NICE National Institute for Health and Care Excellence

NICE guidance

Vandetanib for treating medullary thyroid cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Vandetanib is not recommended, within its marketing authorisation, for treating aggressive and symptomatic medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease.

1.2 This recommendation is not intended to affect treatment with vandetanib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Vandetanib and cabozantinib are the only systemic treatment options for unresectable, locally advanced or metastatic medullary thyroid cancer. Best supportive care is the only other available option for people who cannot have vandetanib or cabozantinib.

Clinical trial evidence suggests that vandetanib may delay disease progression compared with best supportive care, but the benefit is uncertain. The evidence about whether vandetanib increases the overall length of time people live is unreliable. Clinical experts consider that vandetanib and cabozantinib are similarly effective, so more robust data from a cabozantinib trial are used because of the uncertainties in the evidence.

Cost-effectiveness estimates for vandetanib compared with either best supportive care or cabozantinib are much higher than what NICE normally considers an acceptable use of NHS resources. Vandetanib does not meet NICE's end-of-life or Cancer Drugs Fund criteria. Therefore, it cannot be recommended as a cost-effective use of NHS resources.

2 Information about vandetanib

Marketing authorisation indication

2.1 Vandetanib (Caprelsa, Sanofi) 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 mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decisions.

Dosage in the marketing authorisation

2.2 300 mg taken orally once daily until disease progression or until the benefits of treatment continuation no longer outweigh its risk. Dose reductions of 200 mg or 100 mg are available if needed.

Price

2.3 £5,000 per 30×300-mg pack, or £2,500 per 30×100-mg pack (excluding VAT; British national formulary July 2017). The company has a commercial arrangement, which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (see section 4) 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 impair patients' quality of life and wellbeing. The patient experts commented that because there was no cure, patients would welcome treatments that delay disease progression and control symptoms. The committee noted that vandetanib and cabozantinib are the only systemic treatment options for unresectable, locally advanced or metastatic medullary thyroid cancer. The clinical experts explained that both treatments are associated with side effects, so not all patients will be able to tolerate them. The only alternative for these people is best supportive care. Also, the toxicity profile of vandetanib differs from that of cabozantinib, so some people who can have vandetanib may not be able to have cabozantinib. The committee agreed that the relevant comparators were therefore cabozantinib 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 population is broader than the marketing authorisation population so the company presented subgroup analyses

3.2 Evidence for the clinical effectiveness of vandetanib was from ZETA, a

double-blind, randomised controlled trial comparing vandetanib with placebo. The trial included 331 patients with unresectable, locally advanced or metastatic medullary thyroid cancer. The clinical experts advised that in practice, targeted treatment is only considered for progressive and symptomatic disease. They explained that progressive and symptomatic disease was considered to be the same as aggressive and symptomatic disease, for which vandetinib has a marketing authorisation and is available through the Cancer Drugs Fund. Because the trial's inclusion criteria were not restricted to progressive disease, the trial included patients with less severe disease than covered by the marketing authorisation. Therefore the trial included patients who would not be considered for targeted treatment in clinical practice. To address this, the company presented clinical effectiveness data for 2 subgroups from ZETA:

- a marketing authorisation subgroup, comprising 186 patients with progressive and symptomatic disease (the 'MA subgroup')
- a subgroup comprising patients from the MA subgroup who also had calcitonin (CTN) and carcinoembryonic antigen (CEA) doubling times of 24 months or less (the 'restricted subgroup').

The MA subgroup best reflected the population having treatment in NHS clinical practice

3.3 The company considered the restricted subgroup to represent patients in most need of treatment, and therefore those seen in NHS clinical practice. It noted that the summary of product characteristics emphasised the importance of limiting treatment with vandetanib to patients who are in real need, and that 'rate of change in biomarker levels such as of CTN and/or CEA…might help to identify not only patients in need for treatment but also the optimal moment to commence treatment'. The clinical experts explained that CTN and CEA biomarkers are regularly monitored, can be prognostic and may contribute to a decision to carry out imaging. But the decision to start treatment is based on radiological progression and when the disease becomes symptomatic. The company acknowledged this in its response to consultation on the assessment group's report. The clinical experts

considered that it was likely that patients with progressive and symptomatic disease in clinical practice would have tumour biomarker doubling times of 24 months or less. However, the committee considered it clinically inappropriate to wait for biomarker trends before starting treatment for people with progressive and symptomatic disease. The assessment group considered that the baseline characteristics of the MA subgroup reflected patients seen in clinical practice. Having heard from the clinical experts and the assessment group, the committee concluded that the MA subgroup best reflected patients having treatment in practice.

