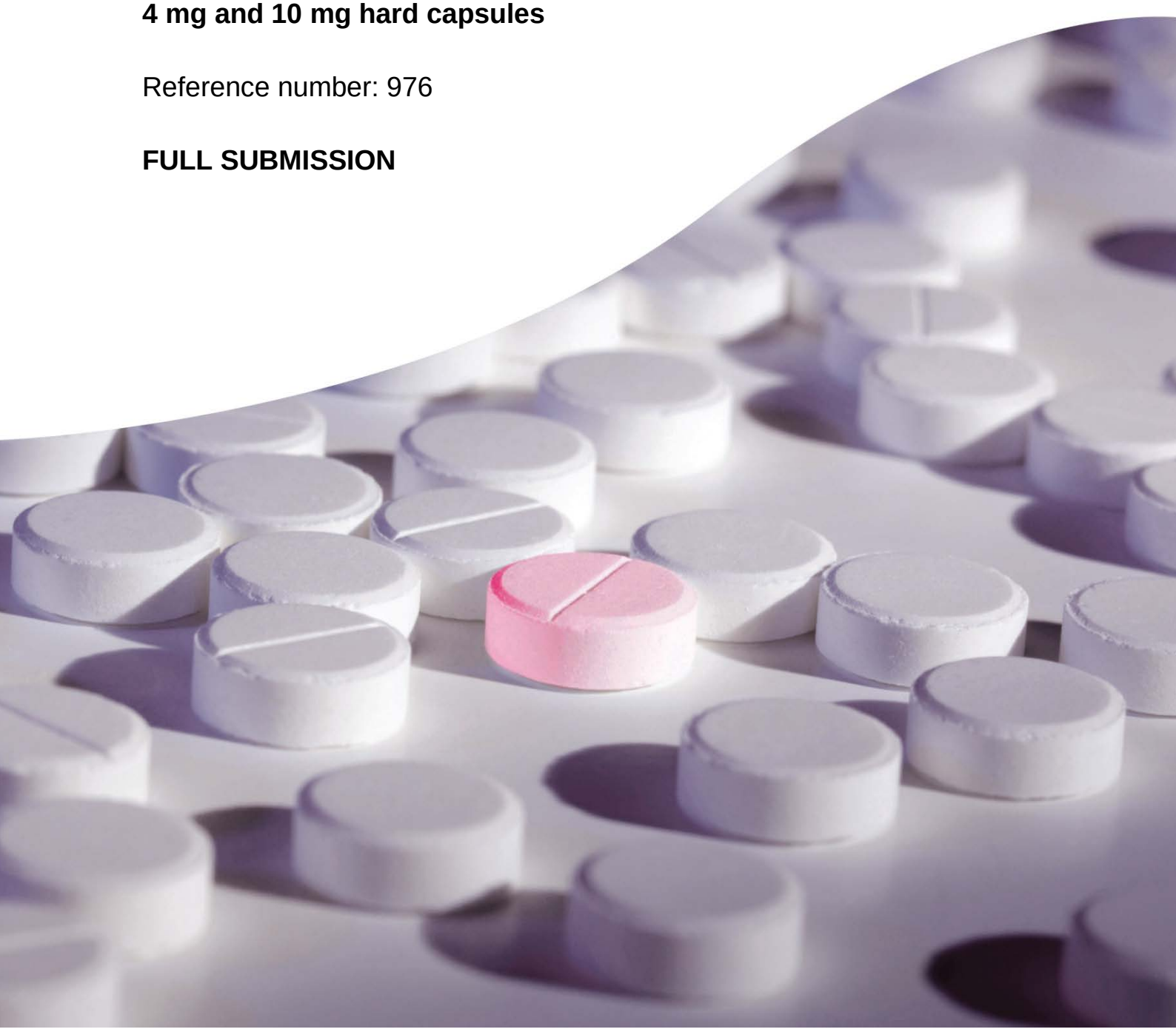
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Lenvatinib (Lenvima®)
4 mg and 10 mg hard capsules

Reference number: 976

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Lenvatinib (Lenvima®▼) 4 mg and 10 mg hard capsules

This assessment report is based on evidence submitted by Eisai Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Lenvatinib (Lenvima®▼) for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)[2]. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Dosing	24 mg (two 10 mg capsules and one 4 mg capsule) taken once daily. The daily dose should be modified as needed according to the dose/toxicity management plan. Refer to the Summary of Product Characteristics for further information[2].
Marketing authorisation date	28 May 2015[2]

2.0 DECISION CONTEXT

2.1 Background

Thyroid cancer is a rare disease and accounts for 1% of all new cases of cancer in the UK[3]. It is more common in women; incidence rates peak at 40–44 years in women and at 75–79 years in men[4]. Differentiated thyroid cancer is the most common type of thyroid cancer, accounting for 90-95% of all cases[5]. It includes papillary, follicular and Hürthle cell types[5].

