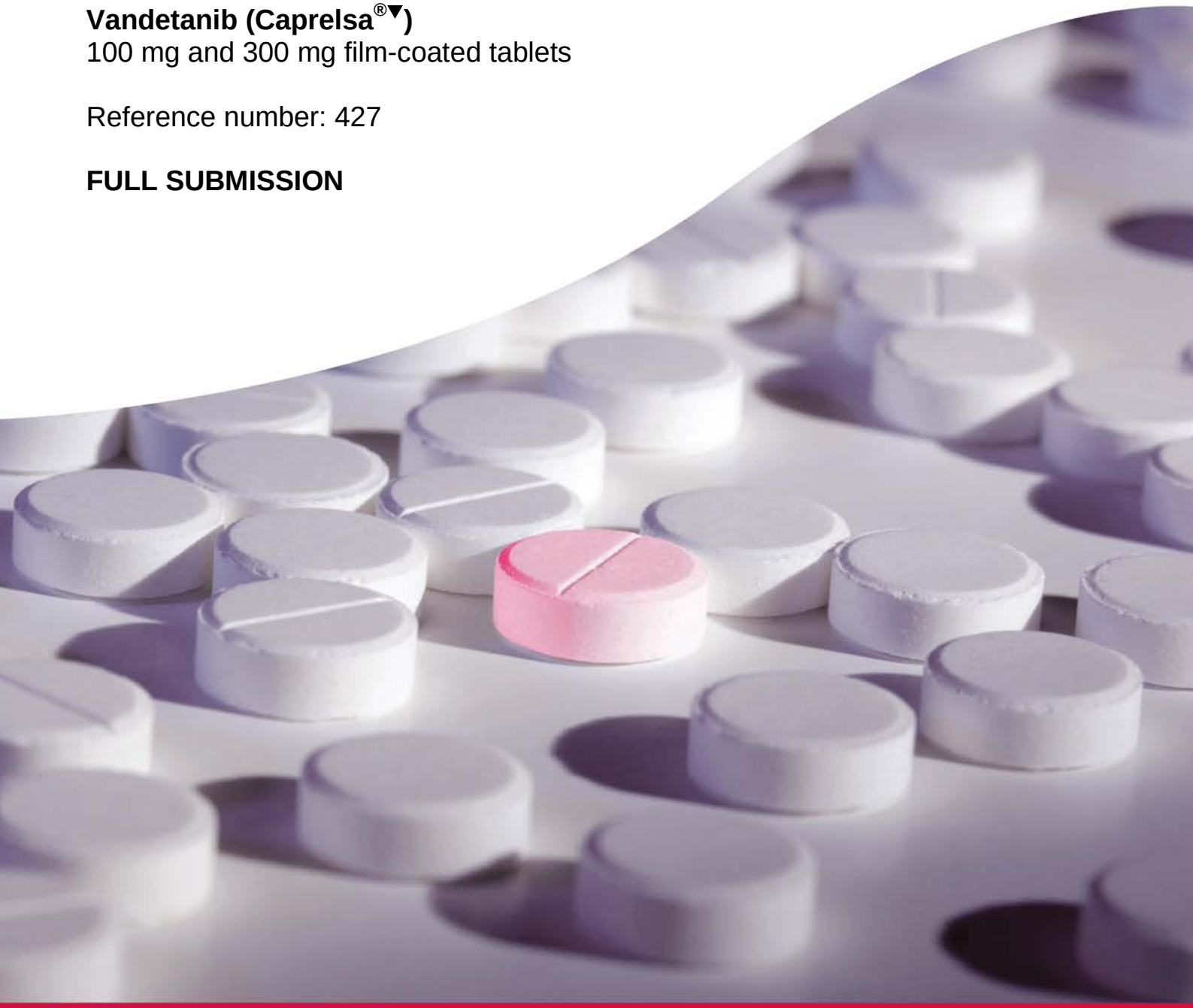
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Vandetanib (Caprelsa®▼)
100 mg and 300 mg film-coated tablets

Reference number: 427

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Vandetanib (Caprelsa®▼) 100 mg and 300 mg film-coated tablets

This assessment report is based on evidence submitted by AstraZeneca UK Ltd on 17 April 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Vandetanib (Caprelsa®▼) is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. For patients in whom *Rearranged during Transfection (RET)* mutation 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 vandetanib (Caprelsa®▼) is 300 mg once a day, taken with or without food at about the same time each day. Patients treated with vandetanib must be given the patient alert card and be informed about the risks of vandetanib. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	17 February 2012[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].