Other subgroups

RET mutation status is not an appropriate subgroup for consideration

3.4 The marketing authorisation for vandetanib 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 needs further research. The committee therefore concluded that it was not appropriate to consider the clinical or cost effectiveness of vandetanib based on patients' RET mutation status alone, so its recommendations would cover the whole population regardless of RET mutation status.

Clinical trial results

In the MA subgroup, vandetanib improves progression-free survival but the exact benefit is uncertain and the overall survival results are confounded

3.5 The ZETA results showed that the overall survival benefit for vandetanib compared with placebo in the MA subgroup analysis was negative, but not statistically significant, with a median follow-up of 105 months (results are academic in confidence and cannot be reported here). ZETA was designed so 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. A large proportion of patients switched to open-label vandetanib after their disease progressed (80% of patients having placebo and 44% of patients having vandetanib), and neither the company nor the assessment group were able to adjust the trial results for treatment switching. This meant that the trial results were more likely to show the effect of immediate vandetanib compared with delayed vandetanib rather than vandetanib compared with placebo. The committee considered that this did not represent how the drug would be used in clinical practice and that the overall survival results presented were confounded and not reliable. For the primary outcome of centrally reviewed median progression-free survival, the results showed a statistically significant benefit for vandetanib compared with placebo, which was 28.0 months for vandetanib and 16.4 months for placebo (hazard ratio [HR] 0.47; 95% confidence interval [CI] 0.29 to 0.77), with a median trial follow-up of 24 months. The investigator-assessed median progression-free survival was 22.1 months for vandetanib and 8.3 months for placebo (HR 0.33; 95% CI 0.20 to 0.53). The committee considered that the substantial difference between the centrally reviewed and investigator-assessed results in the placebo arm (median of 16.4 months compared with 8.3 months) introduced further uncertainty into the evidence. The committee therefore concluded that vandetanib improved progression-free survival compared with placebo, but the exact benefit was difficult to establish, and the overall survival results were confounded.

In the restricted subgroup, overall survival results adjusted for treatment switching are not robust

3.6 In additional evidence submitted after consultation, the company presented overall survival results for the restricted subgroup that were adjusted for treatment switching (crossover) in the placebo group using the rank-preserving structural failure time (RPSFT) method. The company used a covariate adjustment approach to address imbalances in the treatment arms relating to disease duration and whether patients had previous systemic treatment. The assessment group considered that the results of the crossover-adjusted analysis should be interpreted with caution because:

- RPSFT is a randomisation-based crossover-adjustment method but randomisation was broken in the subgroup analysis
- the common treatment effect assumption may not be plausible
- covariates other than those chosen by the company may not be balanced between the treatment groups (for example RET mutation status, performance status, tumour burden)
- the small number of patients results in uncertain survival estimates
- the large proportion of patients in the vandetanib group having vandetanib after disease progression may exaggerate the reduction in placebo benefit generated by the crossover-adjustment method

- other technical methods used, such as those for estimating confidence intervals, were questionable and could not be verified by the assessment group without further information.

  The committee noted that none of the results, with and without the covariate adjustment, were statistically significant (results are academic in confidence and cannot be reported here). Also, in the restricted subgroup the hazard ratio for overall survival in the crossover- and covariate-adjusted analysis showed a greater benefit than the hazard ratio for progression-free survival (academic in confidence), which the committee agreed was implausible. The committee did not have confidence in the reliability of the results of the crossover-adjusted analysis. Therefore it concluded that they were not sufficiently robust for decision making.