First-line treatment of differentiated thyroid cancer is by surgery (thyroidectomy), usually followed by radioactive iodine (RAI) ablative therapy and thyroid hormone suppression therapy[6]. Tumour recurrence will happen in 3–25% of differentiated thyroid cancers and distant metastases occur in up to 10% of cases[5]. Around one-third of metastatic differentiated thyroid carcinomas will stop responding to radioactive iodine therapy[5], at which point the tumours become more aggressive with a reported 10-year survival rate of around 10%[5].

The US National Comprehensive Cancer Network guideline on thyroid cancer recommends lenvatinib and sorafenib for treating progressive or symptomatic disease that is refractory to radioactive iodine; the guideline was updated in 2017 to state lenvatinib as the preferred treatment[7]. European and British guidelines highlight that targeted therapy with tyrosine kinase inhibitors demonstrate clinical benefit in patients with differentiated thyroid carcinoma and support the use of sorafenib and lenvatinib in the context of clinical trials[6,8].

Lenvatinib (Lenvima®) is a receptor tyrosine kinase inhibitor that selectively inhibits the kinase activities of multiple receptors involved in oncogenic and proangiogenic

pathways, including vascular endothelial growth factor (VEGF) receptors, fibroblast growth factor (FGF) receptors and platelet-derived growth factor (PDGF) receptors[2].

2.2 Comparators

The comparator included in the company submission is:

- best supportive care[1].

Sorafenib (Nexavar®) is licensed to treat progressive, locally advanced or metastatic, differentiated thyroid cancer that is refractory to radioactive iodine[9], but it is currently not endorsed for use in NHS Wales[10] and is therefore not an appropriate comparator.

2.3 Guidance and related advice

- National Comprehensive Cancer Network (2017) NCCN Clinical Practice Guidelines in Oncology: thyroid carcinoma[7]
- American Thyroid Association (2015) Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer[11]
- British Thyroid Association (2014) Guidelines for the management of thyroid cancer[8]
- European Society for Medical Oncology (2012) Thyroid cancer: Clinical Practice Guidelines for diagnosis, treatment and follow-up[6]
- National Institute for Health and Care Excellence [ID1059] Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. In development – publication expected March 2018[12]

The All Wales Medicines Strategy Group (AWMSG) has issued a statement of advice for the use of sorafenib (Nexavar®)[10] .

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company's submission includes a phase III study (SELECT) comparing the efficacy and safety of lenvatinib to placebo in patients with differentiated thyroid cancer that is refractory to radioactive iodine[1]. This study formed the basis of the European Medicines Agency's marketing authorisation for lenvatinib and is discussed in section 3.1. The company also included supportive evidence from an open-label phase II study of lenvatinib, as well as an indirect treatment comparison of the SELECT study with a phase III study (DECISION) of sorafenib to treat differentiated thyroid cancer refractory to radioactive iodine[1]. The indirect analysis will not be discussed in detail because sorafenib (Nexavar®) is not currently recommended for use in NHS Wales and is not part of routine clinical practice in Wales.

3.1 SELECT study

This multicentre, double-blind study enrolled 392 adults (200 men; 192 women) with differentiated thyroid cancer refractory to radioactive iodine, who had received either one or no previous treatment with a tyrosine kinase inhibitor[13]. Patients were randomised in a 2:1 ratio to receive either oral lenvatinib (24 mg once daily) or placebo, given in 28-day cycles[13].

The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to death or to the first documented disease progression by independent radiologic review, in the intention-to-treat population[13]. Secondary endpoints were response rate, defined as the best objective response according to RECIST criteria[14]; and overall survival, defined as the time from randomisation to death by any cause. Tumour assessments were done every eight weeks until the end of the randomisation phase. All patients who had confirmed disease progression during the randomisation phase entered an extension phase, in which those who were receiving placebo were

then eligible to be given lenvatinib in an open-label treatment period[13]. To adjust for bias introduced by the treatment crossover in the open-label phase of the study, the company used the rank preserving structural failure time (RPSFT) method to estimate overall survival curves, as well as an unadjusted Kaplan–Meier method[13].

