SMC2967

cabozantinib film-coated tablets (Cabozantinib Ipsen®)

Ipsen Ltd

10 July 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the orphan equivalent medicine process

cabozantinib (Cabozantinib Ipsen®) is accepted for restricted use within NHSScotland.

Indication under review: 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.

SMC restriction: for use when best supportive care would otherwise be considered.

In a phase III study, treatment with cabozantinib resulted in improved progression-free survival in both the epNET and pNET cohorts, compared with placebo; this was considered a proxy for best supportive care. No evidence against active comparators was presented.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Cabozantinib inhibits multiple receptor tyrosine kinases that are implicated in the pathogenesis of neuroendocrine tumours (NETs); these include the vascular endothelial growth factor and hepatocyte growth factor receptor protein. Inhibition of these kinases may inhibit tumour growth, angiogenesis and metastatic progression.[1, 2] The recommended dose of cabozantinib film-coated tablets for this indication is 60 mg orally once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. For further details, please refer to the Summary of Product Characteristics (SPC).[3]

1.2. Disease background

Neuroendocrine tumours are a heterogeneous group of cancers that originate from neuroendocrine cells; they are typically well-differentiated (contain cancerous cells that mimic normal body cells). Patients diagnosed with metastatic NETs have a poor prognosis, with a reported 5-year survival ≤ 50% for all tumour sites.[4] NETs are rare, with a prevalence of 7 per 100,000 people in Scotland.[5] Disease classification is complex and based on a range of factors, including primary tumour site (in the pancreas, pNET, or any other location outside of the pancreas, extra-pancreatic NETs, epNETs), histological characteristics, tumour stage, tumour grade and functional status.[1, 6] NETs can occur within almost any organ in the body with the most common sites being the gastrointestinal (GI) tract (around 50%), lung (around 25%), and pancreas (<10%).[1, 2, 7] Grading of well-differentiated NETs (range: G1 to G3a) is based on tumour proliferation which is assessed via a mitotic count and the Ki-67 index; higher grades are associated with a more aggressive clinical course and worse prognosis.[8, 9] NETs may be functional and lead to syndromes related to hormone excess.[1] Symptoms can also vary depending on tumour site. However, the majority of pNETs (approximately 60% to 90%) are non-functional[6], which means they are generally diagnosed at more advanced stages because of their relatively indolent nature and slow growth causing a delay in onset of symptoms.[10]

1.3. Company proposed positioning

For use when best supportive care would otherwise be considered.

1.4. Treatment pathway and relevant comparators

Treatment of unresectable or metastatic NETs is individualised and dependent on many factors, including the site of the tumour, tumour grading, Ki-67 score, somatostatin receptor (SSTR) expression status, functional and performance status.[5] Since somatostatin receptors are present in approximately 70 to 95% of NETs, somatostatin analogues (SSAs) such as octreotide and lanreotide are commonly used as first-line agents for the management of symptomatic NETs.[5] Treatment options are informed by SMC1337/18 and NICE (multiple) technology appraisal 449; however, there is no standard treatment sequencing for the second line of treatment and beyond. For pNETs, treatment options (excluding prior SSAs) include: everolimus, sunitinib, and for patients with SSTR positive disease (G1 and G2 only), lutetium (^{177}Lu) oxodotreotide (Peptide Receptor Radionuclide Therapy, PRRT); with PRRT and everolimus appearing to be used more frequently in earlier line of therapy than sunitinib.[1] For epNETs, treatment options (excluding prior SSAs)

include: PRRT for SSTR positive disease (G1 and G2 gastrointestinal NETs only) and everolimus.[5] Chemotherapy (off-label) is also a later line option, however there is wide variation in disease response across different types of NET.[5]

There is no Cancer Medicines Outcomes Programme Public Health Scotland (CMOP-PHS) real-world evidence report for this submission.

1.5. Category for decision-making process

Eligibility for a PACE meeting

Cabozantinib meets SMC orphan equivalent criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The evidence to support the use of cabozantinib comes from the CABINET study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study.

Criteria	CABINET study.[1, 2]
Study design	US-based, multicentre, randomised, double-blind, placebo-controlled, phase III study.

