SMC2590

cabozantinib film-coated tablets (Cabometyx®)

Ipsen Ltd

12 January 2024

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 full submission assessed under the end of life and orphan equivalent medicine process.

cabozantinib (Cabometyx®) is not recommended for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

In a double-blind, randomised, phase III study, progression-free survival was significantly improved with cabozantinib compared with placebo in patients with DTC, refractory or not eligible to RAI who had progressed after one or two prior tyrosine kinase inhibitors.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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, including MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. Inhibition of these kinases may inhibit tumour growth, angiogenesis, metastatic progression and pathological bone remodelling. The marketing authorisation has been extended to include use as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy. The recommended dose of cabozantinib film-coated tablets is 60mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.[1, 2]

1.2. Disease background

Differentiated thyroid cancer is the most common type of thyroid cancer and accounts for >90% of cases. It includes papillary thyroid cancer (approximately 80%), follicular thyroid cancer (approximately 10%) and Hürthle cell thyroid cancer (approximately 3%). In about 10% of patients, there is tumour invasion into surrounding tissues and/or distant metastases at the time of diagnosis. For patients with distant metastases, the main predictors of outcome are age, site of metastases and uptake of RAI. The prognosis is poorer in patients who become refractory to RAI with median survival time of approximately 2.5 to 3.5 years.[2]

1.3. Treatment pathway and relevant comparators

The main treatment for DTC is surgery, either as total thyroidectomy or unilateral lobectomy, with or without lymph node removal. Radioactive iodine may be used in patients at high risk of recurrence; with incomplete resection; or with distant metastases. Lenvatinib and sorafenib (both multikinase inhibitors) have been licensed for use as monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma, refractory to RAI; both have been accepted for use by SMC (SMC 1179/16 and SMC1055/15 respectively). However, there is no standard of care for patients after first-line treatment with lenvatinib or sorafenib and the optimal sequencing of treatments remains unclear. In addition, selpercatinib has been licensed for use as monotherapy for adult patients with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.[2-6] In many patients, subsequent treatment may be best supportive care (BSC), which the submitting company considered to be the most relevant comparator.

1.4. Category for decision-making process

Eligibility for a PACE meeting
Cabozantinib meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of cabozantinib for the treatment of DTC comes from the COSMIC-311 study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[2, 7]

Criteria	COSMIC-311
Study design	Double-blind, randomised, phase III study
Eligible patients	– patients aged ≥16 years with histologically or cytologically confirmed diagnosis of DTC, including papillary and follicular subtypes and their histological variants. – measurable disease according to RECIST 1.1 on CT or MRI performed <28 days before randomisation. – received previous treatment or deemed ineligible for treatment with radioactive iodine-131 for DTC. – received at least one prior therapy of either lenvatinib or sorafenib and must have had radiographic progression during treatment or within 6 months after the most recent dose of the VEGFR inhibitor (up to two prior therapies were allowed including, but not limited to, lenvatinib and sorafenib) – experienced documented radiographic progression according to RECIST 1.1 by the investigator during or following treatment with a VEGFR-targeting TKI prior to starting the next anticancer therapy (which may have been treatment in COSMIC-311) – ECOG performance status of 0 or 1 – received thyroxine suppression therapy and TSH must have been below the lower limit of the reference range or <0.50 mIU/L (<0.50 µIU/mL), whichever was lower, within 28 days before randomisation (if hormone replacement therapy was tolerated a TSH level of ≤ 0.1 mIU/L was targeted).
Treatments	Cabozantinib 60mg or matching placebo orally once daily continued until disease progression, confirmed per RECIST version 1.1, or until unacceptable toxicity.
Randomisation	Randomisation in a ratio of 2:1 with stratification according to prior use of lenvatinib (yes or no) and age (≤65 or >65 years).
Primary outcome	There were two co-primary outcomes: – ORR defined as the proportion of patients with a best overall response of confirmed complete or partial response according to RECIST 1.1 assessed by BIRC after ≥6 months of follow assessed in the first 100 patients, OITT population. – PFS defined as the time from randomisation until radiographic progressed disease (assessed using RECIST v1.1 by BIRC) or death from any cause in the ITT population, which included all randomised patients.
Secondary and additional outcomes	OS defined as the time from randomisation to death from any cause. Disease stabilisation rate defined as the proportion of patients achieving a confirmed complete or partial response of stable disease for ≥16 weeks.
Statistical analysis	Only the co-primary outcomes were controlled for type I error. Results for other outcomes are considered descriptive only.

