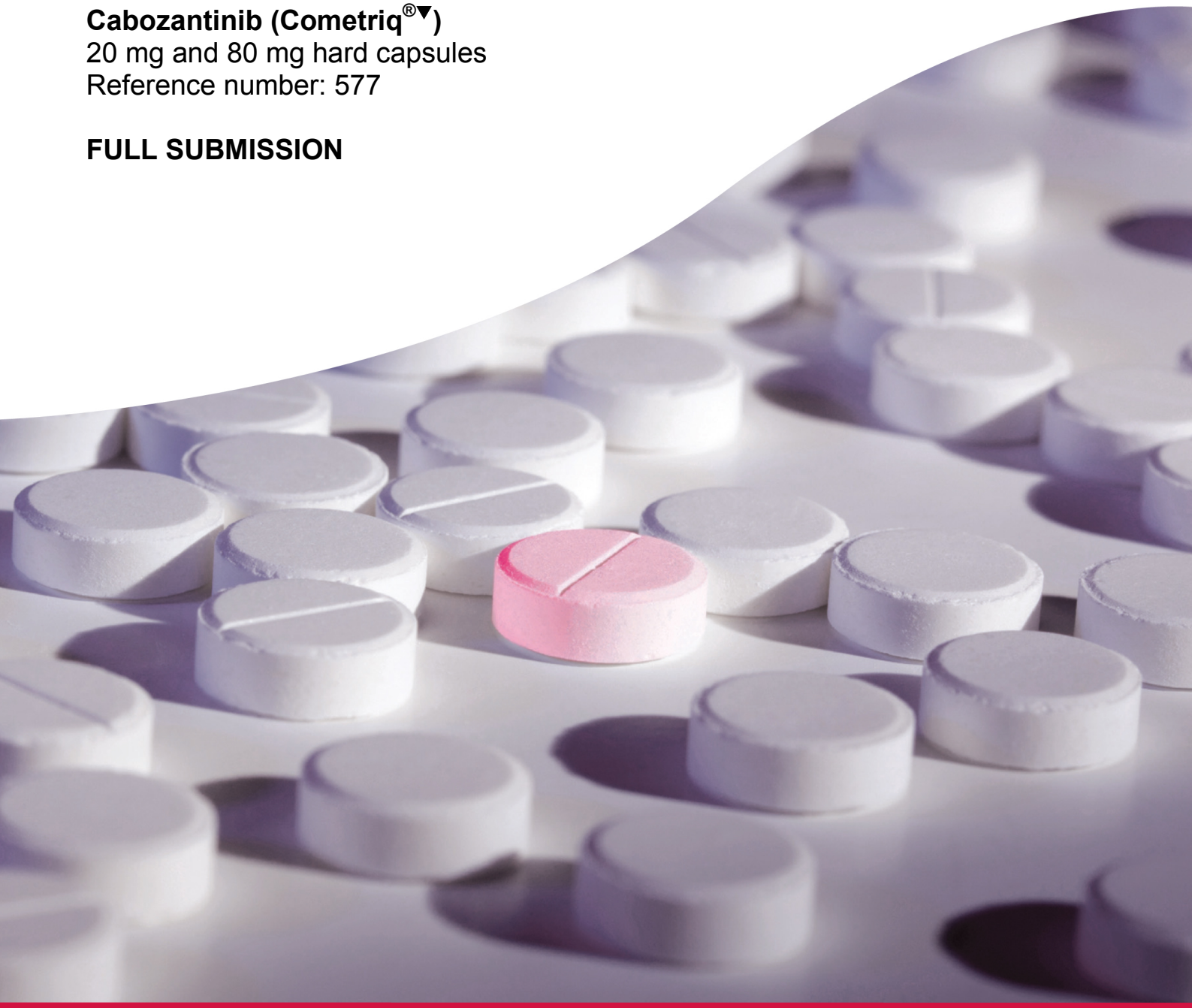
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Cabozantinib (Cometriq®▼)
20 mg and 80 mg hard capsules
Reference number: 577

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Cabozantinib (Cometriq®▼) 20 mg and 80 mg hard capsules

This assessment report is based on evidence submitted by Swedish Orphan Biovitrum Ltd/TMC Pharma Services Ltd on 18 August 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Cabozantinib (Cometriq®▼) is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma. For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision[2].
Dosing	The recommended dose of cabozantinib (Cometriq®▼) is 140 mg once daily, taken as one 80 mg orange capsule and three 20 mg grey capsules. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	21 March 2014[2].