Eligible patients	• Aged ≥18 years, with an ECOG PS of 0 to 2.
	• Histological diagnosis of locally advanced or metastatic NETs of pancreatic (pNET) or extrapancreatic (epNET) origin.
	• Well- or moderately differentiated WHO grade 1 to 3 NETs.
	• Disease progression (≤12 months before enrolment) or intolerance following at least one prior systemic therapy (excluding SSA-only regimens).
	• Prior lines of therapy were to have included one of the following:
	  ○ pNET: everolimus, sunitinib or lutetium (^{177}Lu) oxodotreotide.
	  ○ Lung NET: everolimus.
	  ○ GI NET: everolimus or lutetium (^{177}Lu) oxodotreotide.

Treatments and randomisation	Patients with epNETs and pNETs were allocated into two separate cohorts which were randomised and analysed independently. Within each cohort, patients were randomly assigned in a 2:1 ratio to receive cabozantinib 60 mg orally once daily or placebo. Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent. Prior SSA treatment was allowed, and continuation of SSA treatment whilst on cabozantinib or placebo was allowed (if the SSA dose was stable for ≥2 months before enrolment). Patients in the placebo group were permitted to cross-over to receive open-label cabozantinib following disease progression. Randomisation was stratified by: • epNET cohort: Concurrent SSA use (yes versus no) and primary tumour site (midgut GI or unknown versus non-midgut GI or lung or other). • pNET cohort: Concurrent SSA use (yes versus no) and prior sunitinib use (yes versus no).
Primary outcome	PFS as assessed by BIRC, defined as the time from randomisation to the occurrence of disease progression (according to RECIST, version 1.1) or death, whichever occurred first.
Selected secondary outcome	OS, defined as the time from randomisation to death from any cause.
Statistical analysis	Following a review of the results from the interim analyses, the DSMB recommended stopping enrolment, unblinding the study and cross-over of all placebo-treated patients to open-label cabozantinib. As a result, the final efficacy analysis was not conducted and the second and first interim analyses for the epNET and pNET cohorts respectively (data cut-off August 2023) remain the final analysis of PFS; a prespecified analysis of OS was also conducted at this data cut-off.

	Efficacy analyses were conducted in the ITT population, defined as all patients within each cohort (epNET and pNET) who were randomised.

Abbreviations: BIRC = blinded independent review committee; DSMB = Data and Safety Monitoring Board; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GI = gastrointestinal; ITT = intention-to-treat; NEC = neuroendocrine carcinoma; NET = neuroendocrine tumour; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SSA = somatostatin analogue; US = United States; WHO = World Health Organisation

Across the epNET and pNET cohorts, prior treatments included SSAs (≥ 93% in both cohorts), PRRT (approximately 60% in both cohorts), everolimus (between 64% and 81%), sunitinib (≤ 28% in both cohorts), and chemotherapy (between 33% and 69%).[1, 2]

At the first interim analysis (data cut: August 2023) in CABINET, treatment with cabozantinib resulted in improved PFS in both the epNET and pNET cohorts, compared with placebo. There was no clear difference in OS between the cabozantinib and placebo groups in either cohort at the first interim analysis,[1, 2] and at the unspecified, updated OS analyses with one more year of follow-up (data cut September 2024).[1] See Table 2.2 for details.

Table 2.2. Efficacy results for CABINET in the ITT population (data cut: August 2023, unless otherwise specified).[1, 2]

	epNET cohort[a]		pNET cohort[a]	
	Cabozantinib (n=134)	**Placebo (n=69)**	**Cabozantinib (n=64)**	**Placebo (n=31)**
Primary outcome: Progression-free survival as per BIRC assessment				
Median PFS follow-up	23.3 months	23.0 months	23.2 months	25.2 months
PFS events, n	71	40	32	25
Median PFS	8.5 months	4.0 months	13.8 months	4.5 months
Hazard ratio (95% CI)[b]	0.38 (0.25 to 0.58)		0.23 (0.12 to 0.42)	
KM estimated PFS at 24 months	6.9%	NE	20%	0.0%
Selected secondary outcome: Overall survival				
Median OS follow-up	24.2 months		23.1 months	
OS events, n	60	37	21	11
Median OS	22.0 months	19.7 months	40.1 months	31.1 months
Hazard ratio (95% CI)	0.86 (0.56 to 1.31)[c]		0.95 (0.45 to 2.00)[d]	
KM estimated OS at 24 months	46%	39%	65%	62%
Selected secondary outcome: Overall survival (data cut: September 2024)				
OS events, n	84	42	31	15
Median OS	22.0 months	22.5 months	40.1 months	31.1 months
Hazard ratio (95% CI)	1.04 (0.71 to 1.52)		1.11 (0.59 to 2.09)	
KM estimated OS at 24 months	47%	44%	68%	65%
KM estimated OS at 36 months	33%	31%	55%	40%