DTC=differentiated thyroid cancer; RECIST=Response Evaluation Criteria in Solid Tumours; CT=computed tomography; MRI=magnetic resonance imaging; VEGFR=vascular endothelial growth factor receptor; TKI=tyrosine kinase inhibitor; ECOG=Eastern Co-operative Oncology Group; TSH=thyroid stimulating hormone; ORR=objective response rate; BIRC=blinded independent radiology committee; OITT=ORR intention to treat; PFS=progression-free survival; ITT=intention to treat; OS=overall survival.

At the time of the primary analysis of objective response rate (ORR) (19 August 2020, CCO1), the co-primary outcome of ORR by blinded independent radiology committee (BIRC) in the first 100 patients did not reach statistical significance (p=0.028) at the pre-specified level of 0.01. Interim analysis of co-primary outcome, progression-free survival (PFS) assessed by BIRC, found significantly greater improvements in PFS with cabozantinib compared with placebo.[2, 7] Results are presented in Table 2.2 along with descriptive results for secondary and additional outcomes and for an exploratory updated analysis (8 February 2021, CCO2).

Table 2.2 Results for co-primary and additional relevant outcomes in the OITT and ITT populations at 19 August 2020 and 8 February 2021 data cut-offs of the COSMIC-311 study[1, 2, 7-9]

Analysis and cut-off date	**Primary ORR and interim PFS analysis: CCO1 19 August 2020**		**Updated analysis: CCO2 8 February 2021**	
	Cabozantinib (N = 125)	**Placebo (N = 62)**	**Cabozantinib (N = 170)**	**Placebo (N = 88)**
Co-primary outcome of ORR by BIRC on RECIST v1.1 in first 100 patients (OITT population) at 19 August 2020) and ITT population at 8 February 2021				
Median follow up ORR, months	8.9		10.1	
ORR, % (n/N)	15% (10/67)	0% (0/33)	11% (19/170)	0% (0/88)
Difference (CI)	p=0.028[a]		11% (95% CI 6.4 to 16)	
Co-primary outcome of PFS by BIRC on RECIST v1.1 in ITT population				
Median follow-up, months	6.2		10.1	
PFS Events	31	43	62	69
Median PFS, months	NE	1.9	11.0	1.9
Hazard Ratio (96% CI; stratified), p-value	0.22 (0.13 to 0.36), p<0.001		0.22 (0.15 to 0.32)	
KM estimated PFS at 9-months,	54%	6.3%	54%	12%
Secondary outcome OS				
Number of deaths, n (%)	17	14	37	21
Median OS, months	NE	NE	19.4	NE
Hazard Ratio (95% CI) [b]	0.54 (0.27 to 1.11)		0.76 (0.45 to 1.31)	
KM estimated OS at 12-months	72%	65%	72%	68%

Additional outcomes				
Disease stabilisation rate	43%	16%	53%	19%

CC01= clinical cut-off 1; CC02=clinical cut-off 2; OITT=objective response rate intention to treat; ITT=intention to treat; ORR=objective response rate; BIRC=blinded independent radiology committee; RECIST=Response Evaluation Criteria in Solid Tumours; CI=confidence interval; PFS=progression-free survival; KM=Kaplan-Meier; OS=overall survival; NE=not estimable.

[a] the p-value of 0.028 did not meet pre-specified significance level

[b] placebo patients who crossed over to cabozantinib were not censored at crossover and were analysed according to their randomised treatment group

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

Patients randomised to receive placebo were allowed to cross over to receive open-label cabozantinib on disease progression as confirmed by BIRC. At the time of the primary ORR analysis (19 August 2020, CCO1), 31% (19/62) of patients in the placebo group had crossed over to receive open-label cabozantinib. At the time of the updated analysis (8 February 2021, CCO2), 45% (40/88) of patients in the placebo group had crossed over to receive open-label cabozantinib.[2, 7, 8] The submitting company explored the use of three different methods to adjust the overall survival (OS) data for placebo patients who had crossed over to receive open-label cabozantinib. At the updated analysis, the unadjusted hazard ratio (HR) for OS for cabozantinib versus placebo was 0.76 (95% confidence interval [CI] 0.45 to 1.31), as detailed in Table 2.2. Following adjustment for crossover, the resulting stratified HRs for cabozantinib versus adjusted placebo were:

- the inverse probability of censoring weights (IPCW): HR 0.68 (95% CI 0.37 to 1.27).
- the rank-preserving structural failure time (RPSFT): HR 0.65 (95% CI 0.28 to 1.53).
- the two-stage method: HR 0.70 (95% CI 0.41 to 1.22).