Evidence from ZETA is highly uncertain and not suitable for decision making

3.7 The committee considered the advice from NICE's guide to the methods of technology appraisal that when considering subgroup analyses, it should take specific note of the biological or clinical plausibility of a subgroup effect in addition to the strength of the evidence in favour of such an effect. The committee noted that subgroup analysis according to CTN and CEA doubling times was prespecified in the ZETA trial protocol, alongside a number of other subgroups. The committee noted that the very small numbers of patients included in the restricted subgroup of ZETA made any survival estimates imprecise, and any analysis subject to significant uncertainty. The committee also noted that the summary of product characteristics suggested that rate of change in biomarkers such as CTN or CEA or both might help identify patients in need of treatment. However, the company's subgroup analyses only included patients from ZETA who had both CTN and CEA doubling times of 24 months or less, meaning that patients with missing CTN or CEA data were excluded. Because clinical advice suggested that CTN was the more clinically relevant biomarker and an increase in 1 biomarker indicates an increase in the other, the assessment group re-ran the unadjusted subgroup analysis to include patients with missing CEA data. This analysis suggested a much lower treatment benefit with vandetanib than that shown in the subgroup that included only patients with CTN

and CEA doubling times of 24 months or less. The committee considered that this further increased uncertainty about the treatment effect in the restricted subgroup. In addition, the company had reported that a crossover-adjusted analysis had not been attempted in the MA subgroup because initial statistical analysis showed a negative treatment effect for vandetanib compared with placebo in this group. The committee was concerned by the plausibility of the large treatment effect shown by the crossover-adjusted results in the restricted subgroup when a negative effect had been shown in the larger MA subgroup, when the patients in both subgroups had progressive and symptomatic disease. Therefore, given the smaller size of the restricted subgroup, the extensive crossover in ZETA, the limitations with the crossover adjustments (see section 3.5 and section 3.6) including the implausibility of the results, the committee did not consider the evidence showing a differential treatment effect for the restricted subgroup to be robust. Overall, because the restricted subgroup was not considered to best reflect clinical practice in the NHS (see section 3.3) and the results of ZETA were not robust in either subgroup, the committee could not use evidence from ZETA in its decision making.

Indirect treatment comparison

Clinical trial evidence for cabozantinib is robust and reflects clinical practice

3.8 There was no head-to-head evidence comparing vandetanib with cabozantinib. Evidence for the clinical effectiveness of cabozantinib was from EXAM, a double-blind, randomised controlled trial comparing cabozantinib with placebo in 330 patients with unresectable, locally advanced or metastatic, progressive medullary thyroid cancer. The committee recalled the clinical experts' advice that in practice, targeted treatment is only considered for progressive and symptomatic disease (see section 3.2), and agreed that the patients in EXAM represented those who would be seen in clinical practice. The results of EXAM showed a statistically significant progression-free survival benefit for cabozantinib compared with placebo (median of 11.2 months compared with 4.0 months [HR 0.28; 95% CI 0.19 to 0.40]; investigator-assessed

results were similar) and an overall survival benefit that was not statistically significant (median of 26.6 months compared with 21.1 months [HR 0.85; 95% CI 0.64 to 1.12]). The committee noted that EXAM did not allow for cabozantinib treatment after disease progression, which it agreed reflected clinical practice and reduced the risk of bias compared with ZETA (see section 3.5). It also noted that progression-free survival in the placebo arm was short, and indeed shorter than in the placebo arm of ZETA (both subgroups). This suggested that these patients had a worse prognosis than those in both ZETA subgroups and were in most need of treatment. It was aware, however, that patients in both arms of the trial had subsequent cancer treatments after progression that may have confounded the overall survival results, although it could not be certain to what extent. The committee concluded that the evidence for cabozantinib was robust and reflected clinical practice.

Vandetanib and cabozantinib are likely to be similarly effective

3.9 The assessment group did an indirect treatment comparison of vandetanib with cabozantinib using a network meta-analysis, which showed that for 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 EXAM and ZETA 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 results of ZETA were not sufficiently robust to be used in decision making (see section 3.7). The clinical experts stated that in their opinion, both drugs have similar effectiveness in 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 vandetanib or cabozantinib in clinical practice was more about their different 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 because there were no robust comparative data and based on clinical advice, vandetanib and cabozantinib were likely to be similarly effective.