Results showed that the median progression-free survival was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (Table 1). Therefore, lenvatinib treatment was associated with significant improvements in progression-free survival compared with placebo treatment ($p < 0.0001$[15]; hazard ratio = 0.21; 99% confidence interval 0.14 to 0.31)[13].

Table 1. Endpoint data from the SELECT study[1,13,15-17]

Endpoint	Lenvatinib (n=261)	Placebo (n=131)	Hazard ratio (95% CI)	p value
Primary endpoint: progression-free survival - at first data cut-off Nov 2013				
Median progression-free survival (95% CI)	18.3 months (15.1 to NE)	3.6 months (2.2 to 3.7)	0.21 (0.14 to 0.31)†	p< 0.001*
Secondary endpoint: Median overall survival (at three data cut-offs)				
Median OS (Nov 2013) (95% CI)	NE (22.0 to NE)	NE (14.3 to NE)	0.73 (0.50 to 1.07)	p=0.1032
			0.62 (0.40 to 1.00)§	p=0.0510
Median OS (Jun 2014) (95% CI)	NE (30.9 to NE)	19.1 months (14.3 to NE)	0.80 (0.57 to 1.12)	p=0.1993
			0.53 (0.34 to 0.82) §	p=0.0051
Median OS (Aug 2015) (95% CI)	41.6 months (31.2 to NE)	34.5 months (21.7 to NE)	0.84 (0.62 to 1.13)	p=0.2475
			0.54 (0.36 to 0.80) §	p =0.0025
Secondary endpoint: objective tumour response rate at first data cut-off Nov 2013				
Objective response rate (95% CI**)	64.8% (n=169) (59.0 to 70.5)	1.5% (n=2) (0.0 to 3.6)	-	p<0.0011¶

* Stratified Log-rank test
† Stratified by region, age group, and prior VEGFR-targeted therapy; HR is expressed as lenvatinib/placebo and estimated from a Cox proportional hazard model
§ Adjusted hazard ratio – using rank preserving structural failure time
¶ Calculated using asymptotic normal approximation
** Calculated using Cochran-Mantel-Haenszel test
CI: confidence interval; HR: hazard ratio; NE: not estimable; OS: overall survival; VEGFR: vascular endothelial growth factor receptor

For the secondary endpoint of overall survival a significant difference between treatment groups was only observed for the adjusted hazard ratio at the second and third data cut-off (Table 1)[16].

For the secondary endpoint of objective tumour response, results showed that lenvatinib reduced tumour size in 64.8% of patients (Table 1): there were 4 complete responses giving a 1.5% complete response rate; and 165 partial responses, giving a 63.2% partial response rate[13]. The difference in the objective tumour response rate between the lenvatinib and placebo groups was 63.2% (95% CI: 57.1 to 69.4). The odds ratio was 28.87 (95% CI: 12.46 to 66.86) which was statistically significant in favour of lenvatinib treatment ($p < 0.0001$)[13]. The median time to response was 2 months (range 1.9–3.5 months); this was also the point in time of the first data assessment[1].

3.2 Comparative safety

In the SELECT study the most frequently reported adverse reactions associated with lenvatinib treatment (occurring in more than 30% of patients) are hypertension, diarrhoea, decreased appetite, weight loss, fatigue, nausea, proteinuria, stomatitis, vomiting, dysphonia, headache and palmar-plantar erythrodysaesthesia syndrome[2].

Safety data from the SELECT study show that 37 patients (14.2%) discontinued lenvatinib treatment due to adverse events, compared with 3 patients (2.3%) who discontinued placebo treatment[13]. There were 6 fatal treatment-related adverse events in the lenvatinib group and none in the placebo group[13]. Overall, 89.7% of patients

treated with lenvatinib had dose modifications (reductions or interruptions)[5], and the daily dose of lenvatinib was linked with the incidence of treatment-emergent adverse events of grade 3 or 4 and therefore with the number of treatment interruptions[5]. The most common dose-limiting toxicities seen with lenvatinib treatment in clinical studies were hypertension and proteinuria[5]. Hypertension was also associated with the rare occurrence of posterior reversible encephalopathy syndrome[5]. The Summary of Product Characteristics for lenvatinib recommends that blood pressure should be well controlled before starting lenvatinib treatment, and it should be monitored during treatment[2]. It also recommends regular monitoring of urine protein levels[2].

