Cost-effectiveness of cobimetinib (Cotellic®) for the treatment of unresectable or advanced metastatic melanoma with a BRAF V600 mutation, only in combination with vemurafenib.

The NCPE has issued a recommendation regarding the cost-effectiveness of cobimetinib (Cotellic®). Following NCPE assessment of the applicant’s submission, cobimetinib (Cotellic®) is not considered cost-effective for the treatment of unresectable or advanced metastatic melanoma with a BRAF v600 mutation, and therefore is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant’s (Roche) economic dossier on the cost effectiveness of cobimetinib (Cotellic®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.
Summary

In July 2016, Roche submitted a dossier examining the cost effectiveness of cobimetinib in combination with vemurafenib for the first line treatment of adults with unresectable or advanced melanoma. Final data submitted by the Applicant was received on 29th September 2016.

The recommended dose of cobimetinib is 60mg once daily via the oral route for Days 1-21 of a 28 day cycle, given concurrently with vemurafenib 960mg twice daily on a continuous basis. Treatment continues until the patient no longer derives benefit or until the development of unacceptable toxicity. Dose reductions are permitted to manage toxicity; if vemurafenib is discontinued treatment with cobimetinib must be discontinued also.

In the submission, the primary comparators are vemurafenib monotherapy, dabrafenib monotherapy and dabrafenib and trametinib combination therapy. A scenario analysis comparing cobimetinib and vemurafenib to nivolumab, pembrolizumab and ipilimumab was also presented.

1. Comparative effectiveness of cobimetinib

The relative efficacy of cobimetinib with vemurafenib to vemurafenib monotherapy was investigated in the coBRIM clinical trial. This trial was a double blind, placebo controlled Phase III randomised clinical trial, with progression free survival (PFS) as the primary endpoint, and overall survival (OS) as one of the secondary endpoints. The trial recruited 495 patients who were randomly assigned to receive either cobimetinib and vemurafenib or vemurafenib and placebo. Treatment beyond progression or crossover between trial arms was not permitted.

The combination of cobimetinib and vemurafenib was associated with a statistically significant increase in PFS. Based on a database lock with median 14.2 months of follow up, the median PFS with cobimetinib and vemurafenib was 12.25 months (95% CI 9.46, 13.37) compared to 7.2 months (95% CI 5.55, 7.49) with vemurafenib and placebo (hazard ratio (HR) for PFS or death 0.575 (95% CI 0.46, 0.719).
Using the data from the final OS analysis, with median 18.3 months follow up, the median OS in the cobimetinib and vemurafenib arm was 22.3 months (95% CI 20.3, not reached) compared to 17.4 months (95% CI 15, 19.8) in the vemurafenib and placebo arm, HR 0.7 (95% CI 0.55, 0.9, p=0.005). The overall response rate (defined as a complete response or partial response) was 69.6% in the cobimetinib and vemurafenib arm compared to 50% in the vemurafenib and placebo arm. While no crossover was permitted in the coBRIM trial, patients did go on to receive subsequent treatment with immunotherapies. More patients in the vemurafenib and placebo arm received subsequent therapy than in the cobimetinib and vemurafenib arm, but it is not possible to estimate to what extent this may confound the OS results.

The company presented a Bayesian network meta-analysis (NMA) to derive the relative treatment effects of cobimetinib and vemurafenib to the other comparators in the model. Rather than using Cox proportional hazard modelling, treatment effects were expressed in terms of the accelerated failure time (AFT) method. This involved recreating the published trial data for each comparator, deriving an estimate of the AFT, and synthesising the AFTs in the NMA.

The NCPE expressed a number of concerns surrounding some of the assumptions and methodologies employed in the NMA, which introduced significant uncertainty into the NMA outcomes. Among these concerns is the risk that confounding due to treatment crossover and subsequent treatments in the network is not dealt with appropriately, potentially biasing the outcomes in favour of cobimetinib and vemurafenib, the use of digitised data necessitated by the use of the AFT method rather than using published hazard ratios, and the considerable heterogeneity between the trials in the networks which is not considered.

2. Safety of cobimetinib
Almost all of the patients enrolled in the coBRIM trial experienced an adverse event (AE), regardless of treatment arm. Cobimetinib and vemurafenib was associated with a higher number of Grade ≥3 AEs (71.3% versus 59.3%) and higher number of serious AEs (34.4% versus 26%) than the placebo and vemurafenib arm. The most common AEs that occurred with higher frequency in the cobimetinib and vemurafenib arm of the pivotal study coBRIM, compared with the placebo and vemurafenib arm, include diarrhoea (56.7% vs. 28.0%),
nausea (39.0% vs. 23.8%), blood creatine phosphokinase increased (29.9% vs. 2.9%), photosensitivity reaction (28.3% vs. 15.9%), aspartate aminotransferase (AST) increased (22.0% vs. 12.6%), and vomiting (21.3% vs. 12.1%). The most common Grade ≥ 3 AEs that occurred at a higher frequency were elevated liver enzymes, maculo-papular rash (6.9% versus 5.3%), hypertension (4.5% versus 2.4%), basal cell carcinoma (4.5% versus 2.4%), hyponatraemia (2.4% versus 0.4%) and retinal detachment (2.4% versus 0%).