2.0 DECISION CONTEXT

2.1 Background

Thyroid cancer is a relatively rare form of cancer, with 99 cases diagnosed in Wales during 2011[3]. Medullary thyroid cancer (MTC) is a distinct subtype, arising from the parafollicular cells (C-cells) of the thyroid, which comprises around 2.5%–10% of thyroid cancer diagnoses[4]. Thyroidectomy is the only potentially curative treatment for MTC, performed when the tumour is confined to the thyroid gland; MTC is relatively unresponsive to conventional doses of radiation therapy and to available chemotherapeutic regimens[4]. However, many patients present with unresectable cancer at diagnosis, with around 35% of patients presenting with regional lymph node involvement and 13% with metastatic disease[4].

Cabozantinib (Cometriq®▼) inhibits receptor tyrosine kinases, implicated in tumour growth and angiogenesis, pathologic remodelling, and metastatic progression of cancer[2]. Tyrosine kinases inhibited by cabozantinib include Rearranged during Transfection (RET), hepatocyte growth factor receptor protein (MET) and vascular endothelial growth factor (VEGF) receptors[2].

2.2 Comparators

The comparator included in the company submission was best supportive care (BSC)[1].

2.3 Guidance and related advice

- British Thyroid Association. Guidelines for the management of thyroid cancer: third edition (2014)[5].
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Thyroid Carcinoma. Version 2.2013 (2013)[6].

- European Society for Medical Oncology. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2012)[7].
- European Thyroid Association. 2012 European Thyroid Association guidelines for metastatic medullary thyroid cancer (2012)[8].
- American Thyroid Association. Medullary thyroid cancer: management guidelines of the American Thyroid Association (2009)[9].

The All Wales Medicines Strategy Group (AWMSG) has previously issued guidance on the use of vandetanib (Caprelsa®▼)[10].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The applicant company has submitted results from a phase III pivotal study, EXAM (XL 184-301), to provide evidence of the clinical effectiveness of cabozantinib for the treatment of patients with unresectable, locally advanced, or metastatic MTC. A phase I dose-escalation study (XL 184-001) was also included in the company submission, but will not be discussed further as it does not inform the comparative effectiveness of cabozantinib versus BSC[1].

3.1 EXAM study

This is an international, multicentre, double-blind, randomised, placebo-controlled study that evaluated the effectiveness of cabozantinib in patients with histologically-confirmed, unresectable, locally advanced, or metastatic MTC[1,11]. Patients (n = 330) were randomised (2:1) to receive either once-daily 140 mg cabozantinib or placebo until either intolerable toxicity or disease progression as determined by the investigator using modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines[12]. Patients were stratified by age and prior tyrosine kinase inhibitor use. Radiological tumour assessments were performed every 12 weeks and were evaluated by a blinded independent review committee.

The primary endpoint of the duration of progression-free survival (PFS; defined as the time from randomisation to either disease progression or death) was met in favour of cabozantinib (see Table 1). In a pre-specified analysis, all subgroups demonstrated prolongation of PFS with cabozantinib (hazard ratio < 1), including those with or without prior tyrosine kinase inhibitor use. RET mutation-positive and RET mutation-unknown subgroups showed statistically significant prolongation of PFS; the RET mutation-negative subgroup showed a non-significant trend of prolongation with a wide 95% confidence interval[11].

An interim analysis demonstrated no statistically significant difference in median overall survival (OS) (see Table 1). The secondary endpoint, objective response rate (ORR; a measure of tumour response), was significantly greater in the cabozantinib arm (see Table 1)[1,4].

Table 1. Summary of endpoints for EXAM study[1,4,11].