Vandetanib (Caprelsa®▼) is an orally administered tyrosine kinase inhibitor with activity against the following: Rearranged during Transfection (RET) proto-oncogene, vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR). Inhibition of these tyrosine kinases suppresses tumour cell migration, proliferation, survival and angiogenesis mediated by these proteins[2].

2.2 Comparators

The comparator included in the company submission was best supportive care (BSC), which includes a number of options to manage symptoms, based on patients needs. The applicant company suggests that vandetanib is expected to be used in conjunction with any required BSC.

The applicant company noted that although cabozantinib (Cometriq®▼) received marketing authorisation on 23 March 2014 for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma[5], it has not yet been launched in the UK[1,6,7].

2.3 Guidance and related advice

- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Thyroid Carcinoma. Version 2.2013 (2013)[8].
- European Society for Medical Oncology. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2012)[9].
- European Thyroid Association. 2012 European Thyroid Association guidelines for metastatic medullary thyroid cancer (2012)[10].
- American Thyroid Association. Medullary thyroid cancer: management guidelines of the American Thyroid Association (2009)[11].
- British Thyroid Association and the Royal College of Physicians. Guidelines for the management of thyroid cancer: second edition (2007). Third edition is also available for public consultation in draft form (2014)[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

As evidence of clinical effectiveness, the company submission includes the pivotal trial, study 58 (ZETA study), which evaluated vandetanib for the treatment of patients with unresectable, locally advanced or metastatic MTC[1]. This study had no specific provisions to ensure recruitment of patients with aggressive and symptomatic disease[13], and so the applicant company has provided several subgroup analyses from the ZETA study as evidence for the effectiveness of vandetanib for the licensed indication under consideration[1].

Additionally, the applicant company has provided two phase I studies and two phase II studies; however, these trials do not provide information regarding the comparative clinical effectiveness of vandetanib in the licensed indication under consideration, and so will not be discussed further[1].

3.1 ZETA study

This was an international, multicentre, double-blind, randomised, placebo-controlled, phase III study that evaluated the effectiveness of vandetanib in adult patients with measurable, unresectable locally advanced or metastatic MTC[4,13]. Patients (n = 331) were randomised (2:1) to receive either vandetanib at a starting dose of 300 mg per day or placebo until disease progression, after which patients discontinued study treatment, were unblinded, and could elect to receive open-label treatment with vandetanib; all patients were followed for survival (median duration of follow-up: 24 months). Eligible patients had a life expectancy of 12 weeks or longer, a World Health Organisation (WHO) performance status 0–2 and serum calcitonin (CTN) levels ≥ 500 picograms/ml[4,13].

The primary endpoint was to demonstrate an improvement in progression-free survival (PFS; see Glossary for endpoint definitions) on the basis of independent central review, which was significantly improved in vandetanib-treated patients (number of events: 73 [31.6%] versus 51 [51.0%] placebo-treated patients); hazard ratio [HR]: 0.46; 95% confidence interval [CI]: 0.31–0.69; p = 0.0001). This was supported by analysis of a number of secondary assessments, including objective response rate (ORR), where significantly more vandetanib-treated patients demonstrated a response compared with those in the placebo group, as displayed in Table 1[4]. Of the 13 patients in the placebo group who had an objective tumour response, only one had a response that began during the double-blind period; the remaining 12 responders in the placebo group had a response that began after the patient began receiving open-label vandetanib[1]. No

significant effect was detected for vandetanib in terms of number of overall survival (OS) events at time of data cutoff; an updated, final analysis of OS is scheduled to be performed once total mortality reaches 50% of enrolled patients[13]. There were no observed differences between treatment groups for changes in health-related quality of life, measured using the Functional Assessment of Cancer Therapy-General (FACT-G) scale[4].