Cases of serous retinopathy have occurred, and cases of new or worsening visual disturbances require ophthalmological investigation and may require treatment interruption, dose reduction or discontinuation. Decrease in LVEF from baseline has also been reported, and should be monitored at baseline and then every three months. Photosensitivity also occurs at a greater frequency than with vemurafenib monotherapy. Other important potential risks identified in the Risk Management Plan (RMP) include rhabdomyolysis, hepatotoxicity, impaired female fertility, teratogenicity and developmental toxicity.

3. Cost effectiveness of cobimetinib

For the cost-effectiveness analysis, the key effectiveness inputs in the model are progression free survival and overall survival. Inputs for the comparison of cobimetinib and vemurafenib to vemurafenib monotherapy are derived from the coBRIM trial. Inputs for the comparison with dabrafenib monotherapy, dabrafenib and trametinib, nivolumab, ipilimumab and pembrolizumab are derived from the NMA. Cost effectiveness was investigated using a health state model with a 30 year time horizon.

The model simulates patients through three health states: ‘pre-progression’, ‘post-progression’, and ‘death’. All health states are mutually exclusive, and death is the absorbing state. All patients start in the pre-progression state; transitions to the death state can occur from either the pre-progression or post-progression states. The model assumes patients continue to receive treatment until disease progression. All patients are assumed to receive subsequent treatments in the post-progression state. Patient characteristics, dose intensity, utility measurements and adverse event frequency used in the model are derived from the coBRIM trial. For the comparators, dose intensity is assumed to be 100%, and treatment is assumed to continue to progression.
PFS and OS outcomes from the coBRIM trial are extrapolated to the full time horizon of the model, using parametric extrapolation and data from a US cancer registry. The comparators are modelled by applying the AFT values derived from the NMA to the extrapolated survival curves from the coBRIM trial.

Resource use in the model was assumed to be captured by the costs of treatment acquisition, adverse event costs and monitoring and administration costs, and no additional resource use costs were included. Health state utility values were estimated using a combination of the values collected during the coBRIM trial and from a literature review. Drug acquisition costs used in the model reflect changes introduced under the IPHA agreement in August 2016. Because trametinib list price is not yet published, the applicant assumed price parity between the monthly cost of dabrafenib and trametinib and cobimetinib and vemurafenib.

A fully incremental cost utility analysis is not presented; rather pairwise comparisons are presented. The incremental cost effectiveness ratios for cobimetinib and vemurafenib in the primary comparison are given in Table 1 below.

<table>
<thead>
<tr>
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<th>Cobimetinib and vemurafenib versus</th>
<th>Vemurafenib</th>
<th>Dabrafenib</th>
<th>Dabrafenib and trametinib</th>
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<tr>
<td>Incremental QALY gain</td>
<td>0.51</td>
<td>0.59</td>
<td>0.15</td>
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<td>Incremental costs</td>
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<td>€189,936</td>
<td>€15,806</td>
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<tr>
<td>Cost/QALY</td>
<td>€326,868</td>
<td>€324,192</td>
<td>€108,284</td>
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</tbody>
</table>

Probabilistic and deterministic sensitivity analyses were presented in the submission. The probability of cost effectiveness at a willingness-to-pay threshold of €45,000/QALY is 0% versus vemurafenib and dabrafenib, and 35.6% versus dabrafenib and trametinib. The deterministic analysis suggests that the main drivers of cost-effectiveness in the submission are the choice of parametric distribution for OS, utility values and treatment duration.

4. **Budget impact of cobimetinib**

Cobimetinib is available in a pack of 63 x 20mg tablets, at a price to wholesaler (PTW) of €5,727.62. The price per patient is €79,433 for cobimetinib alone, and the cost of both
cobimetinib and vemurafenib is €177,479, assuming the patient receives treatment for 12.3 months, in line with the estimates of PFS from the coBRIM trial.

The company estimate the gross budget impact as €7.8 million over 5 years, with a net budget impact of €4.6 to €7.3 million depending on the comparator displaced. The NCPE estimated the gross budget impact to be €22.1 million over 5 years, with a net budget impact of €15-€16.5 million.

5. Patient submissions

No patient submissions were received during the evaluation process.

6. Conclusion

Previously vemurafenib was found not to be cost-effective at the list price submitted. It was reimbursed after the negotiation of a confidential discount. Following review of the company submission, cobimetinib and vemurafenib in combination are not considered to be cost-effective relative to vemurafenib, dabrafenib or dabrafenib and trametinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF v600 mutation. Therefore the NCPE do not recommend reimbursement at the price submitted by the applicant.