

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma

1 Recommendations

- 1.1 Cobimetinib in combination with vemurafenib is not recommended within its marketing authorisation for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation.
- 1.2 This guidance is not intended to affect the position of patients whose treatment with cobimetinib in combination with vemurafenib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Cobimetinib (Cotellic, Roche) is an inhibitor of MEK 1 and MEK 2 kinases. Vemurafenib (Zelboraf, Roche) is an inhibitor of the BRAF protein. Both are taken as tablets. The BRAF protein and MEK 1 and 2 kinases are part of the same cell-signalling pathway. Inhibiting these proteins stops proliferation and survival of melanoma cells.
Marketing authorisation	Cobimetinib in combination with vemurafenib is indicated for the treatment of unresectable or metastatic melanoma in adults with a BRAF V600 mutation. Vemurafenib has a marketing authorisation for use as monotherapy for this indication. Cobimetinib does not have a marketing authorisation for use as monotherapy.

<p>Adverse reactions</p>	<p>The following common adverse reactions affect more than 1 in 5 people: diarrhoea, rash, nausea, vomiting, fever, light sensitivity reaction, abnormal liver function tests, and abnormal results for an enzyme related to muscle breakdown (creatine phosphokinase). Less common adverse reactions include swelling of the retina (retinopathy) or effects on cardiac function (reduced left ventricular ejection fraction). People taking cobimetinib plus vemurafenib should be monitored for new and worsening visual disturbances, and for heart function. For full details of adverse reactions and contraindications, see the summary of product characteristics.</p>
<p>Recommended dose and schedule</p>	<p>Cobimetinib: 3 tablets per day for 21 days followed by a 7-day break (days 22 to 28) before the next cycle is started.</p> <p>Vemurafenib: 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg).</p>
<p>Price</p>	<p>The company has stated that the cost of cobimetinib (excluding VAT) is £4,275.67 for a 63-tablet pack of 20 mg tablets.</p> <p>The company has agreed a patient access scheme with the Department of Health for vemurafenib as monotherapy. It is provided to the NHS with a simple discount to the list price of vemurafenib, 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.</p> <p>If cobimetinib with vemurafenib had been recommended, the company would have provided vemurafenib for use in combination with cobimetinib with the same discount as that agreed for vemurafenib as monotherapy. Costs may vary in different settings because of negotiated procurement discounts.</p>

3 Evidence

The appraisal committee ([section 6](#)) considered evidence submitted by the company and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of cobimetinib in combination with vemurafenib, having considered evidence on the nature of advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma and the value placed on the benefits of cobimetinib plus vemurafenib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management of advanced melanoma

- 4.1 The committee discussed the clinical need of people with advanced BRAF V600 mutation-positive melanoma. It heard from the patient expert that the symptoms of advanced melanoma vary, partly depending on the sites of metastases, but they can be severe and wide ranging. Symptoms such as pain can have a major effect on quality of life. The patient expert explained that having a choice of effective treatments to switch to if there are side effects is greatly valued by people. However, prolonging survival is of such importance to people that many would be willing to accept considerable side effects if their chance of survival is improved. The committee concluded that the symptoms and effect on quality of life vary between people with advanced melanoma, and that people welcome having a choice of life-extending treatment options available to them.
- 4.2 The committee noted that people with BRAF V600 mutation-positive advanced melanoma could have an immunotherapy agent (ipilimumab, pembrolizumab or nivolumab) or a targeted BRAF inhibitor (vemurafenib or dabrafenib). The clinical expert stated that about 70% of people with BRAF V600 mutation-positive disease have immunotherapy first line because of the long-term benefit that has been shown in trials. BRAF inhibitors would usually be used first line only for people with rapidly progressing disease, high disease burden or elevated LDH (lactate

dehydrogenase) levels, when a rapid onset of action is needed. BRAF inhibitors are considered to be equally effective whether given before or after immunotherapy. The committee concluded that most people with BRAF V600 mutation-positive melanoma would have a targeted therapy at some point in their treatment.