In general, the adverse events reported with lenvatinib treatment were expected and consistent with those associated with VEGF/VEGFR-targeted agents, and could be managed with the planned dose/toxicity management plan[5].

3.3 AWTTC critique

- AWTTC-sought clinical expert opinion states that in Wales best supportive care is currently the only option for patients with differentiated thyroid cancer refractory to radioactive iodine. Best practice set out in clinical guidelines suggests treatment with a multiple receptor kinase inhibitor and these treatments are not currently available to patients in Wales[6-8].
- In the SELECT study lenvatinib demonstrated statistical significance in prolonging progression-free survival compared with placebo[13]. No quality of life data were collected from the randomised part of the SELECT study[5]. Health-related quality of life data are being collected in an ongoing study (211) of lenvatinib in differentiated thyroid cancer refractory to radioactive iodine, which is expected to complete in October 2020[18].
- The SELECT study included 21 patients from sites in the UK. However, no patients recruited were from Wales. It is therefore unclear how generalisable the study results are to the Welsh clinical context and population.
- Lenvatinib has a safety profile expected and consistent with other VEGF/VEGFR-targeted agents[5]. Adverse events in the SELECT study were manageable by dose reductions and modifications[5]. Results are expected in 2020 from study 211 which is evaluating a lower dose of lenvatinib to treat differentiated thyroid cancer refractory to radioactive iodine[18].
- There are no long-term safety data; however studies (SELECT study and study 201) are currently ongoing and the data will better inform on the long-term safety profile of lenvatinib[5].
- Lenvatinib is an oral treatment that can be given to patients at home. Monitoring of blood pressure and protein urine levels are recommended during lenvatinib treatment[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost-utility analysis of oral lenvatinib 24 mg once daily compared with best supportive care for the treatment of adults with progressive, locally advanced or metastatic, differentiated (papillary, follicular or Hürthle cell) thyroid cancer which is refractory to radioactive iodine[1].

A four-state partition survival Markov model with an NHS perspective is used to assess the cost-effectiveness of lenvatinib compared with best supportive care in 1-month cycles over a lifetime horizon (33.35 years). Patients enter the model in the "stable disease" state and receive either best supportive care or lenvatinib in 28-day cycles. Based on patient-level data from the SELECT study, they then transition between the "stable disease" and "response" states until disease progression when they enter the

"progressive" state where they remain until death. Patients in the "stable disease" and "response" health states can also transition directly to the "death" state. Time-dependent transition probabilities are derived from the Kaplan–Meier survival function, parametric survival functions (or both) for response, progression-free survival and overall survival from the SELECT study with expected response[13], progression-free survival and expected overall survival calculated as the area under the respective survival curves. Overall survival was adjusted for the crossover of patients from placebo treatment to lenvatinib treatment after disease progression using RPSFT models and extrapolated using a piecewise exponential framework because around 50% of patients were still alive at the third data cut-off point of the SELECT study[17]. Progression-free survival was extrapolated using a piecewise gamma model for consistency. Time to treatment discontinuation and adverse events was taken from patient-level data of the SELECT study with no treatment assumed in the "progressive" health state.

Costs considered in the model include treatment and administration costs, costs of adverse events, general healthcare costs and mortality-related costs. The model assumes a mean dose for lenvatinib of 17.4 mg once-daily based on the average dose in the SELECT study, taking into account dose reductions due to treatment toxicity. Applying a simple Wales patient access scheme (WPAS) [commercial in confidence text removed]. No additional cost is assumed for best supportive care. Administration costs are based on cost for oral chemotherapy as reported in published literature[19]. General healthcare resource use was estimated according to an online retrospective chart review[20] which provided healthcare resource utilisation data on 623 patients with radioactive iodine-refractory differentiated thyroid cancer, including 72 patients in the UK. Resource use was validated by four practising clinical experts in the UK and included a consultant medical oncology visit, hospitalisation and radiotherapy which were costed using published unit costs[19]. Mortality-related costs were obtained from published data and included acute hospital care, local authority-funded social care, district nursing care, and GP visit costs[21]. Adverse event costs included hospitalisation costs and costs for grade 3 and 4 adverse events obtained from published unit costs[19,22].