Endpoint	Cabozantinib (n = 219)	Placebo (n = 111)	Hazard ratio* (95% CI)	p-value†
Primary endpoint				
Median PFS	11.2 months	4.0 months	0.28 (0.19–0.40)	p < 0.001
Secondary/ancillary endpoints				
Median OS§	21.1 months	NR	0.98 (0.63–1.52)	p = 0.9304
Median OS¶	26.0 months	20.3 months	0.83 (0.60–1.14)	p = 0.2432
ORR	27.9%	0%	NR	p < 0.001

CI: confidence intervals; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.
* Cox proportional hazard model adjusted for stratification factors (age [≤ 65, > 65 years] and prior tyrosine kinase inhibitor use).
† Stratified log-rank test; adjusted for stratification factors.
§ A total of 96 deaths were reported, representing 44% of the total required for the pre-specified primary analysis of OS. The median time of follow-up (from randomisation through June 2011) was 13.9 months (range 3.6–32.5 months).
¶ Updated analysis (not pre-specified; cut off June 2012) based on 162 deaths, representing 75% of the deaths required for the final analysis.

3.2 Comparative safety

Safety data were available from the pivotal EXAM study for 214 patients who received cabozantinib and 109 patients receiving placebo[1,11]. The safety profile of cabozantinib was largely typical for a small molecule inhibiting tyrosine kinase pathways[4]. Serious adverse events (SAEs) occurred for 90 patients (42.1%) in the cabozantinib arm and for 25 patients (22.9%) in the placebo arm[4,11]. Discontinuation due to adverse events (AEs) or SAEs unrelated to disease progression occurred in 35 patients (16.4%) in the cabozantinib arm compared to nine patients (8.3%) in the placebo arm[4]. SAEs occurring more frequently in the cabozantinib arm than in the placebo arm included hypocalcaemia (2.8% versus 0%), mucosal inflammation (2.8% versus 0%), hypertension (2.3% versus 0%), and pulmonary embolism (2.3% versus 0%), all of which were considered treatment-related[4].

3.3 AWTTC critique

- Patients with metastatic MTC have limited treatment options. Vandetanib is the only other medicine licensed for MTC patients[13]; however, it is not recommended for use in NHS Wales[10]. The Committee for Medicinal Products for Human Use (CHMP) considered that in the EXAM study cabozantinib gave a clinically relevant increase in PFS (7.2 months) and an acceptable safety profile[4].
- Data for the licensed population were available from two interim analyses showing a non significant improvement in OS; final results were not available at the time this report was prepared.
- The EXAM study demonstrated that cabozantinib efficacy was reduced in patients with RET mutation-unknown or -negative status[1,11] and the SPC advises that a possible lower benefit should be taken into account in these patients before individual treatment decisions are made[2].
- The SPC suggests that the majority of patients treated with cabozantinib are likely to require dose reduction or interruption due to toxicity[13]. The company will conduct a dose comparative study (XL-184-401, planned report in March 2019) to address the possibility of giving lower effective doses with reduced toxicity[1,4]. In addition the study will further examine the impact of RET mutation status on the efficacy of cabozantinib[4].
- CHMP noted that in the evaluation of patient-reported outcome according to the M.D. Anderson symptom inventory-THY Module[14] questionnaire, several

cancer-related symptoms (nausea, lack of appetite, dry mouth and feeling cold) were significantly more frequently observed, and occurred with greater severity, in the cabozantinib versus placebo arm at week 12, possibly related to the toxicity of the drug[4]. However at week 24 the interference with quality of life did not differ between treatment arms[4].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-effectiveness analysis and cost-utility analysis of cabozantinib compared to BSC for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic MTC[1]. Vandetanib (Caprelsa®▼) is the only other medicine licensed for MTC[13]; however, it is not recommended for use within NHS Wales[10].

The patient population considered in the economic evaluation was as per the EXAM study, i.e. not otherwise allowed any anti-tumour treatment. Consequently, the economic evaluation was restricted to patients who were not otherwise suitable for chemotherapy. An expert has confirmed that this is reflective of Welsh clinical practice. A subgroup analysis was also undertaken for metastatic MTC patients positive for the RET M918T mutation using the same methodology as for the base case analysis[1].