Comparators

- 4.3 The clinical expert stated that the 2 comparators listed in the scope, vemurafenib and dabrafenib, are considered to have similar clinical effectiveness but some people will experience adverse reactions with either drug. The clinical expert noted that photosensitivity and rashes are more common with vemurafenib than dabrafenib, so dabrafenib tends to be prescribed more often, although the clinical expert also stated that fevers are less common with vemurafenib than dabrafenib. Because it is not possible to predict who will have adverse reactions with either drug before starting treatment, it is valuable to have 2 BRAF inhibitors available for patients. The committee noted that NICE recently recommended another combination treatment ([trametinib](#), a MEK inhibitor, in combination with dabrafenib) which has a similar mechanism of action to cobimetinib plus vemurafenib. However, it noted that the final guidance had not yet been issued and this treatment combination could not be considered established practice. The clinical expert stated that if the NHS routinely funded a combination of a BRAF inhibitor plus a MEK inhibitor this would be preferred over BRAF-inhibitor monotherapy, because of the longer survival shown in trials. The committee recognised that the treatment options for melanoma are likely to increase in the near future but concluded that, at present, the comparators in the scope issued by NICE were appropriate for its decision-making.

Clinical effectiveness

Evidence from the coBRIM trial

- 4.4 The committee discussed the generalisability of the clinical evidence from the coBRIM trial that compared cobimetinib plus vemurafenib with vemurafenib plus placebo. It noted that most patients in coBRIM had not previously had an immunotherapy agent, and in this regard the population in coBRIM was different to the population who would have cobimetinib plus vemurafenib in clinical practice in England. However, the committee took into account the comments from the clinical expert that the clinical effectiveness of cobimetinib plus vemurafenib is not expected to differ if it is taken before or after an immunotherapy agent. It was therefore satisfied that the clinical-effectiveness evidence from coBRIM is generalisable to melanoma that has or has not been treated with immunotherapy.
- 4.5 The committee examined the results of coBRIM. It noted that, at the time of the latest data cut-off in the company's submission, the combination of cobimetinib plus vemurafenib increased overall survival by 4.9 months compared with vemurafenib alone (median survival 22.3 months and 17.4 months respectively). The committee concluded that cobimetinib plus vemurafenib is clinically effective compared with vemurafenib alone.

Company's network meta-analyses

- 4.6 The committee considered the company's indirect comparison of cobimetinib plus vemurafenib with dabrafenib alone, noting that there were no direct head-to-head clinical trials comparing cobimetinib plus vemurafenib with dabrafenib. It agreed with the evidence review group (ERG) that the rationale and methods for the indirect comparison were appropriate. The committee noted the ERG's comments that the trials in the network were broadly comparable, based on selected characteristics, but the potential heterogeneity of the trials in the network had not been fully explored in the company's submission. The committee noted that the

trials comparing dabrafenib with dacarbazine (BREAK-3) and vemurafenib with dacarbazine (BRIM-3), which were included in the meta-analysis, included similar populations to coBRIM but there were differences in the trial designs. For example, BREAK-3 and BRIM-3 allowed crossover from the dacarbazine arm to the dabrafenib or vemurafenib arm, but coBRIM did not allow crossover between treatment arms. The committee noted, and the company confirmed, that crossover had not been adjusted for in the network meta-analysis. The committee agreed with the ERG that the clinical effectiveness of dabrafenib and vemurafenib as monotherapies may have been underestimated in the network. The committee also noted that there was only 1 trial for each comparator in the network, which increased its uncertainty in the results. It concluded that taking into account the unexplored potential heterogeneity between the trials, and the limited number of trials in the network, the indirect comparison of cobimetinib plus vemurafenib with dabrafenib was associated with considerable uncertainty.

- 4.7 Given the uncertainty surrounding the indirect comparison, the committee discussed whether it would be more appropriate to assume that the BRAF inhibitors (dabrafenib and vemurafenib) were sufficiently similar in clinical effectiveness to be considered clinically interchangeable. In response to the appraisal consultation document, the company stated that it considered that the results from the indirect comparison were more robust for the comparison with dabrafenib than an assumption of clinical equivalence between the 2 drugs. The committee agreed that there may be some differences in the tolerability of the 2 drugs, but noted that in the company's modelled base case, the total estimated life years and the total quality-adjusted life years (QALYs) for cobimetinib plus vemurafenib compared with vemurafenib or dabrafenib alone were similar (3.392 life years for vemurafenib compared with 3.281 for dabrafenib, and 2.489 QALYs for vemurafenib compared with 2.417 for dabrafenib). The committee considered that the company's modelling did not contradict the

committee's preferred assumption of similar efficacy of vemurafenib and dabrafenib monotherapies, and this was also consistent with what the committee had heard from the clinical expert (see section 4.3). The committee therefore concluded that the most robust comparative data on which to base its decision were from the coBRIM trial of cobimetinib plus vemurafenib compared with vemurafenib alone, and that it would be reasonable to assume that a comparison of cobimetinib plus vemurafenib with dabrafenib alone give similar results.