Adverse events

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

3.10 Almost all patients in ZETA (99.6%) had an adverse event while having vandetanib. The committee was aware that patients with unresectable, locally advanced or metastatic medullary thyroid cancer have a substantial disease burden. This was shown by high levels of adverse events in the placebo arms of the trial and the comorbidities of patients at baseline. The patient expert described side effects such as frequent diarrhoea, rash and fatigue, but considered that the disease would have a more severe effect without treatment. The clinical experts explained that adverse events tend to occur soon after treatment starts, and 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 treatment with vandetanib, and that treatment is usually started only when the disease becomes symptomatic so that the benefits of treatment outweigh the burden of side effects.

Economic models

The company's economic model for vandetanib is not appropriate for decision making

3.11 Both the company's original economic model for vandetanib and its updated analysis (including crossover-adjusted results and a revised commercial arrangement) were based only on the restricted subgroup. The assessment group noted that the overall survival extrapolation across the time horizon had been done incorrectly because the parametric curves had been fitted to the crossover-adjusted data as if it were actual trial data rather than modelled data from the crossover-adjustment method. The results therefore did not fully account for the uncertainty that arises from using crossover- and covariate-adjusted data. It noted a further error about the application of costs after discontinuing vandetanib. Having previously concluded that the MA

subgroup best reflected the population having treatment in clinical practice in the NHS (see section 3.3), and that the ZETA trial results (including crossover-adjusted analysis) were not appropriate for decision making (see section 3.6 and section 3.7), the committee concluded that the company's economic model for vandetanib was not appropriate for decision making.

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

3.12 Given the assessment group's concerns about the company's economic model, it ran its cost-effectiveness analysis in its original model, updating it to take account of the company's crossover-adjusted results from ZETA and revised commercial arrangement. The assessment group did an analysis comparing vandetanib with cabozantinib and best supportive care using EXAM data (assuming the same progression-free and overall survival benefit for both vandetanib and cabozantinib). The committee concluded that this provided a more robust cost-effectiveness estimate for vandetanib than estimates using the ZETA trial results. The committee concluded that the assessment group's model was therefore appropriate for decision making.

Costs

Analyses including treatment after progression do not reflect clinical practice so are not appropriate

3.13 The company's new base-case analysis did not include the costs of vandetanib after progression because the analysis had been adjusted for patients switching from placebo to vandetanib when their disease progressed. However, the assessment group considered that patients in the vandetanib arm having vandetanib after disease progression would be likely to have some benefit and so the costs should also be included. The assessment group explained that because this analysis used a partitioned survival model, after disease progression patients could only transition to the death state. This meant that treatment after disease progression continued until death. The committee noted that this

resulted in an unrealistic overestimation of costs. The clinical experts stated that if imaging showed disease progression, clinicians would normally stop treatment. They explained that treatment may continue if imaging showed only 1 lesion growing and others to be stable, but emphasised that this was uncommon and treatment would only continue for another 1 or 2 months. Because treatment after disease progression does not reflect how the drugs are used in clinical practice, the committee concluded that analyses including treatment with vandetanib after disease progression were not appropriate for decision making.

The assessment group's method of dealing with treatment discontinuation in its model is acceptable

3.14 The assessment group considered that the company's method of dealing with treatment discontinuation before disease progression in its original model underestimated costs. This was because it removed all the costs of vandetanib from the proportion of patients who stopped treatment before progression. The assessment group stated that it was unrealistic that no vandetanib costs would be incurred for patients who stopped treatment, particularly given that in clinical practice vandetanib may be stopped early because of toxicity and restarted again later. In its revised model, the company applied vandetanib costs before progression at an increasing rate in the first year, and no costs were incurred thereafter. The assessment group instead applied half the costs of vandetanib to the proportion of patients who stopped treatment before progression. The committee noted that both the company's and assessment group's methods were arbitrary, but agreed that it could not be certain that no costs would be incurred after the first year for patients who stopped treatment before the disease progressed. Because there were no data showing when patients stopped treatment, or if they restarted treatment later, the committee accepted the assessment group's method as a more acceptable approach.

Utility values

Utility values for medullary thyroid cancer are unknown but the

assessment group's approach is the most acceptable

3.15 There are no direct estimates of health utilities for people with medullary thyroid cancer. For utility values before progression, the company mapped data from ZETA to the EQ-5D; for utility values after progression it used data from Beusterien et al. (2009), a study of melanoma. The assessment group preferred to use the same source of data for utility values both before and after progression, 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 less generalisable. It noted that Fordham et al. had been used in a previous appraisal submission for thyroid cancer. The committee agreed that it was appropriate to use the same source of data for utility values before and after disease progression and because there were no other data relevant to medullary thyroid cancer it would therefore accept the assessment group's estimates.