In subgroups of patients with aggressive disease, PFS improvement for vandetanib compared with placebo was at least as good as in the full population (see Table 1)[1]. As a proxy for aggressive and symptomatic disease, the company submission includes a subgroup analysis of patients with progressive and symptomatic MTC (see Glossary for subgroup definition), undertaken at the time of licensing. PFS data from this subgroup of patient population were similar to those observed in the full population (see Table 1)[1].

Table 1. Summary of endpoints from the ZETA study[1,4,13,14].

Endpoint	Vandetanib (n = 231)	Placebo (n = 100)	Treatment difference	95% CI (p-value)
Primary endpoint				
Total number of PFS events*	73 (31.6%)	51 (51.0%)	HR: 0.46	0.31–0.69 (p = 0.0001)
Median PFS*	30.5 months†	19.3 months	NR	NR
Rate of PFS at six months*	91%	74%	NR	NR
Secondary endpoints				
Number of OS events	32 (13.9%)	16 (16.0%)	HR: 0.89	99.98% CI: 0.28–2.85 (p = 0.7115)
ORR	104 patients (45.0%)	13 patients (13.0%)	Odds ratio: 5.48	2.99–10.79 (p < 0.0001)
Subgroup analysis: patients with aggressive MTC defined as CTN doubling time ≤ 24 months				
Number of patients	124	46	-	-
Total number of PFS events*	39 (31.5%)	27 (58.7%)	NR	NR
Subgroup analysis: patients with aggressive MTC defined as CEA doubling time ≤ 24 months				
Number of patients	69	33	-	-
Total number of PFS events*	25 (36.2%)	26 (78.8%)	NR	NR
Subgroup analysis: patients with progressive and symptomatic MTC (see Glossary)				
Number of patients	126	60	-	-
Total number of PFS events*	NR	NR	HR: 0.47	0.29–0.77 (p < 0.0024)
Median PFS*	28 months†	16 months†	NR	NR

CEA: carcinoembryonic antigen; CI: confidence intervals; CTN: calcitonin; HR: hazard ratio; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.
* PFS as evaluated by independent central review[15].
† Predicted median as estimated by Weibull model.

3.2 Comparative safety

Evidence of comparative safety in the company submission comes from the ZETA study, where treatment duration in the vandetanib group was longer than in the placebo group during the double-blind, randomised phase (prior to disease progression and subsequent open-label treatment with vandetanib)[4]. Adverse events (AEs) were reported by 230/231 (99.6%) patients in the vandetanib group and 90/99 (90.9%) patients in the placebo group. Serious AEs (SAEs) were reported by 71 (30.7%)

patients in the vandetanib group and 13 (13.1%) patients in the placebo group. Further, the incidence of AEs leading to discontinuation was higher in the vandetanib group (28 [12.1%] versus 3 [3.0%]); however, the incidence of SAEs with an outcome of death was comparable (5 [2.2%] versus 2 [2.0%], respectively)[4].

The most frequently reported AEs were diarrhoea, rash, nausea, hypertension, and headache. A total of 35 cardiac AEs, including 5 SAEs (4 deaths) were reported in 30 patients receiving vandetanib, compared with 16 AEs in 13 placebo-treated patients, of which 2 were serious and none were fatal. In the vandetanib group, 36 (15.6%) patients had an event-related to electrocardiogram (ECG) QTc prolongation, compared with 4 (4.0%) in the placebo group[4].