The submitting company used results adjusted using the RPSFT method in the economic case.

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the EuroQol Health questionnaire instrument (EQ-5D-5L). Assessments continued regardless of whether study treatment was given until confirmed disease progression or permanent study treatment discontinuation. HRQOL assessments were not collected for the placebo patients who crossed over to receive open-label cabozantinib.[2]

Overall, there were no clinically meaningful treatment differences in either group with all mean changes from baseline measurements in EQ-5D-5L index score being <0.06 to Week 33 and in EQ-5D-5L visual analogue scale being <7of which is below the minimal important difference threshold of 0.06 to 0.08 and 7 respectively.[2]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

The submitting company conducted a feasibility assessment of indirect treatment comparisons (ITCs) between cabozantinib and other approved treatments including lenvatinib, sorafenib and selpercatinib. However, these were not considered feasible since no data were available for sorafenib as a second-line treatment for RAI-refractory DTC. Furthermore, there was a lack of reporting of patient characteristics and survival outcome data for the second-line population of

the key lenvatinib study and selpercatinib use was limited to patients with RET fusion positive disease.

3. Summary of Safety Evidence

The overall safety profile of cabozantinib in the COSMIC-311 study for the treatment of DTC was considered manageable with dose modifications and was consistent with its expected safety profile. No new safety signals were identified.[2]

In the COSMIC-311 study at updated analysis (8 February 2021, CCO2), the median duration of treatment in the cabozantinib group was 6.0 months (range 0.2 to 18.8 months) and in the placebo group was 2.6 months (range 0.2 to 15.2 months). The safety population was assessed based on the study treatment patients were initially randomised to receive and was not adjusted for crossover. Any treatment-emergent AE was reported by 98% (166/170) of patients in the cabozantinib group and 85% (75/88) in the placebo group; the proportion with treatment-related AEs was not reported. In the cabozantinib group and placebo groups respectively, patients reporting a grade 3 or 4 AE were 62% versus 28% and with a serious AE were 39% versus 27%. Patients with a dose interruption due to treatment emergent AEs were 71% versus 27%, with a dose reduction due to treatment emergent AEs were 67% versus 3.4% and with discontinuation due to an AE was 9% versus 0%, respectively.[8]

At the latest cut-off, the most frequently reported AEs of any grade in the cabozantinib versus placebo groups respectively were diarrhoea (62% versus 3.4%), palmer-plantar erythrodysaesthesia syndrome (PPE) (47% versus 1.1%), hypertension (32% versus 3.4%), increased alanine aminotransferase (25% versus 2.3%), nausea (28% versus 2.3%), increased aspartate aminotransferase (25% versus 2.3%), decreased appetite (31% versus 12%), hypocalcaemia (25% versus 3.4%), decreased weight (22% versus 2.3%) and fatigue (29% versus 8.0%).[8]

The most frequently reported treatment-emergent AEs of grade 3 or 4 with an incidence of greater than 5% in the cabozantinib group versus the placebo group, respectively were: hypertension (12% versus 2.3%), PPE (10% versus 0%), fatigue (8.8% versus 8.0%) and diarrhoea (7.6% versus 3.4%).[8]

The SPC notes that the most common serious AEs reported in ≥1% of the differentiated thyroid cancer population are diarrhoea, pleural effusion, pneumonia, pulmonary embolism, hypertension, anaemia, deep vein thrombosis, hypocalcaemia, osteonecrosis of jaw, pain, PPE syndrome, vomiting and renal impairment.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Cabozantinib is the first medicine to be licensed for second and subsequent lines of use in patients with locally advanced or metastatic DTC refractory to or not eligible for RAI, without a targetable mutation.[1]
- In the double-blind, randomised phase III study (COSMIC-311), cabozantinib significantly improved, compared with placebo, the co-primary outcome of independently assessed PFS at

the planned interim analysis. At the updated analysis, there was a PFS benefit of 9.1 months (11.0 months versus 1.9 months). Although, this analysis was exploratory in nature, the results were considered clinically relevant for a patient population with limited treatment options.[2, 7]

- Other outcomes including ORR, disease stabilisation rate and OS numerically favoured cabozantinib over placebo at the primary ORR analysis and at the updated analysis.[2, 7, 8]
- The co-primary outcomes of ORR and PFS were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by BIRC to minimise potential bias.