Cost-effectiveness estimates

The most plausible scenario to assess the cost effectiveness of vandetanib uses EXAM data but some uncertainty remains

3.16 The committee had concluded that the ZETA trial results were not appropriate for decision making (see section 3.7 and section 3.11). It recalled that data from EXAM were robust (see section 3.8), but noted that the analysis using these data relied on strong assumptions about the similar effectiveness of vandetanib and cabozantinib. However, having heard clinical advice that the choice of drug is based more on adverse event profile than on effectiveness, and that clinicians generally do not prefer 1 drug over the other, the committee had concluded that vandetanib and cabozantinib were likely to be similarly effective (see section 3.9). Therefore, although the assumption of equal progression-free and overall survival benefit for vandetanib and cabozantinib was uncertain, because there was no other appropriate analysis for vandetanib, the committee concluded that the analysis using the EXAM

data represented the most reliable scenario to assess the cost effectiveness of vandetanib.

The most plausible ICERs are higher than £50,000 per QALY gained

3.17 Including the confidential commercial arrangements for vandetanib and cabozantinib and using EXAM data, the probabilistic incremental cost-effectiveness ratio (ICER) in the incremental analysis of vandetanib compared with cabozantinib was much higher than £100,000 per quality-adjusted life year (QALY) gained (the exact ICER is commercial in confidence and cannot be reported here). The committee was aware that some people who can have vandetanib may not be able to have cabozantinib and that best supportive care was also a relevant comparator (see section 3.1). The probabilistic ICER for a pairwise comparison of vandetanib with best supportive care, using EXAM data, was higher than £50,000 per QALY gained (the exact ICER is commercial in confidence and cannot be reported here).

Uncaptured benefits

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

3.18 The committee acknowledged the company's comments that vandetanib was the first systemic therapy for medullary thyroid cancer to gain a marketing authorisation, and that the disease is rare. It considered however that although vandetanib may work well for some people, others may have substantial side effects. The committee concluded that all relevant health-related quality-of-life benefits were captured in the economic modelling and that there were no additional benefits not already captured in the QALY calculations.

End of life

Vandetanib meets the extension to life criterion

3.19 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The ZETA trial results were confounded and the crossover-adjusted analysis was not considered robust (see section 3.5 and section 3.6) so the committee considered the survival estimates from EXAM. EXAM showed overall survival benefit of more than 3 months for cabozantinib compared with placebo, and the model estimated a mean survival benefit of about 7 months. So the committee agreed that cabozantinib met the end-of-life criterion for extension to life (see NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer). Given the expected similarity in the drugs' efficacy (see section 3.9), the committee concluded that vandetanib could also be considered to meet this criterion.

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

3.20 For the short life expectancy criterion, the company's new analysis predicted a mean survival with best supportive care of less than 24 months in the restricted group. However, the committee had concluded that this analysis was not sufficiently robust for decision making (see section 3.6 and section 3.7), and that data on cabozantinib from EXAM were a more reliable source of survival estimates in the population that reflected clinical practice (see section 3.8). The committee was aware that the modelled mean and median overall survival estimates were 47 and 21 months respectively and that some patients with unresectable, locally advanced or metastatic medullary thyroid cancer live for a long time (see NICE's technology appraisal guidance on cabozantinib). The committee had not seen any new evidence that was robust enough to change its conclusion that vandetanib did not meet the short life expectancy criterion. It agreed, on balance, that the end-of-life criteria did not apply. The committee concluded that the most plausible ICERs for vandetanib were much

higher than the range normally considered cost effective, that is £20,000 to £30,000 per QALY gained. Therefore vandetanib could not be recommended for routine use in the NHS.

Cancer Drugs Fund

The company proposed that vandetanib could be used in the Cancer Drugs Fund for data collection

3.21 Having concluded that vandetanib could not be recommended for routine use, the committee then considered if it could be recommended for treating medullary thyroid cancer within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The company expressed an interest in vandetanib being considered for use in the Cancer Drugs Fund. It proposed that data on the baseline characteristics of patients could be collected to address uncertainty about the nature of the patient population having vandetanib in clinical practice in the NHS: specifically whether patients had progressive and symptomatic disease (the MA subgroup), or progressive and symptomatic disease and CTN or CEA doubling times of 24 months or less (the restricted subgroup).