3.3 AWTTC critique

- The clinical efficacy evaluated at the time of licensing was based on one pivotal trial (ZETA study), which enrolled patients with unresectable locally advanced or metastatic MTC[13]. The Committee for Medicinal Products for Human Use (CHMP) concluded that the treatment fulfils an unmet medical need due to the lack of available alternative treatments in this population[4]. However, in view of the associated risks of treatment, it was considered important to limit use of vandetanib to patients who are in real need for treatment, as identified by those having a symptomatic-aggressive disease course[4]. As the patient population enrolled into the ZETA study was not limited to patients with aggressive and symptomatic disease, the applicant company has provided analyses of subgroups of patients with aggressive disease or with progressive and symptomatic disease, all of which demonstrated comparable efficacy to that in the full population (see Section 3.1)[1].
- During the pivotal trial (ZETA study), vandetanib-treated patients had a significantly lower rate of PFS events and demonstrated more objective responses compared with patients in the placebo group; however, no significant benefit was observed in terms of OS[13]. It is likely that any effect of vandetanib on OS could be confounded by open-label use of vandetanib following disease progression on randomised treatment[4]. While only one placebo-treated patient developed an objective response during the randomised phase, 12 patients of the 58 from the placebo arm who received open-label vandetanib following disease progression demonstrated an objective response[1,4].
- At the time of licensing, CHMP noted that vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc interval, a measure used to identify patients at risk of developing ventricular arrhythmias and sudden death[4]. This risk is compounded by the fact that the treatment has a very long half life (19 days). CHMP concluded that, in view of the toxicity profile of vandetanib at the 300 mg dose, there is a need to further study the optimal dose with the aim to maximise the benefit-risk balance[4].
- During the ZETA study, only eight patients were confirmed as *RET* mutation negative, of which only two were randomised to receive vandetanib[4]. Although the available data and post-hoc analyses support the efficacy of vandetanib in *RET* mutation negative tumours, CHMP concluded that it is difficult to draw an unequivocal conclusion of the size of the benefit of vandetanib in patients with *RET* mutation negative tumours, which is reflected in the SPC. Additionally, CHMP reports that data will be provided from a further open-label study comparing *RET* mutation negative and *RET* mutation positive patients with sporadic MTC treated with vandetanib[4].
- The applicant company has suggested that delaying disease progression using vandetanib treatment has the potential to improve quality of life in patients with MTC by delaying disease burden and onset of increased symptoms[1]. This is supported by significant delays in time to worsening of pain in vandetanib-treated patients; however, no significant improvement was demonstrated in

terms of quality of life scores, opioid analgesic medication use or time to worsening of WHO performance state during the pivotal study[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-utility analysis (CUA) of vandetanib as an add-on to BSC compared with BSC alone in patients with unresectable, locally advanced or metastatic MTC[1]. The base case analysis relates to patients with aggressive and symptomatic disease to reflect the licensed population.

A Markov model has been developed, consisting of three main health states through which patients may transition over time: pre-progression; post-progression, and death. As the key, phase III ZETA study did not specify aggressive, symptomatic disease as inclusion criteria, the company has undertaken post-hoc analyses of the available PFS data in patients with progressive and symptomatic disease (defined as in Section 3.1). These data were based on investigator-determined PFS, and as these data were immature they have been extrapolated using a Weibull distribution (company data on file; not verified)[1]. These provide the estimated proportions of patients in the pre-progression health state over time.

Median OS data from the ZETA study are not yet available; therefore, the applicant company used observational cancer survival data collected from patients with thyroid cancer with distant metastases in the USA from 1998 to 2008. A Weibull distribution has been fit to these data, and OS is modelled by applying the relative risk of death due to MTC observed from these data to the age-adjusted all cause mortality risk in each model cycle. It is assumed that patients may only die after they have experienced disease progression, and as such, the same risk of death post-progression is assumed for both vandetanib plus BSC and BSC alone. However, as PFS is longer with the addition of vandetanib to BSC, an OS advantage for vandetanib is effectively maintained throughout. AEs of grade 3 or worse by broad system organ class, as observed in the ZETA study, are included in the first one-month cycle of the model only, on the assumption that AEs beyond this point occur at low rates[1].

Utility values specific to MTC are lacking; therefore, utility values for weighting the pre-progression health state have been estimated by mapping FACT-G scores collected in the ZETA study (data on file; not verified) to time-trade-off utility values, using a published algorithm produced in a large sample of patients with various cancer types in the USA[16]. As inadequate FACT-G data were collected in patients post-progression in the ZETA study, the post-progression utility values are assumed to be a proportion of the pre-progression utility value, based on the decrement observed from pre- to post-progression in a study of UK melanoma patients using standard gamble techniques to value generic cancer states[17]. Utility decrements associated with each AE are simply assumed to be −0.11 or −0.13, as estimated for severe toxicities leading to hospitalisation in the UK melanoma study[17], and are assumed to apply in the model for the first one month cycle[1].

