NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Cabozantinib for treating medullary thyroid cancer

The scope for this technology appraisal includes vandetanib. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

1 Recommendations

1.1 Cabozantinib is recommended, within its marketing authorisation, as an option for treating progressive medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease only if the company provides cabozantinib with the discount agreed in the patient access scheme.

Why the committee made these recommendations

Cabozantinib and vandetanib are the only systemic treatment options for unresectable, locally advanced or metastatic medullary thyroid cancer. Both drugs are currently available through the Cancer Drugs Fund for progressive and symptomatic disease. Best supportive care is the only other available option for people who cannot have cabozantinib or vandetanib.

Clinical trial evidence suggests that cabozantinib is effective in delaying disease progression compared with best supportive care, but may not prolong survival. Without reliable comparative data, it was considered that cabozantinib and vandetanib are likely to be similarly effective.

The cost-effectiveness estimates for cabozantinib compared with best supportive care and vandetanib are less than £30,000 per quality-adjusted

life year gained. Therefore, cabozantinib can be recommended as a cost-effective use of NHS resources.

2 Information about cabozantinib

Marketing authorisation indication	Cabozantinib (Cometriq) is indicated for use in 'adults with progressive, unresectable locally advanced or metastatic medullary thyroid cancer. For patients in whom rearranged during transfection mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision'.
Dosage in the marketing authorisation	140 mg taken orally once daily until patient is no longer clinically benefitting from therapy or until unacceptable toxicity occurs. Dose reductions of 100 mg or 60 mg are available if needed.
Price	£4,800 per 84x20 mg pack, 28x20 mg + 28x80 mg pack and 84x20 mg + 28x80 mg pack (excluding VAT; British national formulary July 2017). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of cabozantinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 6) considered evidence from a number of sources. See the committee papers for full details of the evidence.

The condition and current treatment

There is a clinical need for active treatments for unresectable, locally advanced or metastatic medullary thyroid cancer

3.1 Medullary thyroid cancer is rare and around 25% of cases are hereditary. The most common symptoms, such as diarrhoea and fatigue, can significantly affect patients' quality of life and wellbeing. The patient experts commented that in the absence of a cure, patients would welcome treatments that delay disease progression and control symptoms. The committee noted that cabozantinib and vandetanib are the only systemic

treatment options for unresectable, locally advanced or metastatic medullary thyroid cancer, and are only available through the Cancer Drugs Fund for people with progressive and symptomatic disease. The clinical experts explained that both treatments are associated with side effects, so not all patients can tolerate them. The only alternative for these people is best supportive care. Furthermore the toxicity profile of cabozantinib differs to that of vandetanib, so some people who can have cabozantinib may not be able to have vandetanib. The committee agreed that the relevant comparators were therefore vandetanib and best supportive care. It concluded that there is a clinical need for active treatment options for unresectable, locally advanced or metastatic medullary thyroid cancer.

Clinical trial evidence

The clinical trial evidence is relevant to clinical practice in England

3.2 Evidence for the clinical effectiveness of cabozantinib was from EXAM, a double-blind, randomised controlled trial comparing cabozantinib with placebo. The trial included 330 patients with unresectable, locally advanced, metastatic and progressive medullary thyroid cancer. The clinical experts advised that in practice, targeted treatment is only considered for progressive and symptomatic disease, so the patients in EXAM represented those that would be seen in clinical practice. The committee concluded that the EXAM trial was relevant to clinical practice in England.

Subgroups

RET mutation status is not an appropriate subgroup for consideration

3.3 The marketing authorisation for cabozantinib specifies that a possible lower benefit should be taken into account for patients in whom rearranged during transfection (RET) mutation status is negative or unknown. The committee was aware that germline RET mutation testing

is standard practice to identify hereditary disease, but that somatic RET mutation testing (to identify RET mutations in those with sporadic or non-hereditary disease) is not funded in the NHS. The clinical experts explained that RET mutation testing is not reliable enough to inform treatment decisions and remains subject to further research. The committee therefore concluded that it was not appropriate to consider the clinical or cost effectiveness of cabozantinib based on patients' RET mutation status alone, meaning that its recommendations would cover the whole population regardless of RET mutation status.