Health-related quality of life data were not collected as part of the SELECT study. Utility values recorded in the DECISION study of sorafenib compared with placebo were used in the model base case[23]. Disutilities for adverse events associated with lenvatinib treatment were applied as a weighted proportion based on a published vignette-based time trade-off study identified in a systematic literature review and conducted by the company on 100 members of the UK general public[24]. All costs and benefits are discounted at 3.5%.

Extensive deterministic sensitivity analysis and probabilistic sensitivity analysis are undertaken to assess parameter uncertainty. Furthermore, scenario analyses investigate the effects of different extrapolation techniques for overall survival and progression-free survival data, alternative utility values derived from the vignette study[24] and alternative treatment duration for lenvatinib based on treat to progression data from the SELECT study on the cost-effectiveness of lenvatinib. The company also provides a cost-utility analysis comparing lenvatinib and sorafenib based on an indirect treatment comparison of clinical data from the SELECT and DECISION studies, assuming a mean dose of sorafenib of 651 mg.

4.1.2 Results

The results of the company's base case suggest that treatment with lenvatinib is associated with 3.18 discounted quality-adjusted life years (QALYs) compared with 1.84 discounted QALYs in the best supportive care arm, at an incremental cost of [commercial in confidence text removed] per patient. This gives an incremental cost-effectiveness ratio (ICER) of [commercial in confidence text removed] per QALY gained. Furthermore, the model estimates that the mean life expectancy of people receiving lenvatinib is increased by 1.54 years.

Table 2. Results of the base case analysis

	Lenvatinib	Best supportive care	Difference
Cost-utility analysis			
Total cost per patient	¶¶	£42,115	¶¶
Treatment costs	¶¶	£0	¶¶
Healthcare costs	£31,022	£35,582	-£4,560
Adverse events costs	£107	£0	£107
Mortality-related costs	£6,316	£6,532	-£217
Total life years	4.34	2.80	1.54
Total QALYs per patient	3.18	1.84	1.34
ICER (£/QALY gained)	¶¶		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
¶¶ commercial in confidence figure removed

Table 3 summarises the scenarios provided by the company to address uncertainty around the key input parameters of the cost-utility analysis. Several scenario analyses were tested using alternative data sources. The ICERs using these alternatives range from [commercial in confidence text removed] per QALY gained. Comparing these with sorafenib resulted in an additional 1.08 QALYs [commercial in confidence text removed].

Table 3. Results of the scenario analyses

Scenario	ICER	Plausibility
Scenario 1a: Using different extrapolation techniques for OS and PFS	Piecewise gamma: ¶¶ Piecewise exponential: ¶¶ Piecewise Weibull: ¶¶	These scenarios are plausible because other piecewise extrapolation techniques were considered a good fit.
Scenario 1b: Using different extrapolation techniques for OS and PFS	Parametric OS-exponential, PFS-gamma: ¶¶ Parametric gamma: ¶¶	These scenarios are plausible because parametric extrapolation techniques were considered an average fit.
Scenario 1c: Using different extrapolation techniques for OS and PFS	Individual models OS-exponential, PFS-gamma: ¶¶ Individual models OS-Weibull, PFS-gamma: ¶¶	These scenarios are implausible because individual model techniques were considered below average fit.
Scenario 2: Lenvatinib treatment until progression (instead of clinical study duration in base case)	¶¶	This scenario is plausible because most people treated with lenvatinib can be expected to remain on treatment until disease progression.
Scenario 3: Utility data sourced from vignette study[24]	¶¶	This scenario is plausible because the vignette study is highly relevant for the population in question, investigating HRQoL for people with RAI-refractory DTC based on time trade-off data from 100 UK residents.
Scenario 4: Baseline utility in response rate equal to stable disease state	¶¶	The plausibility of this scenario is uncertain because there is no evidence for increased or stable utility after response.
Scenario 5: AE disutility excluded	¶¶	This scenario is implausible because it is likely that adverse effects will impact on HRQoL
Scenario 6 : Cut-off for OS and PFS 20 weeks (instead of 50 and 47 weeks in the base case)	¶¶	This scenario is implausible because longer-term follow-up data are available that will result in a more robust extrapolation.
Scenario 7: CUA comparing lenvatinib to sorafenib	¶¶	This scenario is implausible because sorafenib is currently not recommended for use to treat RAI-refractory DTC in Wales
CUA: cost-utility analysis; DTC: differentiated thyroid cancer; HRQoL: health-related quality of life; OS: overall survival; PFS: progression-free survival; RAI: radioactive iodine ¶¶ commercial in confidence figure removed.		