Cost effectiveness

The company's model

- 4.8 The committee noted that the 3-state partitioned model used by the company was similar to the structure of models used in previous appraisals of technologies for treating melanoma, and met the NICE reference case. The committee also considered that the time horizon of 30 years was appropriate. The committee concluded that the model was in line with accepted NICE methods and appropriate for its decision-making.

Utility values

- 4.9 The company used 2 approaches to convert EQ-5D-5L data from coBRIM into utility values for the progression-free-survival health state. The committee accepted the company's rationale for choosing between these 2 approaches; that is, the company used the method that produced lower utility values, which were more plausible than the alternative approach that produced utility values above those for people without melanoma. The committee accepted that because the company had not been able to collect EQ-5D-5L data from many people after their melanoma had progressed, the utility values derived from the trial may not reflect quality of life for people with progressed disease. The committee noted that the company's preferred alternative came from a study (Beusterien et al.

2009) that did not meet the NICE reference case, and which reported that quality of life would be much worse in the first 5 years of progressed disease (0.590) than if a person survived for more than 5 years with progressed disease (0.770). The committee considered that this may be plausible but noted that the difference between the 2 values was large. The committee was aware that several approaches to calculating utility values had been used in previous melanoma appraisals, without uniform agreement on the most appropriate method. The ERG's alternative utility value for the progressed-disease state (0.73) was the same as that used in NICE's technology appraisal guidance on nivolumab for treating advanced (unresectable or metastatic) melanoma. The committee considered that there was uncertainty surrounding the most appropriate utility value, especially for people with progressed disease, because of data limitations. It noted that the patient expert had highlighted that the extent to which melanoma affects quality of life may vary (see section 4.1). The committee concluded that there was uncertainty surrounding utility values and it was appropriate to take into account the effect of a range of utility values, provided by sensitivity analyses, in its decision-making.

Assumptions

4.10 The company used different model inputs when comparing cobimetinib plus vemurafenib with vemurafenib alone, than it did for cobimetinib plus vemurafenib compared with dabrafenib. The committee noted the following differences:

- Cobimetinib plus vemurafenib compared with vemurafenib alone:
 - extrapolating progression-free-survival and overall-survival data from coBRIM data; the same extrapolation distribution was used for each treatment arm

- extrapolating time on treatment from coBRIM data; different extrapolation distributions were used to extrapolate the trial data over the long term for each treatment arm
- estimating the drug dosages using data from coBRIM, in which people could have dose reductions.
- Cobimetinib plus vemurafenib compared with dabrafenib:
 - extrapolating progression-free-survival and overall-survival data from coBRIM for cobimetinib plus vemurafenib, but from the network meta-analysis for dabrafenib monotherapy; the same extrapolation distribution was used for each treatment arm
 - assuming that time on treatment was the same as progression-free survival for cobimetinib plus vemurafenib and for dabrafenib; the same extrapolation distribution was used to extrapolate progression-free-survival data for each treatment arm
 - estimating the drug dosages using data from coBRIM for cobimetinib plus vemurafenib, and using the licensed dose for dabrafenib (with no adjustments for drug dose reductions).

The company's rationale for using different assumptions for each comparison was that it did not have access to the patient-level data needed to model time on treatment and dose modifications for dabrafenib. The committee accepted this, but noted that the costs for dabrafenib may have been overestimated because the company did not account for dose modifications of dabrafenib. The committee considered that using progression-free survival as a proxy measure for time on treatment would overestimate time on treatment and consequently drug costs, because people may stop treatment before disease progression. The committee noted that the total costs for cobimetinib plus vemurafenib in the company's base case were higher when using assumptions from the comparison of cobimetinib plus vemurafenib with dabrafenib, than using those for the comparison with vemurafenib. The higher costs seemed to be due to using progression-free survival as a surrogate for time on

treatment in the comparison with dabrafenib. The committee concluded that the differences in modelling assumptions had a substantial effect on costs, but only a marginal effect on the QALY estimates.