Drug acquisition costs for vandetanib are based on list prices and observed doses used in the ZETA study, including dose reductions and interruptions (data on file; not verified). Monitoring costs include ECG and tests for serum potassium, calcium and magnesium, and thyroid stimulating hormone levels eight times per year in the first year (broadly as per the SPC[2]) and then four times per year thereafter for 20% of patients. Unit costs for AEs are based on healthcare resource groups in English NHS reference costs 2009–2010, which are aligned with the broad system organ classes

assumed for AEs. BSC is assumed to be the same in both arms of the model, with costs based on one oncology visit per month and one computerised tomography (CT) scan every two months, as assumed for the pre-progression state in a manufacturer's submission for National Institute for Health and Care Excellence (NICE) Technology Appraisal 285, describing bevacizumab in the treatment of advanced ovarian cancer[18].

For the base case analysis, costs and outcomes beyond one year are discounted at 3.5% per annum, and a lifetime horizon of analysis is adopted.

4.1.2 Results

The results of the base case analyses are presented in Table 2. Over a lifetime horizon of analysis, the incremental cost per quality-adjusted life-year (QALY) gained for vandetanib plus BSC compared with BSC alone is around £185,000. This is based on additional costs of around £105,500, due mainly to the acquisition costs of vandetanib, and a gain of 0.57 QALYs, due mainly to the modelled increase in pre-progression survival of 10.08 months and modelled decrease in post-progression survival of 2.41 months.

Table 2. Base case CUA results[1].

	Vandetanib plus BSC	BSC	Difference
Total costs	£119,489	£13,984	£105,505
Total LYs	6.65	6.01	0.64
Total QALYs	4.66	4.09	0.57
ICER	**£185,193/QALY gained**		
PSA: Probability ICER < £30,000/QALY gained	0%		

BSC: best supportive case; ICER: Incremental cost-effectiveness ratio (incremental cost per QALY gained) for vandetanib plus BSC versus BSC alone; LY: life-year; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year.

A range of scenario analyses have been conducted to test key structural assumptions of the base case analysis. The base case-modelled incremental cost-effectiveness ratio (ICER) was relatively insensitive to the use of alternative types of distribution fitted to OS data (e.g. lognormal, log-logistic), a doubling of the utility decrement associated with AEs and their duration, variation of BSC costs in the range 0–100%, and annual discount rates assumed. Table 3 summarises the other key scenario analyses presented by the company.

Table 3. Key scenario analyses.

Scenario description	Scenario details	Incremental cost per QALY	Plausibility considerations
Base case analysis	Vandetanib plus BSC compared against BSC alone in MTC patients with aggressive symptomatic disease (licensed indication), using site-read PFS data and life-time horizon.	£185,193	Main issues relate to limited data: • Post hoc subgroup analysis of site-read PFS data • OS data lacking from trial; observational OS data from thyroid cancer patients in USA adopted • Unclear how OS modelled to show ongoing benefit and how time in progressive disease is modelled • *RET* mutation status, which may influence effectiveness and cost-effectiveness not considered • Utility weights for post-progression health state largely assumed.
No assumed OS benefit for vandetanib	As base case but OS same for vandetanib plus BSC and BSC alone	£656,681 (incremental cost: £104,048; QALY gain: 0.16)	Given the PFS data consistently show benefit, unlikely that vandetanib has no benefit on OS; however, this demonstrates the reliance of the model on the assumed OS benefit, the magnitude of which is currently unknown.
Licensed indication; PFS data from centrally-read data	PFS data from centrally-read data (as for primary endpoint of ZETA) rather than site-read PFS	£267,098 (incremental cost: £131,975; QALY gain: 0.49)	Company suggests site-read PFS more akin to clinical practice; use of centrally-read PFS data confounded by open-label use of vandetanib. Other uncertainties of base case analysis still apply.
Overall ZETA study population rather than licensed subgroup	a) Overall cohort (site-read PFS data) b) Overall cohort (central-read PFS data)	a) £234,061 b) £361,999	PFS data from the whole ZETA study cohort may be more reliable; however, this cohort does not reflect the licensed subpopulation, so analyses are of limited informative value.
Alternative extrapolation of PFS data	As base case analysis but using different parametric distributions to extrapolate PFS data: a) lognormal b) log-logistic	a) £137,695 (incremental cost: £135,528; QALY gain: 0.98) b) £158,316 (incremental cost: £128,064; QALY gain: 0.81)	Base case uses Weibull distribution based on statistically better fit than these alternative distributions. Lognormal and log-logistic distributions may have long tails that would overestimate the survival benefits of vandetanib, as demonstrated by the lower ICER estimates and greater QALY gains. Base case analysis would seem more plausible in this regard.
Alternative utility weights for health states	a) Post-progression utility value based on mapping of FACT-G ZETA data b) Pre- and post-progression utilities based on values of melanoma patients for generic cancer states c) Double utility decrement assumed for post-progressive disease versus pre-progressive disease	a) £198,216 (QALY gain: 0.53) b) £202,238 (QALY gain: 0.52) c) £172,789 (QALY gain: 0.61)	All associated with uncertainty. Unclear if any of these more plausible than base case. Demonstrate influence of the modelled longer time in pre-progression and shorter time in post-progression health states with vandetanib. Other uncertainties of base analysis still apply.
Alternative time horizons of analysis	Range of 3–10 years time horizon	£306,708 to £203,707	Life time horizon of analysis would be appropriate as in the base case analysis; however, demonstrates that the ICER is sensitive to the long-term modelled benefits of vandetanib.
BSC: best supportive care; ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained) for vandetanib plus BSC versus BSC alone; MTC: medullary thyroid cancer; OS: overall survival; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year.			