4.2. Key uncertainties

- At the primary analysis of ORR in the first 100 patients, cabozantinib failed to achieve a significant improvement in ORR compared with placebo.
- The study was only powered to analyse ORR in the first 100 patients and PFS in the ITT population. Analysis of OS and other secondary and additional outcomes were not controlled for type I error and are considered descriptive only. The PFS results are from the interim analysis based on 38% (74/193) of the total PFS events and the p-values were adjusted accordingly to account for the reduced sample size and ensure appropriate analysis. The results of the updated analysis at data cut-off 8 February 2021 were not pre-specified and are considered exploratory only.[2, 7, 8]
- The median duration of follow up for PFS and OS are relatively short and the number of PFS events and deaths observed are low. At both analysis points, there was a high level of censoring: at CCO1, 86% of cabozantinib patients and 77% of placebo patients were censored for OS and at CCO2, 78% and 76% were censored, respectively. This results in uncertainty in the longer term survival benefits of cabozantinib over placebo. The EPAR notes that no further updates of the OS analysis are available or planned.[2, 7, 8]
- The available OS results are confounded by the crossover of patients randomised to placebo to open-label cabozantinib following disease progression. The OS analysis was performed according to ITT principles and patients who crossed over were not censored at time of crossover but were analysed as if randomised as placebo patients. This confounding makes the OS results difficult to interpret and uncertain. The submitting company provided results for the treatment effect on OS for cabozantinib versus placebo adjusted for the effect of crossover and the results using the RPSFT method were used in the economic case. However, given the level of detail provided, it is unclear if the assumptions that underpin this method are met in the COSMIC-311 data.
- Cabozantinib is licensed for use in patients with locally advanced or metastatic DTC refractory to or not eligible for RAI who have progressed during or after prior systemic therapy. Since more than 70% of study patients had only received one prior tyrosine kinase inhibitor, the evidence mainly represents the use of cabozantinib in the second-line setting. There is no evidence supporting the use of cabozantinib in patients with DTC after more than two previous lines of VEGFR TKI medicines.[1, 2]

- Although BSC may be a relevant comparator for many patients after progression on or after prior systemic therapy, some patients may receive further treatment and there is no direct or indirect comparative evidence against potential active comparators.
- Study patients had an ECOG performance status score of 0 and 1 and the results may not be generalisable to patients with poorer performance status in clinical practice.[2, 7, 8]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that cabozantinib fills an unmet need and is a therapeutic advancement in this indication, offering a licensed second-line treatment option.

4.4. Service implications

The service implications from the introduction of cabozantinib are likely to be limited.

5. Summary of Patient and Carer Involvement

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

The key points expressed by the group were:

- Advanced DTC that is refractory to RAI is rare and has a very poor prognosis. It is associated with a significant symptom burden including difficulties with breathing, swallowing and speech, nausea, dyspnoea, bone pain, fractures and spinal cord compression. Patients may also suffer the physical effects of previous treatment. Advanced DTC often affects relatively young or middle-aged patients, many of whom are working and have children or dependents to care for. This all has a substantial physical, psychological and financial impact and negatively affects the quality of life of patients.
- There is no standard second-line therapy for patients with advanced DTC, refractory to RAI. Lenvatinib is the first-line treatment of choice and sorafenib is rarely used. Selpercatinib can be used as a second-line option in the small proportion of patients who have a RET-fusion mutation. However, for the majority of patients with no targetable mutation, there is no evidence-based second line option and most people receive best supportive care. Cabozantinib would offer an additional treatment option for these patients following prior systemic therapy and fills a substantial unmet need.
- Improved disease control and longer progression-free survival with cabozantinib may lead to improvements in patients' daily functioning, increased mobility, self-care and greater independence. It may allow patients to continue to live more productive and normal lives for longer and enable them to drive or to work. This may allow patients to spend more quality time with family, which can be especially important when patients have a young family. The availability of cabozantinib may relieve the despair of living with an incurable cancer with no further active treatment.
- Cabozantinib may reduce the burden of disease, allowing patients to be treated at home with less contact with healthcare, fewer adjunctive therapies and potentially fewer hospital

admissions for symptom control. Overall, this may mean that patients who respond maintain or improve their quality of life.