Abbreviations: BIRC = blinded independent review committee; CI = confidence interval; ITT = intention-to-treat; epNET = extrapancreatic neuroendocrine tumour; KM = Kaplan-Meier; NE = not estimable; OS = overall survival; PFS = progression-free survival; pNET = pancreatic neuroendocrine tumour

[a] Due to issues with cohort allocation and stratification between the study registration systems, three epNET patients were misallocated to the pNET cohort and seven pNET patients were misallocated to the epNET cohort.

[b] Estimated using the Cox proportional hazard model. The CABINET study was stopped for efficacy at the time of an interim analysis that was planned for futility only. Type I error was not formally controlled and p-values are not presented. The presented 95% confidence interval is descriptive and does not imply statistical significance was reached.

[c] In the placebo arm, 29% of patients (n=20) crossed over to receive open-label cabozantinib after disease progression; these patients were not censored at the time of cross-over and were analysed under the group to which they were randomised (that is placebo) for OS under ITT principles.

[d] In the placebo arm, 39% of patients (n=12) crossed over to receive open-label cabozantinib after disease progression; these patients were not censored at the time of cross-over and were analysed under the group to which they were randomised (that is placebo) for OS under ITT principles.

OS sensitivity analyses adjusting for crossover (at the September 2024 data cut) were conducted using three different methods: a rank preserving structural failure time model (RPSFT), inverse probability of censoring weights (IPCW) and a two-stage estimation method. Results for each of the methods produced wide confidence intervals including 1.0, and central estimates varied either side of 1.0.[1]

2.2. Health-related quality of life outcomes

Within the CABINET study, a substudy (A021602-HO1) was conducted to assess if cabozantinib would improve health-related quality of life (HRQoL) and decrease disease-related symptoms in the epNET and pNET cohorts as compared with placebo. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Core Quality of Life Core 30 (EORTC QLQ-C30), EORTC QLQ Gastrointestinal Neuroendocrine Tumours 21 (EORTC QLQ-GINET21) and Patient Global Impression of Change questionnaires. Data were collected at baseline and every 12 weeks until disease progression or the start of a new anticancer treatment. Cross-over patients were not permitted to be included in the sub-study. Overall, HRQoL was similar between the cabozantinib and placebo groups in both cohorts and remained relatively stable over time.[1, 2]

3. Summary of Safety Evidence

Evidence from CABINET supports the relative safety of cabozantinib compared with placebo for the treatment of patients with unresectable or metastatic epNET or pNET. The placebo arm (as a proxy for best supportive care) is considered a relevant comparator in this submission. At the first interim analysis (data cut: August 2023), the median duration of treatment was 5.4 months versus 2.8 months in the epNET cohort and 8.3 months versus 2.9 months in the pNET cohort.[1]

For the epNET cohort, in the cabozantinib group (n=132) and placebo group (n=67) respectively, treatment-related adverse events (AEs) that were grade 3 or 4 (59% versus 27%) and led to treatment discontinuation (26% versus 13%) were more common in the cabozantinib group. For the pNET cohort, in the cabozantinib group (n=63) and placebo group (n=31) respectively, treatment-related AEs that were grade 3 or 4 (65% versus 23%) and led to treatment discontinuation (14% versus 3.2%) were more common in the cabozantinib group.[1]