4.1.3 AWTTC critique

There is a lack of data with which to model the long-term treatment effects of vandetanib. Consequently, most of the parameter values assumed in the model are based on assumptions and extrapolations, rather than robust data. The approach to modelling OS assumes an OS advantage for vandetanib throughout, and scenario analyses demonstrate that the model is sensitive to the assumed magnitude of OS benefit. The model does not consider *RET* mutation status, which may influence the effectiveness of vandetanib treatment. Collectively the estimates of cost-effectiveness are subject to considerable uncertainty, although the analyses that have been provided demonstrate that the estimated incremental cost per QALY gained is likely to far exceed the usual threshold range of £20,000–30,000 per QALY gained.

Strengths of the economic evidence include:

- The modelled pathway appears to be appropriate.
- The company has conducted systematic literature reviews to identify potentially relevant vandetanib studies for consideration in the modelling of cost-effectiveness.
- The company has attempted to model the effectiveness of vandetanib using a range of sources of data and assumptions in the absence of robust effectiveness data from clinical trials, and has tested the impact of those key assumptions in a range of scenario analyses.

Key limitations and uncertainties in the economic evidence include:

- There is a lack of data with which to robustly model key elements of the effectiveness of vandetanib over BSC, and most data are company data on file that are not verifiable:
  - PFS data for the whole ZETA study population were immature. The model uses a post hoc subgroup analysis of these data (from around 55–60% of the ZETA study population) to model PFS in the licensed patient population.
  - OS data are lacking from the ZETA study, so observational survival data from the USA have been adopted. Vandetanib is modelled to improve OS, and the model is sensitive to the magnitude of the OS improvement; however, the basis of that improvement is not clear.
- The SPC notes that *RET* mutation testing is recommended, as patients without *RET* mutations may have a decreased benefit from vandetanib treatment and the benefit/risk balance for this group of patients may therefore differ from that of the group with *RET* mutations[2]. *RET* mutation testing and differential cost-effectiveness based on *RET* mutation status is not considered in the economic analyses.
- Utility values used to weight health states are largely assumed due to a lack of MTC-specific values.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost-effectiveness analyses of vandetanib in 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 GLOBOCAN data for 2012, the 5-year thyroid cancer prevalence in the UK is reported to be 9,471 cases[19]. Based on observational data from the USA, 3% are assumed to be MTC[20], and of these 48% have advanced disease[21]. Cancer Research UK data indicate that, of 2,727 thyroid cancer cases in the UK in 2011, 99 (3.36%) were reported in Wales[3]. Applying this proportion to the above estimates, equates to 5 prevalent cases of advanced MTC with a maximum history of 5 years, and 2 incident cases per year. Based on the economic model, the company estimates an overall average survival of 6–7 years; therefore, in year 1 there would be 5 prevalent and 2 incident cases, and 2 incident cases in each subsequent year. Additional (undiscounted) costs of vandetanib, taking account of dose reductions and interruptions, and associated resource use, are derived from the economic model[1].