The results of the deterministic sensitivity analyses show that the model is robust with ICERs between [commercial in confidence text removed]. The results are most sensitive to changes in discount rates, overall survival and progression-free survival and lenvatinib daily dose.

Probabilistic sensitivity analysis suggests a mean probabilistic ICER of [commercial in confidence text removed]. The probability of lenvatinib being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 is 0% and 9%, respectively. This increases to 97% at a threshold of £40,000.

4.1.3 AWTTC critique

The results of the base case cost-utility analysis show that using lenvatinib is more costly but produces increased life years and quality of life compared with best supportive care in people with progressive, locally advanced or metastatic, differentiated thyroid cancer which is refractory to radioactive iodine, resulting in a base case ICER of [commercial in confidence text removed] per QALY gained. The

sensitivity analyses show that the results are robust with a probability of cost-effectiveness of 0% at the £20,000 and 9% at the £30,000 willingness-to-pay threshold. Scenario analyses using alternative data sources for key parameters suggest ICERs from [commercial in confidence text removed] per QALY gained.

Strengths of the economic analysis:

- In the absence of other licensed treatments in Wales for the patient population, best supportive care is the most appropriate comparator for the cost-utility analysis.
- The partition survival model is well constructed and described, logically laid out and appears robust. Methods used in the model and for data population are transparent, clearly described and well referenced.
- Extensive deterministic and probabilistic sensitivity analyses are conducted to investigate the effects of parameter uncertainty on the results.

Limitations of the economic analysis:

- The model uses treatment duration data from the SELECT study which is limited to the study follow-up period. It is conceivable that most people receiving lenvatinib will continue treatment until disease progression which would increase the ICER to [commercial in confidence text removed] due to longer treatment and higher treatment acquisition costs. However, the company state that treatment discontinuation is common, the SELECT data is the most robust available data to date and not all patients will continue treatment until progression. Still, any differences in routine use compared to the study period will impact the cost of treatment and increase the ICER compared to the base case.
- The model uses clinical data from the third data cut-off point of the SELECT study at a median follow-up time of 37.8 months for lenvatinib and 37.9 months for placebo[17]. At this point, 58.4% of the lenvatinib group and 46.6% of the placebo group were still alive. It was therefore deemed critical to extrapolate overall survival using a piecewise exponential extrapolation framework. Progression-free survival was extrapolated using a piecewise gamma framework for consistency. Although the company chose the best fitting extrapolation techniques, the immaturity of the overall survival data and the limitations of the extrapolation techniques will introduce bias.
- The model assumes a mean daily dose of lenvatinib of 17.4 mg based on the average dose observed in the SELECT study which was caused by dose reductions due to toxicity. The recommended dose of lenvatinib is 24 mg once-daily. If it was assumed that all patients receive the recommended daily dose throughout their treatment period, the ICER would be £47,181. While this may be unrealistic considering that two thirds of patients (67.8%) had adverse events that required dose reduction in the SELECT trial, any differences in actual dose will affect the ICER as lenvatinib treatment cost is the main cost driver in the model.
- The crossover design of the SELECT study allowed people in the placebo group to join the lenvatinib arm after disease progression. Although this would not influence the progression-free survival results, it will confound the overall survival data because placebo patients will benefit from the active treatment. While it is acknowledged that withholding an effective treatment from the placebo group would be unethical, the cross-over will cause an underestimation of the efficacy of lenvatinib compared with placebo. The company adjusted for the crossover effect using an RPSFT model, a randomisation-based method for estimating the survival times that would have been observed without the crossover. Although this will reduce the effect of the crossover design on the overall survival results of the study, the RPSFT model makes several assumptions and has limitations that will introduce bias. The estimated

difference in overall survival between placebo and lenvatinib may therefore be conservative.

- Since the SELECT study did not collect data on patient health-related quality of life, utility values were derived from the sorafenib submission to the Scottish Medicines Consortium based on the DECISION study which compared sorafenib with placebo in radioactive iodine-refractory differentiated thyroid cancer. Considering the comparable patient population and mode of action of the active treatment, these appear to be the best available estimates for the patient population in question. However, the independent treatment comparison conducted by the company suggests that lenvatinib is statistically significantly superior to sorafenib for progression-free survival and has a non-significant absolute risk reduction of 27% for overall survival. Using the utility values of sorafenib could therefore underestimate the effect of lenvatinib on patient health-related quality of life.
- The company assumes administration costs per cycle of oral chemotherapy of £183.50[18] in the model. However, they state in the budget impact calculations that no administration costs should be included as lenvatinib is self-administered orally by the patient at home. The inclusion of administration costs in the model could therefore overestimate the costs of lenvatinib.