4.11 The committee noted that the ERG had presented results using the same assumptions for each modelled treatment arm and a different utility value for the progressed-disease health state. The committee agreed with the ERG that where possible modelling assumptions should be consistent between treatment arms. However, it noted that to do this the ERG had to use data from the network meta-analysis and make further adjustments for possible changes in doses of dabrafenib; it therefore considered that the ERG's modelling was based on less robust data than the company's comparison of cobimetinib plus vemurafenib with vemurafenib. The committee concluded that it preferred:

- using data for cobimetinib plus vemurafenib compared with vemurafenib alone to inform its decision-making, given the lack of patient-level data available for dabrafenib and the uncertainties in the network meta-analysis for the indirect comparison of cobimetinib plus vemurafenib with dabrafenib alone
- adjusting the drug costs for dose modifications using data on doses taken by patients in clinical trials
- using time on treatment seen in clinical trials to estimate duration of drug treatment in clinical practice
- considering sensitivity analyses that reflect the range of utility values presented for other melanoma treatments appraised by NICE, and the potential variation in quality of life experienced by people with advanced melanoma, in its decision-making.

Estimates of cost effectiveness

4.12 The cost-effectiveness estimates provided by the company and the ERG used the list prices for both drugs or used the patient access scheme

prices for vemurafenib and dabrafenib. These produced incremental cost-effectiveness ratios (ICERs) that were over £100,000 per QALY gained. This is substantially above the range usually considered a cost-effective use of NHS resources. The company already provides vemurafenib to the NHS at a discounted price as part of a patient access scheme, but no patient access scheme for cobimetinib in combination with vemurafenib has been agreed with the Department of Health for the current appraisal. The committee noted comments received from consultation stating that with combination treatment significantly fewer excisions by a dermatologist, with the associated costs, are needed for squamous cell carcinomas and keratoacanthomas. The committee noted that the difference in excisions, in favour of the combination treatment, had been included in the base case but had not been explored in any scenario analyses. However, the committee concluded that the cost savings associated with fewer outpatient procedures under local anaesthetic would not have a major impact on the ICERs.

End-of-life considerations

- 4.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [final Cancer Drugs Fund technology appraisal process and methods](#). The committee noted that the median survival of people having vemurafenib monotherapy in coBRIM was around 17 months. The committee noted that in its recent appraisal of [trametinib plus dabrafenib](#) it had agreed that life expectancy in people with advanced BRAF V600 mutation-positive melanoma was likely to be under 24 months. There was no evidence to suggest that life expectancy has changed since that decision because the recommendations from that appraisal have not yet become established practice. However, the treatment pathway for advanced melanoma is changing as new treatments become available so life expectancy of this patient population is expected to improve. The committee accepted that results from coBRIM

showed that cobimetinib plus vemurafenib extended life by more than 3 months compared with vemurafenib monotherapy. The committee concluded that cobimetinib plus vemurafenib met the end-of-life criteria and that this should be taken into account in its decision-making.

4.14 The committee noted that even taking into account end-of-life considerations, the cost-effectiveness estimates for cobimetinib plus vemurafenib compared with vemurafenib or dabrafenib alone were above the range considered to be a cost-effective use of NHS resources. The committee considered the company's statement that even if it provided cobimetinib free of charge, the ICER would remain above this range so there was no price at which it could offer cobimetinib that would allow it to be recommended. The committee noted that this assertion was made using the list prices for both products, but there was already a patient access scheme for vemurafenib and therefore this statement, although factually correct, did not apply to routine NHS commissioning in the presence of an agreed patient access scheme. The company had itself presented a scenario showing that a price of zero for cobimetinib would not be needed for the combination to result in an ICER within a similar range to previous melanoma appraisals, in which those technologies had been recommended. The committee was not convinced that there was no price for cobimetinib, taken in combination with vemurafenib, which had the potential to be considered a cost-effective combination. Cobimetinib is not licensed for use as a monotherapy and must be taken with vemurafenib. Therefore the committee stated that the combined drug costs for both cobimetinib and vemurafenib compared with BRAF-inhibitor monotherapy were relevant for its cost-effectiveness analysis. The committee noted the company's comments received in consultation that a scenario of a positive price is possible but it would need a very large discount, and that these scenarios are neither sustainable for companies nor supportive of expanding patient access to innovative technologies.