Clinical trial results

Cabozantinib improves progression-free survival compared with placebo but the exact overall survival benefit is unclear

3.4 The results of EXAM showed a statistically significant benefit for cabozantinib compared with placebo for the primary outcome of centrally assessed median progression-free survival: this was 11.2 months for cabozantinib and 4.0 months for placebo (hazard ratio [HR] 0.28; 95% confidence interval [CI] 0.19 to 0.40), with a median trial follow-up of 13.9 months. The investigator-assessed progression-free survival results were similar (median 13.8 months for cabozantinib and 3.1 months for placebo [HR 0.29; 95% CI 0.21 to 0.42]). Median overall survival was 26.6 months for cabozantinib and 21.1 months for placebo but this was not statistically significant (HR 0.85; 95% CI 0.64 to 1.12), with a median trial follow-up of 52 months. The committee noted that the trial design did not allow for cabozantinib treatment after disease progression, which it agreed reflected clinical practice. It was aware, however, that patients in both arms had subsequent cancer treatments after progression which may have confounded the overall survival results, although it was not clear to what extent. The committee concluded that cabozantinib improved progression-free survival compared with placebo, but that the exact overall survival benefit is difficult to establish.

Indirect treatment comparison

Clinical trial evidence for vandetanib is confounded by crossover

3.5 There was no head-to-head evidence comparing cabozantinib with vandetanib. Evidence for the clinical effectiveness of vandetanib was from ZETA, a double-blind, randomised controlled trial comparing vandetanib with placebo in 331 patients with unresectable, locally advanced and metastatic medullary thyroid cancer. The trial inclusion criteria were not limited to patients with progressive and symptomatic disease, so a subgroup analysis was needed to assess the treatment effect in patients that would be considered for targeted treatment in clinical practice (section 3.2), similar to the intention-to-treat population in EXAM. ZETA was designed in such a way that patients with progressed disease (at investigator-assessed progression) in the placebo arm could switch to open-label vandetanib, and those in the vandetanib arm could continue with open-label vandetanib. The committee considered that this did not represent how vandetanib would actually be used clinical practice. It also noted the substantial difference between the centrally reviewed and investigator-assessed progression-free survival results in the placebo arm (median of 16.4 months compared with 8.3 months, respectively), which suggested that some patients in the placebo arm may have crossed over to have vandetanib before their disease had progressed. The committee concluded that the overall survival results (a non-statistically significant benefit for placebo compared with vandetanib) were confounded by extensive crossover and not reliable, and that the progression-free survival results were also difficult to interpret.

Cabozantinib and vandetanib are likely to be similarly effective

3.6 The assessment group conducted an indirect treatment comparison of cabozantinib with vandetanib using a network meta-analysis, which showed that in terms of progression-free survival the 2 treatments were broadly similar. However, the assessment group did not include overall survival in the analysis because of the significant crossover in ZETA.

Because the network only contained data from the EXAM and ZETA trials and was subject to uncertainty, the assessment group did not consider the results robust enough to use in the economic model. The committee also recalled its conclusion that the progression-free survival results from ZETA were difficult to interpret (section 3.5). The clinical experts stated that in their opinion, both drugs have similar effectiveness in terms of delaying progression and controlling symptoms, although there is no evidence to show that they prolong survival. They explained that the decision about whether to use cabozantinib or vandetanib in clinical practice related more to their differing toxicity profiles than their relative effectiveness. The committee considered that an indirect comparison using data from ZETA would not be sufficiently robust to inform its decision-making. It therefore concluded that in the absence of more robust comparative data, cabozantinib and vandetanib were likely to be similarly effective.

Adverse events

Adverse events are common and the decision to use cabozantinib is based on careful consideration of the risks and benefits

3.7 All patients in EXAM had an adverse event while having cabozantinib. The committee was aware that patients with unresectable, locally advanced or metastatic medullary thyroid cancer have a substantial disease burden, demonstrated by high levels of adverse events in the placebo arm of the trial and the comorbidities of patients shown in the baseline characteristics data. The patient expert described side effects such as frequent diarrhoea, rash and fatigue, but considered that the disease would have had a more severe effect without treatment. The clinical experts explained that treatment toxicities tend to occur soon after treatment starts, and that for most patients the dosage is reduced after the initial treatment period. The experts explained the importance of balancing the risks and benefits when considering starting treatment with cabozantinib, and that treatment is usually started only when the disease

becomes symptomatic to the extent that the benefits of treatment outweigh the burden of side effects.

Economic model

The assessment group's economic model is appropriate for decision-making

3.8 The assessment group presented 3 analyses for the cost effectiveness of cabozantinib compared with best supportive care and vandetanib, using a partitioned survival model:

- a pairwise comparison of cabozantinib and best supportive care
- an incremental comparison of all treatment options using EXAM trial data, applying the vandetanib progression-free survival treatment effect from ZETA to the placebo arm of EXAM and assuming the same overall survival benefit for both vandetanib and cabozantinib
- an incremental comparison of all treatment options using EXAM trial data (assuming the same progression-free and overall survival benefit for both vandetanib and cabozantinib).