4.2 Review of published evidence on cost-effectiveness

One full publication was identified which reports the cost-effectiveness of lenvatinib compared with sorafenib and placebo. A US study compared lenvatinib with sorafenib and placebo from a limited societal perspective using a 3-state Markov model[25]. Clinical data were sourced from the SELECT and DECISION studies (without access to patient-level data). Costs and utility data were sourced from published literature. Lenvatinib was found cost-effective compared with sorafenib (ICER: $25,275 per QALY, equating to £17,815 in 2016) and placebo (ICER: $40,869 per QALY gained equating to £28,806 in 2016).

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The incidence of thyroid cancer is estimated to be 4.0 in 100,000 people[4] with 124 cases in Wales. Considering a mortality rate of 0.3 in 100,000 population[26] and an annual population growth rate of 0.71%[27], this gives a patient number of 124 in year 1, increasing to 127 in year 5. Of these cases, 90% are assumed to be differentiated thyroid cancer of which 10% are refractory to radioactive iodine[6]. This results in 11 patients eligible to receive lenvatinib per year in Wales. Assuming an uptake rate of [commercial in confidence text removed] in the first year that increases to [commercial in confidence text removed] in year 5, the number of people treated with lenvatinib is expected to be 1 in year 1 and 6 in year 5.

The price for one month's treatment of lenvatinib is £4,371 [commercial in confidence text removed] which equates to an annual cost per patient of £52,451 or [commercial in confidence text removed]. This cost is based on an average dose of 17.4 mg as observed in the SELECT study. No treatment administration costs are included because lenvatinib is self-administered at home. Grade 3 or 4 adverse events are costed at £738 per year. No costs are assumed for best supportive care.

5.1.2 Results

The estimated net budget impact as presented by the company is shown in Table 4. The introduction of lenvatinib is estimated to result in additional costs [commercial in confidence text removed] in year 5. The total budget impact over 5 years would be expected to be in the region of [commercial in confidence text removed] including adverse event treatment costs).

Table 4. Company-reported costs associated with use of lenvatinib

Net costs	2018	2019	2020	2021	2022
Number eligible patients (indication under consideration)	11	11	11	11	11
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition cost	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition costs (savings/costs)	¶¶	¶¶	¶¶	¶¶	¶¶
Net administration costs	£0	£0	£0	£0	£0
Net adverse events costs	£738	£1,475	£2,213	£3,689	£4,426
Total net costs	¶¶	¶¶	¶¶	¶¶	¶¶

Please note: these budget impact estimates were recalculated by AWTTC using adjusted budget impact analysis inputs (incidence rate, mortality rate and administration costs) provided by the company.
¶¶ commercial in confidence figure removed.

Varying the uptake rate of lenvatinib by 10% per year and the acquisition cost by 30% results in budget impact estimates over five years ranging from [commercial in confidence text removed] (excluding administration and adverse event costs).

5.1.3 AWTTC critique

- The data sources and calculations used for the budget impact model provided by the company are generally well described and basic sensitivity analysis is undertaken.
- Prevalence is not taken into account in the model and the company assumes for ease of calculation that newly diagnosed patients receive lenvatinib for one year. However, a median duration of treatment of 13.8 months was reported in the SELECT study and the company suggests in the scenario analysis that treatment might continue until disease progression (median 18.3 months). This assumption will therefore underestimate the number of patients treated each year and thus the total cost of treatment.
- Uptake rates are estimates based on the company's experience and data on file not available for review. Any changes to the uptake rate will affect the budget impact of lenvatinib.

5.2 Comparative unit costs

Monthly acquisition costs of lenvatinib are described in Table 5. To date, no other treatment options are recommended for use in Wales for treating progressive, locally advanced or metastatic, differentiated (papillary, follicular or Hürthle cell) thyroid carcinoma which is refractory to radioactive iodine.