A Markov model has been developed, consisting of three main health states through which patients may transition over time: non-progressed disease, progressed disease, and death. The patient cohort starts in the non-progressed disease state with state transitions permitted at four week intervals. The probabilities of transitioning among health states are based on an analysis of data from the EXAM study[11]. The company estimated the transition to progressed disease for use in the economic model by fitting a parametric model to the PFS data. The company explored five different parametric models and concluded that the Weibull model was the best fit for use in the economic analysis. Modelled patients with progressed disease are unable to return to the non-progressed state.

As utility values were not collected in the EXAM study, and utility values specific to non-progressive disease and progressive disease for MTC were reportedly lacking, the company identified three methods to synthesise utility estimates from the literature with clinical experts selecting the most appropriate method to use in the base case analysis. For the base case analysis, utility values were taken from two published studies in thyroid cancer, though in patients with less severe disease than the progressive MTC population[1]. The company selected the maximum utility value from the two studies for non-progressed disease and the minimum utility value from the two studies for progressed disease. Utility decrements for AEs were derived from the published literature. The other two methods were tested in sensitivity analyses.

Medicine costs, monitoring (biochemical tests) costs and the cost of AEs were included for cabozantinib. Medicine acquisition costs for cabozantinib were based on a list price of £4,800 (excluding VAT) per 28 day period and at the full dose, i.e. excluding any assumptions of dose reductions or interruptions[1]. As the EXAM study protocol did not allow any other cancer treatment, the costs for BSC were assumed to be zero. Similarly, monitoring costs and costs of AEs for BSC were also zero. Costs in the non-progressed disease and progressed disease health states were based on different rates of specialist visits: every six months for non-progressed disease, and every ten days for progressed disease. In addition, end-of-life costs were applied to patients in the death health state.

4.1.2 Results

Results of the base case analysis suggests incremental cost-effectiveness ratios (ICERs) for cabozantinib compared to BSC for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic MTC to be £93,142 per quality-adjusted life-year (QALY) gained, £73,316 per life-year (LY) gained and £114,444 per progression-free life-year (PFLY) gained (Table 2). The company also reported the results of a subgroup analysis for metastatic MTC patients positive for the RET M918T mutation.

Table 2. Results of the base case analysis.

	Cabozantinib	BSC	Difference
Treatment costs	£65,060	£0.00	£65,060
Monitoring costs	£6	£0.00	£6
Health state costs	£18,011	£17,128	£883
AE related costs	£256	£0	£256
Total cost	£83,332	£17,128	£66,204
QALYs	2.3897	1.6789	0.7108
LYs	3.2527	2.3497	0.9030
PFLYs	1.0398	0.4613	0.5785
ICER (£/QALY gained)	**£93,142**		
ICER (£/LY gained)	**£73,316**		
ICER (£/PFLY gained)	**£114,444**		

AE: adverse event; BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; LY: life-year; PFLY: progression-free life-year

[Commercial in confidence data removed]

The company conducted sensitivity analysis to explore the impact of uncertainty in model parameters on the ICER. The company stated that the price of cabozantinib was the main driver of the results of the model but did not present the results. Other parameters shown to impact cost-effectiveness were the health state utility values and the probability of progression, with the incremental cost per QALY gained ranging from £85,491 to £116,542 (Table 4).

Table 4. Results of the sensitivity analysis.

	Cost per QALY gained	Plausibility
Base case analysis	**£93,142**	**-**
One–way sensitivity analyses		
Alternative health state utility scenario (1)	£116,542	More conservative approach but also associated with uncertainty. Unclear if more plausible than base case.
Alternative health state utility scenario (3)	£85,491	Less conservative approach but also associated with uncertainty. Unclear if more plausible than base case.
Decrease cost of treating hypertension by 30%	£93,084	Plausible though has little impact on ICER.
Increase cost of treating hypertension by 30%	£93,198	Plausible though has little impact on ICER.
Decrease health state costs by 30%	£92,769	Associated with uncertainty as base case based on expert opinion and differences for progressed disease and non-progressed disease health states assumed to move in same direction.
Increase health state costs by 30%	£93,514	Associated with uncertainty as base-case based on expert opinion and differences for progressed disease and non-progressed disease health states assumed to move in same direction.
Probability to progressed disease coefficients defined by EXAM study	£85,520	Plausible as directly elicited from EXAM study. Although survival is overestimated in base case analysis.
10-year time horizon	£99,359	Lifetime analysis appropriate as in the base case. Highlights the fact that most of the costs have already been incurred by year 10, hence increase in ICER.