- Cabozantinib is administered orally and would be given as an outpatient treatment offering convenience to patients, families and carers, possibly allowing them to return to work in some cases.
- There is widespread experience of using tyrosine kinase inhibitors and the toxicity associated with cabozantinib is considered manageable. PACE participants noted that patients felt that the potential benefits of treatment outweighed the side effects.

Additional Patient and Carer Involvement

We received a joint patient group submission from, the British Thyroid Foundation and the Butterfly Thyroid Cancer Trust. Both organisations are registered charities. The Butterfly Thyroid Cancer Trust has not received any pharmaceutical company funding in the past two years. The British Thyroid Foundation has received 3.38% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from The British Thyroid Foundation participated in the PACE meeting. The key points of their joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as presented in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	35 years.
Population	The submitting company requested SMC consider cabozantinib for the treatment of adult patients with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy.
Comparators	Best supportive care (BSC). BSC was defined as no active treatment regimen.
Model description	A three state partitioned survival model was used, with the following health states: progression free; progressed disease; and death. The survival curves for overall survival and PFS determined the proportion in each health state. Patients initially entered into the progression free health state, receiving either cabozantinib or BSC. From this health state patients could transition to progressed disease or the death state, with patients in the progressed disease state transitioning to death. Time on cabozantinib treatment was determined by the time to treatment discontinuation (TTD) curve. There were no subsequent treatments in the model. The model used a cycle length of 1 month and applied a half cycle correction.
Clinical data	Clinical data were from COSMIC-311 (CC02 data cut, median follow up 10.1 months) for overall survival, PFS, TTD and adverse events.[8, 10] Data from the cabozantinib arm were used to model outcomes for the cabozantinib arm in the economic model, with data from the placebo arm used to model outcomes in the BSC arm. The placebo overall survival data were adjusted for crossover using the RPSFT method.
Extrapolation	To estimate long-term efficacy outcomes, overall survival and PFS data from COSMIC-311 were extrapolated. Independent overall survival and PFS curves were fitted to each treatment

	arm. The survival curves were selected through a process that considered statistical fit, visual fit to Kaplan-Meier plots and clinical validation. Several considered overall survival curves crossed, with BSC survival outcomes exceeding cabozantinib survival outcomes. In the base case, the Weibull model was used for PFS in the cabozantinib and BSC arms, with the exponential model used for overall survival in both arms. Time on treatment for cabozantinib was modelled from extrapolated cabozantinib TTD data, using a Weibull model in the base case. For the BSC arm, no time on treatment was modelled as patients in BSC arm were not receiving any active treatment.
Quality of life	Health state utility values were from a vignette study, Fordham et al., 2015,[11] that elicited utility values for radioactive iodine-refractory differentiated thyroid cancer from the UK public. The utility values used for progression free survival and progressed disease were 0.80 and 0.5, respectively. Age-related utility decrements were applied with a utility cap at general population utility.[12] Adverse event dis-utilities were applied as a one-off decrement in the first model cycle.
Costs and resource use	Costs included in the model were treatment acquisition, administration, monitoring, adverse events, and end of life. A relative dose intensity from COSMIC-311 was applied to cabozantinib medicine acquisition costs in the base case.
PAS	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 base case cabozantinib cost per quality adjusted life year (QALY) with PAS result was £34,973. The majority of incremental QALY gain for cabozantinib was from the increased duration in the PFS health state. The majority of incremental cost for cabozantinib was from the medicine acquisition costs.

6.3. Sensitivity analyses

The scenario analyses are shown in Table 6.3 (PAS included). The ICER is most sensitive to alternative overall survival extrapolations, utility values and the application of compliance to medicine acquisition costs.