The committee accepted that not submitting a patient access scheme for

cobimetinib in combination with vemurafenib was a commercial decision for the company. It concluded that it could not recommend cobimetinib in combination with vemurafenib as a cost-effective use of NHS resources.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.15 The committee was aware of NICE’s position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee’s key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
<p>Cobimetinib in combination with vemurafenib is not recommended within its marketing authorisation for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation.</p> <p>In all of the analyses presented to the appraisal committee, the incremental cost-effectiveness ratios (ICERs) were over £100,000 per quality-adjusted life year (QALY) gained. This is substantially over the range usually considered a cost-effective use of NHS resources.</p>		<p>1.1, 4.12</p>

Current practice		
Clinical need of patients, including the availability of alternative treatments	There are numerous treatment options available and more treatments that improve survival are either becoming available or are likely to be available to people in the near future. People value life-extending treatment options but also value having various options available, because some people will experience side effects and need to switch treatment.	4.1 to 4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The combination of cobimetinib plus vemurafenib improves survival compared with a BRAF inhibitor (vemurafenib or dabrafenib) taken alone. Cobimetinib plus vemurafenib is the second MEK inhibitor taken in combination with a BRAF inhibitor to be licensed for use in England. Trametinib plus dabrafenib has been licensed for the same patient population.	4.5, 4.3
What is the position of the treatment in the pathway of care for the condition?	For most people with BRAF V600 mutation-positive melanoma, the combination of cobimetinib plus vemurafenib will be taken after an immunotherapy agent and as an alternative treatment option to a BRAF inhibitor (vemurafenib or dabrafenib).	4.2, 4.3

Adverse reactions	The summary of product characteristics notes that people taking a combination of cobimetinib plus vemurafenib should be monitored for visual disturbances and cardiac function.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	Data from the coBRIM trial (comparing cobimetinib plus vemurafenib with vemurafenib alone) were considered to be the most robust clinical data for decision-making. This was because there were no head-to-head data comparing cobimetinib plus vemurafenib with dabrafenib, the company's indirect comparison was based on a network with a small number of trials, and potential differences between the trials had not been fully explored.	4.4, 4.6, 4.7
Relevance to general clinical practice in the NHS	Clinical-effectiveness evidence from coBRIM was generalisable to clinical practice in England.	4.4

<p>Uncertainties generated by the evidence</p>	<p>The relative clinical effectiveness of cobimetinib plus vemurafenib compared with dabrafenib was uncertain because no trials had directly compared these treatment options. However, the relative clinical effectiveness of cobimetinib plus vemurafenib compared with dabrafenib was expected to be similar to the clinical effectiveness of cobimetinib plus vemurafenib compared with vemurafenib because the committee had heard that vemurafenib and dabrafenib monotherapies are considered to be of similar clinical effectiveness.</p>	<p>4.7</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>No.</p>	
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>Cobimetinib plus vemurafenib extends overall survival by 4.9 months compared with vemurafenib alone.</p>	<p>4.5</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company used a model that has a structure consistent with those used in previous melanoma technology appraisals.</p>	<p>4.8</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The company used different assumptions for comparing cobimetinib plus vemurafenib with vemurafenib alone than for cobimetinib plus vemurafenib compared with dabrafenib because some trial data for dabrafenib were not available to it. The committee preferred the assumptions for cobimetinib plus vemurafenib compared with vemurafenib alone, and thought that the clinical data used to inform these assumptions in the modelling were robust.</p>	<p>4.10, 4.11</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>Utility values for people whose disease had not progressed were derived from coBRIM trial data. Less trial data on quality of life were available for people with progressed disease and the company and ERG presented different estimates for the utility value for these people. The committee thought it was appropriate that a range of utility values should be considered in its decision-making because it had heard from the clinical expert that the quality of life of people with advanced melanoma may vary.</p>	<p>4.9</p>

Are there specific groups of people for whom the technology is particularly cost effective?	No.	
What are the key drivers of cost effectiveness?	The costs of cobimetinib plus vemurafenib and its comparators. The duration of treatment and associated drug costs.	
Most likely cost-effectiveness estimate (given as an ICER)	Over £100,000 per QALY gained.	4.12
Additional factors taken into account		
Patient access schemes (PPRS)	Vemurafenib and dabrafenib have patient access schemes agreed with the Department of Health. These are simple discounts to the list price for vemurafenib and dabrafenib. The levels of these discounts are confidential.	2
End-of-life considerations	Cobimetinib plus vemurafenib met the end-of-life criteria and the committee took this into account in its decision-making.	4.13
Equalities considerations and social value judgements	No equality issues were raised.	

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.

Jane Adam

Chair, appraisal committee

May 2016

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 A](#).

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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