Probabilistic sensitivity analysis undertaken for the base case analysis indicates that the probability that cabozantinib is cost-effective compared to BSC is 0% at cost-effectiveness thresholds of both £20,000 and £30,000 per QALY gained.

The company later submitted an additional analysis based on the dose interruptions that were reported in the EXAM trial[11] and referred to in the SPC[2]. This resulted in a cost per QALY gained of £67,514 for the full EXAM patient population. The company did not provide the corresponding cost per QALY gained for the RET M918T mutation subgroup.

4.1.3 AWTTC critique

The company's estimate of the cost-effectiveness of cabozantinib compared to BSC for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic MTC is dependent on the probabilities of progression and the health state utility values. Given the limitations in the methodologies used to estimate these values, there is significant uncertainty and risk of bias. However, it is not clear whether the company has over or underestimated the ICER.

Strengths of the company's economic evidence include;

- The model structure is clear and largely in line with other pared-down models in oncology.
- The company has attempted to address the decision problem in a reasonable way despite limitations in the available data.
- The economic analysis is based on the EXAM study which largely reflects clinical practice in Wales.

Limitations of the economic evidence include;

- The range of sensitivity analyses was limited, and there were no scenario analyses other than the subgroup of patients with RET M918T mutation. The impact of selecting alternative parametric functions to model progression free and overall survival were not assessed in a scenario analysis.
- Survival appears to have been overestimated in the economic model whilst PFS may be underestimated.
- The health state utility values used in the economic model were not specific to MTC and are thus associated with uncertainty. Whilst they are relevant for thyroid cancer generally, it cannot be assumed that they will have relevance to MTC.
- There are no sensitivity analyses presented for the RET M918T mutation subgroup.
- The number of specialist visits for patients in the progressed disease and non-progressed disease health state were based on expert opinion. These do not appear to have been validated as being appropriate for Wales.
- The SPC notes that a possible lower benefit may be observed in patients whose RET mutation status is not known or negative[2]. The cost of RET mutation testing was not considered in the economic analysis.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost-effectiveness analyses of cabozantinib for the treatment of MTC.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on data collected by Cancer Research UK, the company estimates that there are 99 new thyroid cancer cases in Wales per year[3]. However, as these data do not include specific data on the incidence of MTC, the company uses a US estimate of 2% of patients with thyroid cancer having MTC[15] to calculate that approximately two new patients will be diagnosed with MTC in Wales per year[1]. The company assumes that 50% of patients will receive cabozantinib and that these patients will progress after one year (based on median PFS of 11.2 months) and no longer receive cabozantinib. Consequently, the company estimates the net number of patients receiving cabozantinib to be one patient per year over a five-year time horizon[1]. The budget impact analysis included medicine costs, monitoring costs and the costs of AEs. These were derived from the economic model discussed in Section 4.0.

5.1.2 Results

The estimated number of patients and the associated costs as described by the company in their budget impact analysis are summarised in Table 5. The total cost includes medicine cost, monitoring costs and the cost of AEs. As BSC did not incur any of these costs, the total costs and the overall net costs were the same.

Table 5. Company-reported costs associated with use of cabozantinib

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (all indications)	2	2	2	2	2
Uptake (%)	50%	50%	50%	50%	50%
Treated patients	1	1	1	1	1
Net costs					
Medicine cost	£62,571	£62,571	£62,571	£62,571	£62,571
Administration and monitoring cost	£6	£6	£6	£6	£6
AE treatment cost	£256	£256	256	£256	£256
Overall net cost	**£62,833**	**£62,833**	**£62,833**	**£62,833**	**£62,833**

5.1.3 AWTTC critique

- The company estimated the eligible patient numbers based on incidence rates and assumptions; the number of prevalent cases within Wales has not been considered.
- The company provided a limited sensitivity analysis in which only the percentage of eligible patients receiving cabozantinib was varied (to 100%).