Table 6.3Scenario Analysis Results (with PAS)

#	Scenario	Base case value	Scenario value	ICER (£/QALY)
	Base case			34,973
1	PFS curve - BSC	Weibull	Gompertz	34,987
2	PFS curve - Cabozantinib	Weibull	Gompertz	35,658
3	OS curve - BSC and Cabozantinib	Both use exponential	Both use log normal	38,645
4	OS curve - BSC	Exponential	Log-normal *	58,363
5	OS curve – Cabozantinib	Exponential	Gompertz *	72,719
6	OS curve – BSC	Exponential	Blended survival analysis	30,402
7	TTD curve – Cabozantinib	Weibull	Exponential	36,956
8	Utility values	Fordham et al., 2015 (PFS 0.8, PD 0.5)	COSMIC-311	39,867

9	RDI	Included	Exclude and use compliance	39,461
10	Combine scenarios 8 and 9	Fordham et al., 2015 utilities and RDI.	COSMIC-311 utilities and compliance.	44,984
11	Combine scenarios 8 and 9 and 3	Fordham et al., 2015 utilities and RDI. OS exponential.	COSMIC-311 utilities and compliance. OS lognormal.	53,406
12	Combine scenarios 8 and 9 and 6	Fordham et al., 2015 utilities and RDI. BSC OS exponential.	COSMIC-311 utilities and compliance. BSC OS blended survival analysis.	35,926
13	Combine scenarios 8 and 9 and 4	Fordham et al., 2015 utilities and RDI. BSC OS exponential.	COSMIC-311 utilities and compliance. BSC OS lognormal.*	133,816
14	Combine scenarios 8 and 9 and 5	Fordham et al., 2015 utilities and RDI. Cabozantinib OS exponential.	COSMIC-311 utilities and compliance. Cabozantinib OS Gompertz.*	303,942

Abbreviations: BSC – best supportive care; ICER – incremental cost-effectiveness ratio; LYG – life year gained; OS – overall survival; PFS – progression free survival; QALY – quality-adjusted life year; RDI – Relative dose intensity; TTD – Time to treatment discontinuation. Note. (*) denotes scenarios where the BSC OS extrapolation crosses and would exceed the cabozantinib OS extrapolation. In this event, the BSC OS outcomes were capped at cabozantinib OS outcomes in the model to prevent the BSC OS curve exceeding the cabozantinib OS curve.

6.4. Key strengths

- The model structure was appropriate to capture disease progression for patients receiving treatment for locally advanced or metastatic DTC.
- Key clinical data used in the model were from a phase 3 placebo controlled randomised controlled trial, COSMIC-311.
- A comprehensive selection of variables were considered in one-way deterministic sensitivity analysis.

6.5. Key uncertainties

- There was uncertainty in the overall survival extrapolations due to limitations in the overall survival data from COSMIC-311. Firstly, the survival data in the final CC02 data cut (10.2 months median follow up) were immature and the study was not powered to detect differences in overall survival. Secondly, there was a limited number of events in the ITT population (58 deaths [37 cabozantinib, 21 placebo] at CCO2). There were also low patient numbers at risk (at 12 months, 39 cabozantinib at risk and 17 placebo; at 18 months, 6 cabozantinib at risk and 0 placebo). Thirdly, there was a high censoring rate of the overall survival data (78% in the cabozantinib arm and 76% in the placebo arm were censored at their last known alive dates). The submitting company highlighted an alternative plausible overall survival log-normal extrapolation for both cabozantinib and BSC, which increased the ICER to £38,645 (Scenario 3), and was considered plausible as these extrapolated curves did not cross.

However, several plausible alternative overall survival extrapolations led to BSC overall survival exceeding that of cabozantinib, with BSC overall survival capped at cabozantinib overall survival if this occurred, increasing uncertainty in the face validity of the overall survival extrapolations. For example, if using the log-normal overall survival extrapolation in the BSC arm alone, the ICER increased to £58,363 (Scenario 4). If using the Gompertz overall extrapolation in the cabozantinib arm alone, the ICER increased to £72,719 (Scenario 5). Although these were potentially conservative considerations, they met several selection criteria and highlighted the extrapolation uncertainties present in the model from using immature overall survival data. These uncertainties are challenging to resolve without additional overall survival data. No further data cuts for COSMIC-311 are planned. The Committee considered the range of alternative overall survival extrapolations and noted that the comments from SMC clinical experts on this issue provided some support for the company's extrapolations, however it was noted that further external validation of the longer term overall survival estimates from published sources was limited to provide reassurance to SMC that the scenarios showing a significant increase in the ICER (scenarios 4, 5, 13 and 14) are unlikely to be relevant for decision-making.