The committee had agreed that the results of the ZETA trial were not sufficiently robust for decision-making, and that cabozantinib and vandetanib were likely to be similarly effective (section 3.6). It therefore considered that the most appropriate incremental analysis of all treatment options was the analysis that used treatment effect data from the EXAM trial and assumed the same progression-free and overall survival benefit for both vandetanib and cabozantinib.

Costs

3.9 Monitoring costs used by the assessment group were appropriate The assessment group assumed monitoring costs in the subsequent years after the first year to include 6 outpatient appointments per year. The clinical experts confirmed that in clinical practice patients were seen about once a month, although this varies because open-access clinics are also available. Having heard all relevant clinical expert advice, the committee

concluded that the monitoring costs estimated by the assessment group were reasonable.

Utility values

Utility values for medullary thyroid cancer are unknown but the approach used by the assessment group is acceptable

3.10 There are no direct estimates of health utilities for people with medullary thyroid cancer. The assessment group stated its preference to use the same source of data for both pre- and post-progression utility values, and so used values from Fordham et al. (2015), a study of differentiated thyroid cancer, for both. The committee noted that differentiated thyroid cancer was different to medullary thyroid cancer, but acknowledged that the only other potentially relevant study available was in melanoma, which is more uncertain. It noted that Fordham et al. had been used in a previous health technology assessment submission relating to thyroid cancer, and heard from the assessment group that because of low post-progression utility values it was the most favourable source of utility data for cabozantinib. The committee agreed that in the absence of any data relevant to medullary thyroid cancer it would accept the assessment group's estimates.

Cost-effectiveness estimates

The most plausible ICER for cabozantinib is within the range normally considered cost effective

3.11 Including the updated confidential patient access scheme discount, the probabilistic incremental cost-effectiveness ratios (ICERs) for cabozantinib compared with best supportive care and with vandetanib were less than £30,000 per quality-adjusted life year (QALY) gained (the exact ICERs are commercial in confidence and cannot be reported here). The committee concluded that the most plausible ICER was within the

range that NICE normally considers to be a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained).

Uncaptured benefits

There are no health-related benefits that are not captured in the analyses

3.12 The committee recognised that medullary thyroid cancer is rare, and that cabozantinib is 1 of only 2 targeted treatments available in this indication. However, it heard from the clinical experts that the survival benefit of both drugs is unknown, and so treatment aims to delay disease progression and improve quality of life. The committee acknowledged that although cabozantinib may work well for some people, for many others there may be a substantial side-effect burden. It therefore concluded that there are no additional health-related quality-of-life benefits not already captured in the QALY calculations.

End of life

Cabozantinib meets the end-of-life criterion for extension to life

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. The EXAM trial showed overall survival benefit of more than 3 months for cabozantinib compared with placebo. The model estimated a mean survival benefit of about 7 months, and so the committee agreed that the end-of-life criterion for extension to life was met for cabozantinib.

Cabozantinib does not meet the short life expectancy criterion so the end-of-life criteria do not apply

3.14 For the short life expectancy criterion, the assessment group's model predicted a mean overall survival with best supportive care of over 24 months (about 47 months in the base-case analysis), regardless of the parametric function used to extrapolate survival. The committee was aware that in EXAM, median overall survival in the placebo arm was 21

months. It acknowledged that some patients with unresectable, locally advanced or metastatic medullary thyroid cancer live for a long time. This may have skewed the median estimate, and may explain the difference between the median and mean estimates. Having considered that it had not seen any reliable data on which to consider any subgroups, the committee agreed that the mean estimate from the model was more relevant for end-of-life considerations. Taking this into account, the committee concluded that cabozantinib did not meet the criterion for short life expectancy, and therefore the end-of-life criteria did not apply.

Recommendations

3.15 The committee recommended cabozantinib as a cost-effective use of NHS resources for treating medullary thyroid cancer, because the ICERs for cabozantinib compared with best supportive care and vandetanib were within the range that NICE normally considers to be a cost-effective use of NHS resources.

Equalities

3.16 No equality issues were identified.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources

for it within 2 months of the first publication of the final appraisal determination.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has medullary thyroid cancer and the doctor responsible for their care thinks that cabozantinib is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 The Department of Health and Ipsen have agreed that cabozantinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, appraisal committee D
February 2018

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Technical lead

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