5.1.2 Results

The company estimates the net budget impact in Wales in each of the next five years as in Table 4.

Table 4. Company base case estimates of net cost implications.

	Year 1	Year 2	Year 3	Year 4	Year 5
Treated patients	7	9	11	13	15
Net vandetanib acquisition costs	£355,087	£456,540	£557,993	£421,101	£337,715
Net AE costs	£3,494	£998	£998	£998	£998
Net monitoring costs	£9,269	£2,648	£2,648	£2,648	£2,648
Net BSC costs	£0	£0	£0	£0	£30
Overall net cost	**£367,850**	**£460,187**	**£561,640**	**£424,747**	**£341,391**
AE: adverse events; BSC: best supportive care.					

The company has provided two alternative budget impact scenarios. In the first, the estimated number of prevalent thyroid cancer cases is based on the relative proportion of the UK population that resides in Wales (4.85%), rather than the Cancer Research UK estimates of actual cases. This increases the number of prevalent cases of advanced MTC eligible for treatment. In the second, the incident number of cases is decreased to 1.4, rather than been rounded to 2 as in the base case estimates. Results are presented in Table 5.

Table 5. Alternative estimates of net cost implications.

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 1:	**£472,949**	**£561,640**	**£663,093**	**£458,102**	**£341,399**
Scenario 2:	**£336,320**	**£398,221**	**£469,238**	**£322,339**	**£238,980**

5.1.3 AWTTC critique

- In the absence of robust figures the company has adopted a pragmatic approach to estimate the number of patients with advanced MTC in Wales. Due to the high drug acquisition costs, small differences in the estimates of the prevalence and incidence of advanced MTC impact on the net budget impact estimates, as demonstrated by the alternative scenarios analyses.
- The assumed net costs per patient are based on estimates from the company's economic model. The uncertainties of the economic model therefore feed through to the budget impact estimates.

5.2 Comparative unit costs

Vandetanib is currently the only available agent licensed specifically for the treatment of patients with unresectable, locally advanced or metastatic MTC. Based on its Monthly Index of Medical Specialities (MIMS) list price, at the recommended daily dose of 300 mg/day, vandetanib costs £5,000 for a 30-day (one-month) supply[6].

Cabozanitib (Cometriq®▼) received marketing authorisation on 23 March 2014 for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma[5]; however, it has not yet been launched in the UK and so acquisition costs are not available for comparison[6,7].

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

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

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

The applicant company has highlighted that the ZETA study is expected to undergo an updated OS analysis after 50% mortality (166 patients) has occurred; the applicant company estimates that this analysis will become available in late 2014/early 2015.

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: 28 April 2014
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to ultra-orphan medicines

Consideration is required as to whether vandetanib 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)[22]. EMA granted orphan designation for vandetanib in the treatment of MTC in 2006 on the basis of the seriousness of the condition, the (lack of) alternative effective treatments and the rarity of the condition (estimated to affect less than 0.7 in 10,000 people)[23]. However, orphan designation was withdrawn at the manufacturer's request in 2010[23].

GLOSSARY

Objective response rate (ORR)
The ORR is the proportion of patients that are responders, defined as those patients with a confirmed best objective response of complete response or partial response[24].

Overall survival (OS)
As data was immature at data cut off, OS is quoted as the number of deaths since randomisation[24].

Progression-free survival (PFS)
PFS was defined during the ZETA study as the median time from randomisation until objective disease progression or death (by any cause in the absence of progression), provided death was within 3 months from the last evaluable disease assessment. The PFS assessment was based on an independent radiological review and values were estimated from a Weibull model as the medians were not met[4,24].

Progressive and symptomatic MTC subgroup
The applicant company has provided a subgroup analysis of patients with progressive and symptomatic MTC, defined as patients whose disease fulfils both of the following criteria:

- Progressive disease: documented progression ≤ 12 months prior to enrolment;
- Symptomatic disease: at least one of the following symptoms at baseline: pain score > 4; opioid use ≥ 10 mg/day; diarrhoea; flushing; fatigue; pain; nausea; dysphagia; dysphonia; respiratory symptoms; weight loss[1].