- The progression free utility value of 0.8 from the Fordham et al., 2015 vignette study may have overestimated the utility score in the progression free health state causing the ICER to fall in favour of cabozantinib. The submitting company preferred to use the Fordham et al., 2015 vignette progression free (0.8) and progressed disease (0.5) utility values, due to the limited impact of progression observed in the EQ-5D derived COSMIC-311 utility values. However, this reasoning would not exclude the use of the COSMIC-311 progression free utility value in the economic model. As the majority of the QALY gain was from the progression free health state, this utility value has a greater impact on the ICER than the progressed disease utility value. Applying the COSMIC-311 utility values increased the ICER to £39,867 (Scenario 8). The submitting company also noted the use of the Fordham et al. 2015 vignette utility values prior health technology assessments (NICE TA742, NICE TA516 and SMC1179/16). However, in contrast to COSMIC-311, the trials in the noted health technology assessments did not collect EQ-5D data. In sum, the use of Fordham et al. 2015 vignette utility values may have biased the ICER in favour of cabozantinib.
- The model included a relative dose intensity adjustment applied to cabozantinib acquisition costs. This was to reflect the mean dose the patients actually received in COSMIC-311 compared to the standard dose (60mg daily). However, as cabozantinib has a flat pricing structure across the 20/40/60mg doses, these cost savings would not be realised in NHS Scotland. The use of compliance rather than RDI is more appropriate, as it accounts for the number of tablets actually taken whilst on treatment. When applying compliance data, the ICER increased to £39,461 (Scenario 9).
- The blended survival analysis (based on methods outlined by Che et al., 2022[13]) conducted as a scenario analysis sought to integrate clinical expert opinion to inform the extrapolated BSC overall survival (Scenario 6). The method showed a reduction in the ICER as the BSC overall survival extrapolation estimated lower survival outcomes than the base case extrapolation, reflective of the clinical expert feedback that viewed the base case extrapolations as

overestimating BSC overall survival outcomes. SMC experts also noted reduced BSC overall survival expectations compared to the base case extrapolations. Several scenario analyses were conducted on the blended survival analysis and showed a limited impact. However these may have been limited in scope, with analyses using alternative observed data and clinical expert opinion extrapolated curves not available, which potentially increased uncertainty in the results of the blended survival analysis. It was also noted that the blended survival analysis approach was only explored in the BSC arm and there may have been merit in also applying this to the cabozantinib arm to potentially provide a fairer comparison.

- In COSMIC-311 45% of placebo treated patients crossed over to treatment with cabozantanib upon disease progression. The RPSFT method used to adjust the placebo overall survival data in COSMIC-311 assumes a 'common treatment effect', that is the impact of the experimental therapy is the same whether given at randomisation or from the time of crossover. Counterfactual survival times for the placebo and cabozantinib arms of the COSMIC-311 trial were not presented to determine the performance of the adjustment method. The submitting company provided sensitivity analysis varying the treatment effect size after progression, providing indicative evidence of a relatively small impact on the overall estimated relative treatment effect of cabozantinib versus placebo after adjustment. However, as the estimated relative treatment decreased in this sensitivity analysis, this would likely increase the ICER, although no economic results were available to assess the impact.

As noted in the clinical effectiveness section above, no comparisons were presented against active treatments and as such the economic case against these therapies is unknown.

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

7. Conclusion

The Committee considered the benefits of cabozantanib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as cabozantanib 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 was unable to accept cabozantanib for use in NHSScotland.

8. Guidelines and Protocols

The European Society for Medical Oncology (ESMO) published in September 2019; Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. An update has been published in April 2022 which provides recommendations on the use of systemic therapies, including cabozantinib, in advanced thyroid cancer.[6, 14]

9. Additional Information

9.1. Product availability date

10 May 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
cabozantinib	**60mg orally once daily**	**62,402**

Costs from BNF online on 5 October 2023. 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 45 patients eligible for treatment with cabozantinib in Year 1 and 9 patients in Years 2 to 5. The estimated uptake rate was 20% in year 1 and 85% in year 5. This resulted in 9 patients estimated to receive treatment in year 1 falling to 8 patients in year 5.

It should be noted that the net budget impact assumed a small amount of usage of sorafenib being displaced (at list price). Note that sorafenib was not included as a comparator in the economic evaluation. The gross medicines budget impact provides results consistent with the economic model, as the gross budget impact does not take sorafenib into account.

*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 **17 November 2023.**

**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 is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme 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. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards 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.