Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: a systematic review and economic model

Paul Tappenden,1* Christopher Carroll,1 Jean Hamilton,1 Eva Kaltenthaler,1 Ruth Wong,1 Jonathan Wadsley,2 Laura Moss3 and Sabapathy Balasubramanian4

1Health Economics and Decision Science, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
2Weston Park Hospital, Sheffield, UK
3Velindre Cancer Centre, Cardiff, UK
4Department of Oncology and Metabolism, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

*Corresponding author p.tappenden@sheffield.ac.uk

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Scientific summary

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Scientific summary

Background

Thyroid cancer is the most common malignant endocrine tumour, but represents only \( \approx 1\% \) of all malignancies. According to Cancer Research UK, 3404 new diagnoses of thyroid cancer were reported in England in 2014: 966 cases (28%) were in men and 2438 cases (72%) were in women [Cancer Research UK. Thyroid Cancer Statistics. URL: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer (accessed 27 March 2017)]. There are four main types of thyroid cancer: (1) papillary, (2) follicular, (3) medullary and (4) anaplastic. Medullary thyroid cancer (MTC) is a rare type of cancer that presents as a mass of tumours in the thyroid gland of the neck. MTC occurs in the parafollicular cells (also known as C cells). There are four types of MTC: (1) sporadic, (2) multiple endocrine neoplasia (MEN) 2, (3) MEN 3 and (4) familial MTC. Approximately 75% of cases of MTC are sporadic in nature. MTC is very rare and accounts for \( \approx 5\% \) of all thyroid cancers. The estimated annual incidence of MTC in England is \( \approx 170 \) cases. For patients with regional disease spread, 10-year survival rates are reported to be \( \approx 75\% \), whereas survival estimates of 21–40% have been reported for patients presenting with metastases at diagnosis (stage IV disease). Patients with MTC typically present with a lump in the neck (which may represent a thyroid or lymph node mass) or distant metastases. The lumps are not usually associated with other symptoms but may occasionally cause dysphagia (difficulty or discomfort in swallowing) or dysphonia (difficulty in speaking). Symptoms might also relate to the effect of metastases, especially diarrhoea, flushing, dyspnoea and bone pain.

For many patients, surgery can be curative. Treatment options for patients with unresectable locally advanced or metastatic MTC include tyrosine kinase inhibitor (TKI) therapy and best supportive care (BSC), which typically comprises symptom control and palliative treatments, such as radiotherapy and palliative surgery. Currently, vandetanib (Caprelsa®, Cambridge, MA, USA) and cabozantinib (Cometriq®, Ipsen, Paris, France) are the modality of choice for unresectable progressive and symptomatic MTC. Both cabozantinib and vandetanib are currently available through the Cancer Drugs Fund (CDF) for the first-line treatment of symptomatic and progressive MTC.

The evidence presented within this assessment relates to two populations of patients with MTC: (1) patients with symptomatic and progressive disease [referred to as the ‘European Union (EU)-label population’] and (2) patients with symptomatic and progressive disease with carcinoembryonic antigen (CEA) and calcitonin (CTN) doubling times of \( \leq 24 \) months (referred to as the ‘restricted EU-label population’).

Aims

The aims of the assessment were to:

- evaluate the clinical effectiveness and safety of cabozantinib and vandetanib within their marketing authorisations for treating unresectable locally advanced or metastatic MTC
- estimate the incremental cost-effectiveness of cabozantinib and vandetanib compared with each other and with BSC
- identify key areas for primary research
- estimate the overall cost of these treatments in England.
Methods

Clinical effectiveness
A systematic review was conducted following standard methods. Systematic searches were undertaken in 10 electronic databases up to November 2016 to identify randomised controlled trials (RCTs) of cabozantinib and vandetanib for treating unresectable locally advanced or metastatic MTC. The quality of included studies was assessed using the Cochrane Risk of Bias Tool. Results were reported using narrative synthesis and were presented in a tabular format. In the absence of direct evidence comparing cabozantinib and vandetanib with each other, a network meta-analysis (NMA) was performed using data relating to the ZETA trial EU-label and EXAM [Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer] trial intention-to-treat (ITT) populations.

Cost-effectiveness
A comprehensive search was undertaken to systematically identify economic evaluations of treatments for locally advanced or metastatic MTC and studies reporting on the health-related quality of life (HRQoL) of patients with locally advanced or metastatic thyroid cancer (including MTC, as well as other more common forms of thyroid cancer). The submissions received by the National Institute for Health and Care Excellence (NICE) included one unpublished economic analysis of vandetanib versus BSC in the restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of $\leq$ 24 months) based on a partitioned survival structure implemented using the discretely integrated condition event (DICE) approach. The executable model used to undertake the analysis was also submitted to NICE. The model was scrutinised by the assessment group (AG) and the economic analysis was critically appraised using the key items contained within published checklists. Two errors were identified; hence all submitted analyses were repeated by the AG using a corrected version of the company’s model. The manufacturer of cabozantinib did not submit any economic evidence relating to this product.