For the epNET cohort, the most common grade 3 or 4 treatment-related AEs occurring in >5% of patients in the cabozantinib or placebo group were: hypertension (20% versus 3.0%), fatigue (13% versus 7.5%) and diarrhoea (11% versus 4.5%). For the pNET cohort, the most common grade 3 or 4 treatment-related AEs occurring in >5% of patients in either group were: hypertension (19% versus 9.7%), fatigue (11% versus 3.2%), palmar-plantar erythrodysesthesia syndrome (9.5% versus 0%), nausea (7.9% versus 3.2%), diarrhoea (6.3% versus 0%), stomatitis (6.3% versus 0%) and vomiting (6.4% versus 0%); embolism (6.4% versus 0%) and small intestinal obstruction (0% versus 6.5%).[1]

Overall, the safety profile of cabozantinib in NETs appears to be manageable and was consistent with the known safety profile of cabozantinib for other indications. It was noted that dose modifications were very common with cabozantinib treatment in both cohorts and this resulted in

a median average daily dose of 42.6 mg, which highlights the poor tolerability of the 60 mg dose of cabozantinib.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- CABINET was a randomised, double-blind phase III study that appears to have been well-conducted, with stratification and generally well-balanced baseline characteristics between the treatment groups; this makes it likely there is a low risk of bias for the interim analyses of the primary outcome before the unblinding stage.
- In CABINET, treatment with cabozantinib resulted in improved PFS in both the epNET (median gain of 4.5 months) and pNET cohorts (median gain of 9.4 months), compared with placebo.[1, 2] Regulators commented that the PFS results of CABINET were similar to other available treatments, despite patients in CABINET being more heavily pre-treated at baseline.[1] While the early stopping of the study meant that no formal statistical testing was performed, the overall improvement in PFS can be considered clinically relevant. Sensitivity analysis of PFS were also supportive.[1]

4.2. Key uncertainties

- This licensed indication covers multiple lines of treatment and treatment choice is influenced by patient-specific factors. The company conducted a feasibility assessment for an indirect comparison versus other available systemic therapies but concluded that this was not feasible. Within the proposed positioning in the resubmission, best supportive care is the most relevant comparator. As patients in the clinical study went on to receive subsequent treatments, there is uncertainty in the generalisability of the clinical study results.
- Overall survival was a secondary outcome and at the time of unblinding, patients on placebo crossing-over to open-label cabozantinib, data were immature and did not show a difference between the study arms. Overall survival analyses after this point will be confounded due to crossover to cabozantinib and interpretation will be very uncertain; overall survival analyses intending to adjust for crossover have not shown a clear difference between the treatment groups. In addition, across the epNET and NET cohorts, 45% to 67% of patients went onto receive a subsequent anticancer treatment. The impact of cabozantinib on overall survival is uncertain.[1, 2]
- The magnitude of improvement in PFS observed in the pNET cohort may be overestimated. Due to early termination of the CABINET study, only half of the number of intended patients were recruited for the pNET cohort (95 out of the target of 185 pNET patients). Overall, due to under recruitment, the interim pNET analysis may have reduced statistical power and lacks control for type I error; this may result in an overestimation of treatment effects in this cohort, however, a clinically relevant improvement in PFS is still expected for the pNET cohort.[1, 2]
- HRQoL appeared to be similar between the cabozantinib and placebo groups in both cohorts, however, participation was optional meaning randomisation was broken. Additionally, the response rate was highly variable for each time point.[1, 2]

4.3. Clinical expert input

Most experts contacted by SMC considered cabozantinib to be a therapeutic advancement and would fulfil an unmet need given the lack of treatment options, particularly for those with epNETs.