REFERENCES

1 AstraZeneca UK Ltd. Form B: Detailed appraisal submission. Vandetanib (Caprelsa®▼). Apr 2014.

2 AstraZeneca UK Ltd. Caprelsa®▼. Summary of Product Characteristics. Jan 2014. Available at: http://www.medicines.org.uk/emc/medicine/26040/SPC/Caprelsa+100+mg+%26+300+mg+film+coated+tablets/. Accessed May 2014.

3 Cancer Research UK. Thyroid cancer incidence statistics. Apr 2014. Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/thyroid/incidence/#By. Accessed May 2014.

4 European Medicines Agency. Assessment report: Caprelsa®. Procedure No.: EMEA/H/C/002315//0000. Mar 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002315/WC500123603.pdf. Accessed May 2014.

5 TMC Pharma Services Ltd. Cometriq®▼. Summary of Product Characteristics. Mar 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002640/WC500163703.pdf. Accessed May 2014.

6 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Jun 2014. Available at: http://www.mims.co.uk/. Accessed Jun 2014.

7 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. May 2014. Available at: http://www.bnf.org/bnf/index.htm. Accessed May 2014.

8 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Thyroid Carcinoma. Version 2.2013. Sep 2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed May 2014.

9 Pacini F, Castagna MG, Brilli L et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; 23 Suppl 7: vii110-vii119.

10 Schlumberger M, Bastholt L, Dralle H et al. 2012 European Thyroid Association guidelines for metastatic medullary thyroid cancer. *Eur Thyroid J* 2012; 1 (1): 5-14.

11 Kloos RT, Eng C, Evans DB et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009; 19 (6): 565-612.

12 British Thyroid Association. Guidelines for the management of thyroid cancer: third edition draft for public consultation. Feb 2014. Available at: http://www.british-thyroid-association.org/Guidelines/Docs/BTA_DTC_guidlines.pdf. Accessed May 2014.

13 Wells SA, Jr., Robinson BG, Gagel RF et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012; 30 (2): 134-41.

14 AstraZeneca UK Ltd. Clinical Study Report D4200C00058. An international, phase III, randomized, double-blinded, placebo-controlled, multi-center study to assess the efficacy of ZD6474 versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer. Jun 2010. Accessed May 2014.

15 Wells. Author corrections. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2013.

16 Dobrez D, Cella D, Pickard AS et al. Estimation of patient preference-based utility weights from the functional assessment of cancer therapy - general. *Value Health* 2007; 10 (4): 266-72.

17 Beusterien KM, Szabo SM, Kotapati S et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *Br J Cancer* 2009; 101 (3): 387-9.
18 Roche Products Ltd. National Institute for Health and Clinical Excellence submission. Single technology appraisal: bevacizumab for the treatment of recurrent advanced ovarian cancer. Sep 2012. Available at: http://www.nice.org.uk/nicemedia/live/13586/62630/62630.pdf. Accessed May 2014.
19 International Agency for Research on Cancer. Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. 2012. Available at: http://globocan.iarc.fr/old/summary_table_pop_prev.asp?selection=206826&title=United+Kingdom&sex=0&window=1&sort=0&submit=%C2%A0Execute. Accessed Jul 2014.
20 Gilliland FD, Hunt WC, Morris DM et al. Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. *Cancer* 1997; 79 (3): 564-73.
21 Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. *Cancer* 2006; 107 (9): 2134-42.
22 All Wales Medicines Strategy Group. AWMSG policy relating to ultra-orphan medicines. Mar 2013. Available at: http://www.awmsg.org/docs/awmsg/appraisaldocs/inforandforms/AWMSG%20policy%20relating%20to%20ultra-orphan%20medicine.pdf. Accessed May 2014.
23 European Medicines Agency. Public summary of opinion on orphan designation. Vandetanib for the treatment of medullary thyroid carcinoma. Nov 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500005438.pdf. Accessed May 2014.
24 AstraZeneca UK Ltd. NCT00410761: An international, phase III, randomized, double-blinded, placebo-controlled, multi-center study to assess the efficacy of ZD6474 (ZACTIMATM) versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer. Apr 2014. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00410761. Accessed May 2014.