follow-up in primary care B.Prescribed in secondary care with routine follow-up in primary care C.Prescribed in secondary care with routine follow-up in secondary care D.Other (please give details):	Thank you for your comments. Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are interferons a relevant comparator for cabozantinib for advanced pancreatic or extra-pancreatic NETs that have progressed after systemic therapy? NO **Should any other comparators for cabozantinib be included in scope?** NO Are there any subgroups of people in whom cabozantinib is expected to more clinically effective or cost effective or other groups that should be examined separately? **Answered above** Would cabozantinib be a candidate for managed access? **Possibly** Do you consider that the use of cabozantinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Potentially – hormone hypersecretion may be palliated by tumour control – which provides additional benefit in terms of QoL.	
Additional comments on the draft scope	Ipsen	None	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Neuroendocrine Cancer UK	NA	Thank you for your comment. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

PAWS
Sarcoma UK