4.4. Service implications

No service implications are anticipated with the introduction of cabozantinib.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **cabozantinib (Cabozantinib Ipsen®),** as an **orphan equivalent** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Neuroendocrine tumours (NETs) are a rare and heterogeneous group of cancers that includes those whose primary tumour site is in the pancreas (pNETs) and in any other location outwith the pancreas (extra-pancreatic NETs, epNETs). They are often diagnosed at an advanced stage. Even though NETs can be slow growing, knowing that the disease is incurable and unpredictable causes ongoing anxiety and psychological distress.
- Patients experience a high and enduring symptom burden with common symptoms including extreme fatigue, pain, bowel problems; some can experience hormone-related symptoms that are debilitating, difficult to control, and can be life-limiting. These patients will receive multiple lines of systemic therapy, repeated investigations and monitoring. This can all be physically and emotionally exhausting.
- Families and carers are also deeply affected, often experiencing emotional strain, fatigue, and disruption to their own daily lives as they support someone living with a chronic and ultimately life-limiting illness. Patients describe a loss of independence, financial burden, reduced ability to work, and limitations in social and family roles.
- Despite there being several systemic treatments available in NHS Scotland, these will likely be exhausted as the disease progresses and treatment effectiveness varies depending on NET type. There are fewer options in epNETs (lung and small bowel) in particular. Therefore, there is a need for more treatments. Cabozantinib would offer additional treatment for patients who have been heavily pretreated for this incurable, metastatic cancer.
- In the CABINET study, cabozantinib showed good activity and a clinically meaningful improvement in progression-free survival in heavily pretreated patients with pNETs and epNETs. The overall HRQoL also remained stable over time on cabozantinib treatment and was similar to patients receiving placebo. This suggests patients may able to maintain their current level of functioning and quality of life for longer, whilst having control of cancer-related symptoms. PACE participants highlighted that overall survival is not considered to be the most relevant measure of treatment success due to the multiple lines of therapy people usually receive; progression-free survival and quality of life have the greatest meaning in this patient group. Patients returning to work would likely have financial

benefits for families. Patients may be able to spend more quality time with family.

- Whilst dose modifications are common with cabozantinib, the overall safety profile appears to be manageable within this setting. A PACE clinician also highlighted that, from his experience, reducing the dose does not appear to impact effectiveness.
- Cabozantinib is an oral treatment which has increased convenience, would not require hospital visits for administration, and would allow patients to continue or return to work.

Additional Patient and Carer Involvement

We received a patient group submission from Neuroendocrine Cancer UK, which is a registered charity. Neuroendocrine Cancer UK has received 6.6% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Neuroendocrine Cancer UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime
Population	Adult patients with unresectable or metastatic well-differentiated epNETs and pNETs, with progression following at least one prior systemic therapy other than SSAs.
Comparators	BSC
Model description	A standard three-state partitioned survival model was employed. The three included states were progression-free, progressed disease and dead.
Clinical data	The main source of clinical evidence as the CABINET study.[1, 2] The data cut employed in the economic analysis was from August 2023, following early termination of the study (with unblinding to allow treatment switching for patients in the placebo arm to cabozantinib).
Extrapolation	Proportional hazards were assessed by the submitting company as valid for PFS. A Cox hazard ratio (pNETs: 0.23, 95% CI: 0.12 to 0.42; epNETs 0.38, 95% CI: 0.25 to 0.58) was applied to a cabozantinib arm lognormal model in both pNETs and epNETs group. The submitting company considered statistical and visual fit and found little evidence of any difference between candidate distributions. The lognormal was preferred by the submitting company on the basis this was consistent with external evidence. No significant treatment effect was demonstrated in terms of OS in CABINET. The submitting company employed IPCW analysis to adjust for treatment switching, and IPCW adjusted hazard ratios (HRs) were applied to survival functions for the cabozantinib arm (pNETs exponential; epNETs log-logistic). The selection of OS parametric curve was guided by clinician estimates of long-term survival received by the submitting company.
Quality of life	The submitting company measured HRQoL in the CABINET study using EORTC QLQ-C30 instrument. These data were subsequently mapped to the EQ-5D instrument. Utility values were estimated from a regression model. There were too few observations in progressive disease to estimate plausible values for the post-progression to health state, and the submitting company applied a multiplicative reduction to its progression-free estimate based on a vignette study by Swinburn et al (2012).[11] Decrements were also applied for AEs.
Costs and resource use	Medicine costs were included for concomitant therapies and subsequent treatment costs. On expert clinical advice, the submitting company applied common distributions of subsequent therapies following progression. For pNETs a greater proportion of progressed patients received subsequent therapies in the cabozantinib group, with more equal proportions in epNETs. The greater rate of

	progression for BSC resulted in higher subsequent therapy costs for BSC. Costs were also assigned for health states, terminal care, and AEs.
PAS/contract price	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The economic analysis suggested that cabozantinib was associated with higher costs, but also better health outcomes compared to BSC. The resulting incremental cost-effectiveness ratio (ICERs), inclusive of the PAS on cabozantinib, were £24,164 in the pNETs group and £13,538 in the epNETs group.