In the light of the absence of published evidence relating to the cost-effectiveness of vandetanib or cabozantinib, the absence of a submitted economic analysis of cabozantinib and concerns regarding the submitted economic analysis of vandetanib, the AG developed a de novo health economic model. The AG model used a partitioned survival approach based on three health states: (1) progression free, (2) post progression and (3) dead. Costs and health utilities were assumed to differ according to the presence/absence of disease progression. The model parameters were informed by analyses of individual patient data (IPD) from the EXAM trial, replicated IPD from the ZETA trial, the submissions from Sanofi Genzyme (Cambridge, MA, USA) and Ipsen (Paris, France) and data contained within subsequent clarification responses, as well as published literature, standard reference cost sources and expert judgement. The model was evaluated across five sets of analyses from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. Four sets of analyses related to the evaluation of cabozantinib and/or vandetanib versus BSC in the EU-label population (symptomatic and progressive MTC); the remaining analysis set evaluated vandetanib versus BSC in the restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of $\leq$ 24 months). Costs and health outcomes were discounted at a rate of 3.5% per annum. Costs were valued at 2016/17 prices. Confidential Patient Access Schemes have been proposed for both products. All economic analyses within this report relate to the list prices of vandetanib and cabozantinib; separate analyses including price discounts are presented in separate confidential appendices to this report.

Results

Clinical effectiveness
The systematic review identified and included two placebo-controlled trials. The EXAM trial evaluated the efficacy and safety of cabozantinib in patients with unresectable locally advanced, metastatic and progressive MTC ($n = 330$). The ZETA trial evaluated the efficacy and safety of vandetanib in patients with unresectable locally advanced or metastatic MTC ($n = 331$). The two trials assessed different populations...
because the ZETA trial inclusion criteria did not specify ‘progressive’ disease; therefore, the ITT population in this trial generally had less severe disease (there were more patients with potentially indolent disease). However, the ZETA trial did include a subgroup of patients with ‘progressive and symptomatic disease’ (n = 186), which formed the EU-label population. Clinical advice received by the AG confirmed that this group was comparable to the EXAM trial ITT population.

In terms of efficacy, both cabozantinib and vandetanib significantly improved progression-free survival (PFS) compared with placebo. For the principal comparison between the EXAM trial ITT population and the ZETA trial EU-label population, PFS was similar for cabozantinib versus placebo [investigator-read hazard ratio (HR) 0.29, 95% confidence interval (CI) 0.21 to 0.42; p < 0.001; central review HR 0.28, 95% CI 0.19 to 0.40; p < 0.001] and vandetanib versus placebo [investigator-read HR 0.33, 95% 0.20 to 0.53; p = 0.0226; central review, excluding patients switching treatments, HR 0.47, 95% CI 0.29 to 0.77; p = 0.0024 and including open-label populations, HR 0.32 95% CI 0.19 to 0.54; p < 0.0001).

The NMA undertaken by the AG suggested that the treatment effects on PFS were broadly similar [vandetanib vs. cabozantinib HR 1.14, 95% credible interval (CrI) 0.41 to 3.09]. The magnitude of the treatment effect was more favourable towards cabozantinib when the comparison was based on central-read PFS rather than investigator-read PFS (HR 1.68, 95% CrI 0.61 to 4.62); however, the difference between the two interventions was not statistically significant. The NMA was, however, limited by the sparsity of the network and the use of HRs, which ignore any treatment-by-time interaction.

Based on the trial evidence, there was no significant benefit in terms of overall survival (OS) for either cabozantinib or vandetanib compared with placebo, although the data from the ZETA trial were subject to potential confounding as a result of open-label vandetanib use in the placebo group. Both cabozantinib (p < 0.001) and vandetanib (ITT group, p < 0.001, and EU-label group, p < 0.0001) demonstrated significantly better objective response rates (ORRs) than placebo, as determined by modified or standard Response Evaluation Criteria in Solid Tumours (RECIST). Both cabozantinib (p < 0.001) and vandetanib (p < 0.001) also demonstrated significantly better CTN and CEA response rates than placebo. Both cabozantinib and vandetanib produced frequent adverse events (AEs). The overall incidence rate of any serious adverse event (SAE) in the EXAM trial was 42% in the cabozantinib arm compared with 23% in the placebo arm, whereas in the ZETA trial, the incidence rate of SAEs was 31% in the vandetanib arm compared with 13% in the placebo arm.

**Cost-effectiveness**

The corrected version of the company’s (Sanofi Genzyme) model suggests that the probabilistic incremental cost-effectiveness ratio (ICER) for vandetanib versus BSC in the restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months) is approximately £31,546 per quality-adjusted life-year (QALY) gained. However, the AG noted several concerns with this analysis, in particular (1) the questionable relevance of the restricted EU-label population to current clinical practice, (2) the failure to adjust for open-label vandetanib use in both treatment groups of the ZETA trial, (3) the likely overestimation of the costs of vandetanib use in the post-progression state, (4) questionable assumptions regarding the amount of vandetanib received and (5) concerns regarding the robustness of the company’s covariate-adjusted survival modelling in the restricted EU-label population. The AG considers it likely that the ICER for vandetanib is considerably higher than the estimates presented within the Sanofi submission to NICE.