Vandetanib does not meet the criteria for inclusion in the Cancer Drugs Fund

3.22 The committee had previously agreed that CTN or CEA doubling times were not used to start treatment with vandetanib (see section 3.3). It considered there was limited benefit to the NHS from collecting data on patient characteristics for CTN or CEA doubling times. The key uncertainties in the clinical-effectiveness evidence for vandetanib were about overall survival benefit, and the committee considered that not enough patients would have vandetanib for data collection to address this uncertainty. The committee also did not consider that there was plausible potential to satisfy the criteria for routine use because the most plausible ICERs were much higher than those NICE normally considers to be a cost-effective use of NHS resources. Therefore it concluded that

vandetanib did not meet the criteria for inclusion in the Cancer Drugs Fund.

Conclusions

The disease is rare, but the cost-effectiveness estimates are too high to justify considerable deviation from NICE principles

3.23 The committee acknowledged the small patient population covered by the marketing authorisation for vandetanib. It noted the advice from NICE's social value judgements: principles for the development of NICE guidance, that NICE should evaluate drugs to treat rare conditions in the same way as any other treatment. In response to consultation, the company highlighted that the social value judgements advice specifically refers to orphan drugs, whereas medullary thyroid cancer was very rare and would be classed as 'ultra-orphan' because it affects fewer than 1 in 50,000 people. The committee was aware that despite the ultra-orphan status of medullary thyroid cancer, vandetanib had not met the criteria for consideration through the NICE highly specialised technologies process because the disease is not chronic, does not need lifelong treatment and is not treated exclusively within a highly specialised service. When developing the social value judgements, the Citizens Council considered that rarity alone should not justify accepting high ICERs, but that the committee could take into account other factors such as disease severity in its decision making. The committee acknowledged the difficulty of appraising drugs for very rare conditions, and the severity of medullary thyroid cancer. It was aware that vandetanib was available through the Cancer Drugs Fund based on the same trial evidence reviewed by the appraisal committee, and acknowledged the importance for patients with specific characteristics to have a choice of treatment. However, it considered that the ICERs were too high to justify considerable deviation from NICE principles in terms of what is normally considered a cost-effective use of NHS resources.

Vandetanib cannot be considered cost effective in a subgroup;

therefore it is not recommended

3.24 The committee considered whether vandetanib could be considered cost effective in a subgroup of patients covered by the marketing authorisation:

- CTN and CEA doubling times of 24 months or less: the committee had concluded that patients with progressive and symptomatic disease and CTN and CEA doubling times of 24 months or less did not reflect patients in clinical practice because the decision to start treatment was not based on biomarker trends, although it accepted that some NHS patients' disease would meet this criterion. However, the committee did not consider it appropriate to wait for biomarker trends before starting treatment for people with progressive and symptomatic disease (see section 3.3). It concluded that a change in practice could not reasonably be expected when progressive and symptomatic disease remained the primary driver of treatment, notwithstanding the uncertainty of the effectiveness data in this group (see section 3.6 and section 3.7).

- RET mutation status: the committee recalled its conclusion that it was not appropriate to consider the clinical or cost effectiveness of vandetanib based on patients' RET mutation status alone (see section 3.4).

- Patients who cannot have cabozantinib: the committee recognised that there was an unmet need for patients who could not tolerate cabozantinib, but it had seen no evidence for the effectiveness of vandetanib in this group. Also, the ICER for vandetanib compared with best supportive care was higher than the range normally considered cost effective, that is £20,000 to £30,000 per QALY gained (see section 3.17). Therefore vandetanib could not be recommended for routine use in the NHS in this subgroup.

  Given the lack of robust effectiveness evidence presented for vandetanib, the committee had accepted that vandetanib was likely to be similarly effective to cabozantinib based on clinical opinion. However, it concluded that even having accepted this, the ICER for vandetanib was much too high to consider it a cost-effective use of NHS resources. Therefore the committee could not recommend it for treating medullary thyroid cancer, because the most plausible ICER was much higher than £20,000 to £30,000 per QALY gained.

4 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.

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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