6.3. Sensitivity analyses

To test areas of uncertainty, the submitting company conducted deterministic sensitivity analysis, probabilistic sensitivity analysis and scenario analysis. These analyses suggested that the assumptions related to the modelling OS had the greatest impact upon the estimated cost-effectiveness. A selection of scenario analysis results, inclusive the PAS on cabozantinib, are presented in Table 6.3.

Table 6.3: Scenario analysis PNETs AND epNETs (Cabozantinib PAS price)

	Parameter	Base case	Scenario	pNETs–ICER (£/QALY)	epNETs–ICER (£/QALY)
	Base case			24,164	13,583
1	Cabozantinib PFS and TTD distributions	PFS: Lognormal, TTD: Exponential	PFS: Gompertz, TTD: Weibull	26,835	15,101
2	Cabozantinib OS distribution	Exponential	Log-logistic	20,059	13,860
3	Parametric PFS	Lognormal	Weibull	27,646	15,736
4	BSC PFS and TTD distributions	HRs applied to cabozantinib	PFS: Lognormal TTD: Weibull	24,162	14,252
5	Subsequent therapy costs	Included	Exclude	26,938	20,900
6	Treatment switching analysis for OS	IPCW	RPSFT	42,336	20,329

Abbreviations: lICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weights; PFS = progression-free survival; QALYs = quality-adjusted life years; RPSFT = rank preserving structural failure time; OS = overall survival; TTD = time to treatment discontinuation.

6.4. Key strengths

- CABINET demonstrated the benefits of cabozantinib in terms of progression-free survival.
- Although there were uncertainties regarding long-term outcomes, substantial efforts were made to corroborate modelling assumptions both against expert clinical opinion and external data.

6.5. Key uncertainties

- The submitting company modelled PFS and TTD by estimating HRs from Cox regression and applying those to parametric survival curves estimated from data collected from cabozantinib

patients observed in the CABINET study. This was undertaken to provide consistency with OS analysis, where adjustment for treatment switching was applied. It was unclear whether consistency was strong enough justification for this approach to PFS and TTD, although independently fitted parametric curves in the BSC arm appeared to have little impact on the ICER (see Scenario 4, Table 6.3).

- No effect was demonstrated in the CABINET study for OS, and treatment switching made establishing an estimate of the OS benefits of cabozantinib challenging. The submitting company utilised IPCW to try and establish the base case estimate of cost-effectiveness, feeling this was the most robust approach. An alternative, RPSFT, was explored as a scenario and resulted in a much higher ICER (Scenario 6). Both the IPCW and RPSFT based analyses were associated with significant uncertainty. The model appears to be highly sensitive to reductions in assumed treatment effect for OS.
- It is unclear whether the subsequent therapy costs applied in the model, which generate cost-offsets for cabozantinib, should be expected to arise in clinical practice, given the heavily pre-treated nature of the patient population and, as the submitting company itself argues, the paucity of further treatment options at this stage; in isolation exclusion of subsequent therapies has only a marginal impact on the base case ICER (Scenario 5).

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of cabozantinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as cabozantinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted cabozantinib for restricted use in NHSScotland.

8. Guidelines and Protocols

The European Neuroendocrine Tumour Society (ENETS) published guidance on colorectal NETs[12], appendiceal NETs[13], gastroduodenal NETs[14], functioning pNETs[15] and non-functioning pNETs[16] respectively in 2023. ENETS also published guidance on carcinoid syndrome and carcinoid heart disease among patients with NETs in 2022[17], and the management of well-differentiated small intestine NETs in 2024.[18]

The Scottish Neuroendocrine Tumour Group (SCONET) published Scotland-wide consensus guidelines for the management of patients with NETs in 2022; these guidelines are currently under review.[5]

9. Additional Information

9.1. Product availability date

18 September 2025.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28-day cycle (£)
Cabozantinib tablets	**60 mg orally once daily until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.**	**4,800**

Costs from BNF online on 03 March 2026. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 368 patients eligible for treatment with cabozantinib in year 1 and 75 in years 2 and 3. These values account for the scale of the prevalent population in year 1 and the incident case in years 2 and 3.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 26 June 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.