Table 5. Examples of acquisition costs of specific treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer which is refractory to radioactive iodine

Regimens	Example doses	Approximate costs per month*
Lenvatinib (Lenvima®) 4 mg or 10 mg oral capsules (30-pack)	24 mg once-daily	£4,311 (£1,437 per pack)
Sorafenib (Nexavar®) 200 mg oral tablets (112-pack)	400 mg twice-daily	£3,832 (£3576.56 per pack)
* The company states that the average treatment duration is around 14 months for lenvatinib and 11 months for sorafenib. Costs based on BNF list prices as of July 2017. Sorafenib is recommended for use in England and Scotland only. Costs and doses are from the British National Formulary, accessed June 2017. Both available dosages of lenvatinib are priced equally.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

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.

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: 9 and 12 June 2017
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The applicant company suggests that lenvatinib (Lenvima®) in the given population meets the AWMSG criteria for an ultra-orphan medicine. AWMSG defines an ultra-orphan medicine as a medicine that has been granted European Medicine's Agency-designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[28].

Lenvatinib is designated an orphan medicine by the European Medicines Agency for the treatment of papillary and follicular thyroid carcinoma[29,30]. The European Medicines Agency states that follicular differentiated thyroid cancer affects 0.2 in 10,000 people and papillary differentiated thyroid cancer affects 1 in 10,000 people in the European Union which is below the orphan designation ceiling of 5 in 10,000 population.

For the full licensed indication of progressive, locally advanced or metastatic, differentiated thyroid cancer refractory to radioactive iodine in adults, the estimated annual prevalence is 11 (Section 5.1.1; budget impact).

The criteria for assessing clinical effectiveness and cost-effectiveness of ultra-orphan medicines are the same as those applied to other medicines, but recognising that the evidence base may be weaker. The New Medicines Group (NMG) and AWMSG will consider evidence on the following to inform their decisions (see Table 6).

Table 6. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG and AWMSG

NMG and AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	Differentiated thyroid cancer (DTC) progresses slowly and patients are asymptomatic for long periods of time. Standard treatment of DTC usually starts with surgery (thyroidectomy) followed by radioactive iodine (RAI) ablation of the remaining thyroid tissue with very good prognosis at this stage as treatment is curative for most patients[31]. However, for the 10% of people who develop RAI-refractory DTC prognosis is poor because the disease is aggressive, difficult to treat and progression and metastases are common. The resulting increasing tumour burden can cause severe symptoms for patients which can include pain, difficulty swallowing, coughing up blood, hoarseness, and trouble breathing leading to asphyxia[32,33]. These symptoms are debilitating and many patients rely on carers.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines).	While sorafenib is available for use in England and Scotland, it is currently not endorsed for use in NHS Wales for treating RAI-refractory DTC and therefore lenvatinib addresses an unmet need for these patients in Wales.
Whether the medicine can reverse, rather than stabilise the condition.	Lenvatinib will not reverse or cure the condition.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development.	Lenvatinib does not bridge a gap to a definitive therapy.
The innovative nature of the medicine.	While other treatment options (sorafenib) have been developed for people with RAI-refractory DTC, the company considers lenvatinib to be innovative as it is a multiple receptor tyrosine kinase inhibitor with a novel binding mode that inhibits the kinase activities of several vascular endothelial growth factor receptors and other proangiogenic and oncogenic pathway-related receptor tyrosine kinases[34]. Unlike sorafenib, lenvatinib upregulates fibroblast growth factor FGF23 which was associated with longer PFS[35].
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	The disease burden of RAI-refractory DTC can be significant with severe symptoms for patients that can include pain, difficulty swallowing, coughing up blood, hoarseness, and trouble breathing leading to asphyxia. These symptoms can be profoundly debilitating and frightening with a devastating impact on patients and their families. Lenvatinib yields a rapid and durable response and clinicians have indicated that this radiological shrinkage of lesions which would be expected to reduce symptoms (e.g. shortness of breath and pain) and improve quality of life and general well-being. Furthermore, in a number of patients, benefits are anticipated within just 6-8 weeks of starting treatment. Lenvatinib therefore offers the potential to relieve frightening symptoms of this disease, to the point that patients can return to work and resume their wider societal role, which has economic and quality of life benefits for both patients and their families. Patients can keep their independence for as long as possible.
Added value to the patient's family (e.g. impact on a carer or family life).	Delaying disease progression can allow patients to retain their independence, experience a good quality of life and continue to work or maintain an active life outside work. This reduces the carer burden and financial impact of a family member having to give up work. The psychological benefit of providing hope to patients and their families was also emphasised.
CI: confidence interval; DTC: differentiated thyroid cancer; PFS: Progression-free survival; QALY: quality-adjusted life year; RAI: radioactive iodine	

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