Based on the AG’s probabilistic analysis of cabozantinib versus placebo in the EU-label (symptomatic and progressive) MTC population, the ICER for cabozantinib versus BSC is expected to be £150,874 per QALY gained. Within the EU-label (symptomatic and progressive MTC) population of the ZETA trial, the AG’s probabilistic analysis suggests that the ICER for vandetanib versus BSC is expected to be £352,508 per QALY gained. The fully incremental analysis of cabozantinib, vandetanib and BSC, based on the EXAM trial ITT population and the vandetanib PFS treatment effect from the ZETA trial, suggests that the ICER for vandetanib versus BSC is expected to be £138,405 per QALY gained, whilst the ICER for cabozantinib versus vandetanib is expected to be £195,593 per QALY gained. Within the fully incremental analysis,
in which the PFS and OS outcomes for vandetanib were assumed to be equivalent to the cabozantinib group outcomes in the EXAM trial, cabozantinib is expected to be dominated, whilst the ICER for vandetanib versus BSC is expected to be £144,841 per QALY gained. Within the restricted EU-label population (symptomatic and progressive MTC plus CEA/CTN doubling times of ≤ 24 months), the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained.

Discussion

Two RCTs comparing active treatment with placebo were identified: one of cabozantinib (the EXAM trial) and one of vandetanib (the ZETA trial). The EXAM trial was rated as being at low risk of bias. The ZETA trial was rated as being at moderate or high risk of bias, principally as a consequence of treatment switching that led to the potential confounding of outcome data. There was no direct evidence comparing outcomes for cabozantinib and vandetanib with each other. Both cabozantinib and vandetanib demonstrated significant benefits compared with placebo in terms of PFS and appeared to be broadly similar in terms of efficacy, although neither has demonstrated significant OS benefits compared with placebo. Both cabozantinib and vandetanib produced frequent AEs, with substantial proportions of patients experiencing AEs that led to dose interruption or reduction.

The economic analyses undertaken by Sanofi and the AG are each limited by the evidence used to inform them. In particular, the use of open-label vandetanib in the placebo group of the ZETA trial is likely to have confounded OS outcomes. The Sanofi submission states that, although attempts were made to adjust for this potential confounding in OS using the rank-preserving structural failure time approach, these were not successful. The AG did not have access to the underlying IPD (including data on relevant covariates), hence further attempts to adjust for treatment switching were not possible. Consequently, the pairwise analyses of vandetanib versus BSC may not be meaningful for decision-making. For this reason, the AG undertook fully incremental analyses based principally on the observed outcomes within the EXAM trial. Although these incremental analyses necessarily reflect potentially strong assumptions concerning transferable/equivalent treatment effects between vandetanib and cabozantinib, they are not subject to confounding as a result of post-progression vandetanib use. These analyses suggest that within the EU-label population (symptomatic and progressive MTC), the ICERs for vandetanib and cabozantinib versus BSC are expected to be > £138,000 per QALY gained. The analyses undertaken in the restricted EU-label population (symptomatic and progressive MTC plus CEA/CTN doubling times of ≤ 24 months) suggest that the ICER for vandetanib versus BSC is expected to be more favourable but still remains > £66,000 per QALY gained; these latter analyses are also subject to potential confounding as a result of open-label vandetanib use.

The AG’s economic analysis suggests that NICE’s criteria for life-extending therapies given at the end of life are not met for cabozantinib in the symptomatic and progressive MTC population, or for vandetanib in either the EU-label population or the restricted EU-label population. There is, however, uncertainty surrounding the mean survival duration of patients who do not receive either cabozantinib or vandetanib.

Conclusions

In terms of efficacy, both cabozantinib and vandetanib significantly improved PFS compared with placebo. In the absence of direct evidence comparing the two interventions, a NMA was performed. This analysis suggests that the treatment effect of both drugs on PFS is broadly similar, although these findings depend on the assumption of comparability between the EXAM trial ITT population and the ZETA trial EU-label population and should be treated with caution because of the sparsity of the network. Neither cabozantinib nor vandetanib demonstrated significant OS benefits compared with placebo and both drugs produced frequent AEs.
Based on the economic analyses undertaken by the AG, the ICERs for cabozantinib and vandetanib versus BSC in the EU-label population (symptomatic and progressive MTC) are > £138,000 per QALY gained. The analyses undertaken within the restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months) suggest that the ICER for vandetanib versus BSC is more favourable but remains > £66,000 per QALY gained. The impact of adjusting for open-label vandetanib use on the cost-effectiveness of vandetanib versus BSC is unknown.

Future research priorities include (1) primary research assessing the long-term effectiveness of cabozantinib and vandetanib within relevant subgroups, (2) reanalyses of the ZETA trial to investigate the impact of adjusting for open-label vandetanib use using appropriate statistical methods and (3) studies assessing the impact of MTC on HRQoL.

**Study registration**

This study is registered as CRD42016050403.

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