5.2 Comparative unit costs

Cabozantinib and vandetanib are the only two agents licensed specifically for the treatment of adult patients with MTC[2,13]. The costs of both cabozantinib and vandetanib are highlighted in Table 6.

Table 6. Example of medicine acquisition costs.

Medicine	Example dose	Pack Cost	Cost per day	Cost per year
Cabozantinib (Cometriq®▼) 20 mg and 80 mg tablets	140 mg once daily	£4,800 (per 28 tablets)	£171.43	£62,614
Vandetanib (Caprelsa®▼) 300 mg tablet	300 mg once daily	£5,000 (per 30 tablets)	£166.67	£60,875
Cabozantinib cost was provided by the company[1]. Vandetanib cost is based on MIMS list price as of September 2014[16]. Costs of administration and monitoring are not included. This table does not imply therapeutic equivalence of medicines or the stated doses. See relevant SPCs for full dosing details[2,13].				

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, cabozantinib (Cometriq®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that cabozantinib (Cometriq®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission did not highlight any relevant ongoing studies that are likely to be available within 6–12 months[1].

6.3 AWMSG review
This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search
Date of evidence search: 3 September 2014
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines
The applicant company believe that the use of cabozantinib in the given patient population meets the end-of-life criteria set by the AWMSG Policy on appraising life-extending, end-of-life medicines[17,18].

The criteria for appraising life-extending, end-of-life medicines apply when the most plausible ICER estimate exceeds £30,000 per QALY gained, and all the following conditions are satisfied:

- The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).
- There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression free survival or overall survival.
- AWMSG/NMG will consider the cumulative population of each licensed indication of the medicine to be small[18].

Based on the economic evidence from the applicant company, the most plausible ICER for cabozantinib would exceed £30,000 per QALY when compared with BSC for the licensed indication under consideration.

An analysis of the EXAM trial suggested a median OS in the placebo arm of 20.3 months. The (undiscounted) mean life expectancy as estimated in the comparator arm of the model was 30.4 months. Additionally CHMP state that median OS period for patients with metastatic and progressive MTC is about 2–3 years[4]. It is therefore uncertain if cabozantinib meets the criterion of a life expectancy being normally less than 24 months.

The company believe that there is sufficient evidence that cabozantinib offers an extension to life of at least three months, based on inference from the increase in PFS of 7.2 months observed for cabozantinib treated patients in the EXAM study[17] and the non-statistically significant increase in median interim OS of 5.7 months[1]. The modelled (undiscounted) mean gain in survival was estimated to be 13.0 months.

The company estimate that two patients would be treated per year[1]. This suggests that cabozantinib meets the requirement that the cumulative population of the indication is small.

6.6 Consideration of AWMSG policy relating to ultra-orphan medicines
Consideration is required as to whether cabozantinib in the given patient population meets the AWMSG criteria for ultra-orphan status, which states that ultra-orphan medicines are orphan drugs that are licensed for the treatment of diseases with a prevalence of less than 1 in 50,000 persons in the European Union (EU) at the time of submission of the designation application to the European Medicines Agency (EMA)[19]. The EMA granted orphan designation for cabozantinib in the treatment of MTC in 2009,

recognising that MTC is a rare disease (estimated to affect < 0.7 in 10,000 people) with a prevalence below the threshold for orphan designation[20]. Based on Cancer Research data stating that in 2011 the incidence of thyroid cases in Wales was 99 patients[3], and a published estimate (based on US data) of 2% of thyroid cancer patients having MTC[15], the company estimates that there will be two new patients eligible for treatment per year. The company's estimates of the numbers of patients that would be eligible for treatment falls below the ultra-orphan threshold of 1 in 50,000. This is supported by Welsh clinical expert opinion.

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