Cost-effectiveness of trametinib (Mekinist®) for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation, only in combination with dabrafenib

The NCPE has issued a recommendation regarding the cost-effectiveness of trametinib (Mekinist®). Following NCPE assessment of the applicant's submission, trametinib (Mekinist®) is not considered cost-effective in combination with dabrafenib for the treatment of unresectable or 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 (Novartis) economic dossier on the cost effectiveness of trametinib (Mekinist®). 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.

National Centre for Pharmacoeconomics **March 2017**

Summary

In July 2016, Novartis submitted a dossier examining the cost effectiveness of trametinib in combination with dabrafenib for the first line treatment of adults with unresectable or metastatic melanoma. Final data submitted by the applicant was received in January 2017.

The recommended dose of trametinib is 2mg once daily orally, given concurrently with dabrafenib 150mg 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. Trametinib is also licensed as monotherapy for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation; no submission for the monotherapy indication has been submitted to the NCPE, and therefore the NCPE cannot recommend reimbursement as monotherapy.

In the submission, the primary comparators are dabrafenib and vemurafenib monotherapy, and pembrolizumab.

1. **Comparative effectiveness of trametinib and dabrafenib**

The relative efficacy of trametinib and dabrafenib was investigated in two Phase III randomised controlled trials (RCTs), COMBI-D versus dabrafenib and placebo, and COMBI-V versus vemurafenib. The two trials were almost identical in terms of patient population and trial design; the main difference was the double blind design of COMBI-D which had progression free survival (PFS) as the primary endpoint, and the open-label design of COMBI-V which had overall survival (OS) as the primary endpoint. Treatment beyond disease progression was permitted in both trials.

The combination of trametinib and dabrafenib was associated with a statistically significant increase in PFS in both trials. Combination treatment was associated with a median PFS of 11 months (95% CI 8, 13.9) in COMBI-D and 12.6 months (95% CI 10.7, 15.5) in COMBI-V, and a HR for PFS or death of 0.67 (0.53, 0.84, p=0.0004) and 0.61 (0.51, 0.73. p<0.01) respectively.

The combination of trametinib and dabrafenib was associated with a statistically significant increase in OS in both trials. Combination treatment was associated with a median OS of 25.1 months (95% CI 19.2, not reached) in COMBI-D and 25.6 months (95% CI 22.6, not reached) in COMBI-V, and a HR for OS of 0.71 (0.55, 0.92, p=0.01) and 0.66 (0.53, 0.81. p<0.001) respectively. The overall response rate (defined as complete or partial response) was 69% and 66% in COMBI-D and COMBI-V respectively. In both trials, there was significant use of post-progression systemic anti-cancer treatment, including ipilimumab, pembrolizumab and nivolumab, and so the totality of the OS benefit cannot be attributed to trametinib and dabrafenib alone.

Additional supportive evidence was provided from the Phase II BRF113220 trial and the DESCRIBE II observational study.

The applicant presented a Bayesian network meta-analysis (NMA) to derive the relative treatment effects of trametinib and dabrafenib to dabrafenib and pembrolizumab. The applicant used data from COMBI-V exclusively to model the baseline survival curves for the comparison to vemurafenib.

The NPCE has a number of concerns surrounding some of the assumptions employed for the NMA, particularly for the comparison with pembrolizumab. Among these concerns are the considerable heterogeneity between the included trials and the assumption of proportional hazards between treatments. The NCPE also have concerns about the choice to implement data from the open-label COMBI-V trial to model baseline survival in the model, without using any of the COMBI-D data.

2. Safety of trametinib and dabrafenib

Almost all patients in both treatment arms of the COMBI-D and -V studies experienced an adverse event (AE). Combination treatment was associated with a lower number of Grade ≥3 AEs than either dabrafenib or vemurafenib monotherapy, and with a slightly higher number of serious AEs. The most common AEs with combination treatment, reported with a frequency of >20% were pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting and cough. The most common Grade 3-4 AEs with

combination treatment were pyrexia (5-7%), hypertension (6-15%), neutropenia (3-5%) and hyponatraemia (1-5%). The most common serious AEs were pyrexia, chills and decreased ejection fraction. The percentage of patients experiencing ocular AEs were similar across all treatment arms of both studies, 11-13%. There is a lower incidence of skin and other cutaneous toxicities with the combination treatment relative to BRAF inhibitor monotherapy.

3. Cost effectiveness of trametinib and dabrafenib

For the cost-effectiveness analysis, the key effectiveness inputs into the model were PFS and OS. Inputs for the comparison of trametinib and dabrafenib with vemurafenib are modelled directly using data from COMBI-V. Inputs for the comparison with dabrafenib monotherapy and pembrolizumab are derived from the NMA. Cost effectiveness was investigated using a partitioned survival model with a 30 year time horizon.

The model simulates patients progressing through three health states, 'progression free survival', '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 receive treatment until disease progression for all treatments, and assumes dose intensity of 100% for the model base case. All patients are assumed to receive subsequent treatments in the post-progression state. Patient characteristics are based on the National Cancer Registry of Ireland data.

Survival curves are modelled using three separate segments, the trial segment based on extrapolation of trial data, a projection segment from years 5-20, and an additional projection segment from years 20-30. Resource use is modelled based on the MELODY study, and captures costs including healthcare resource use, AE costs, drug acquisition costs including subsequent treatment costs, administration costs and palliative care. Drug acquisition costs in the model were updated by the NCPE to reflect changes introduced under the IPHA agreement in August 2016.

The NCPE implemented a number of changes to the model, including removing the assumption of no wastage of dispensed treatment, amending the distribution of patients across subsequent therapies to reflect the current treatment guidelines and Irish drug reimbursement patterns, assuming the same utility decrement for vemurafenib and dabrafenib in the pre-progression state, and allowing treatment costs to accrue up to 60 months rather than ceasing at the end of trial follow up. The incremental cost effectiveness ratios (ICERs) in the NCPE preferred base case are given below. The probability of cost effectiveness at a willingness-to-pay (WTP) threshold of €20,000 and €45,000 is zero.

Trametinib and dabrafenib versus	Vemurafenib	Dabrafenib	Pembrolizumab
Incremental QALY gain	0.96	0.745	0.446
Incremental costs	€170,314	€182,417	€56,299
Cost/QALY	€177,275	€244,822	€126,128

The ICERs estimated by the applicant base case assumptions are given below; the probability of cost effectiveness at a WTP threshold of €20,000 and €45,000 is zero.

Trametinib and dabrafenib versus	Vemurafenib	Dabrafenib	Pembrolizumab
Incremental QALY gain	1.018	0.784	0.455
Incremental costs	€97,757	€122,548	€73,773
Cost/QALY	€96,000	€156,304	€162,153

4. Budget impact of trametinib

Trametinib is available in two strengths, 2mg and 0.5mg tablets, both available in a pack size of 30. The price to wholesaler is €6,317.22 and €1,579.31 respectively. The price to wholesaler for dabrafenib is €6,230 and €4,153.60 for the 75mg and 50mg strengths respectively. Assuming 100% dose intensity, the cost to the HSE per month of treatment is €12,954.30 Using median PFS estimates from the COMBI-V study, 12 months, the treatment cost per patient per year, assuming 100% dose intensity, is €155,451.60.

The applicant estimates that between 57 and 64 patients are eligible for treatment annually, and assumes a 40% market share of first line treatment, with 23 patients receiving treatment annually. The applicant estimates the gross budget impact at €18.3 million and

the estimated net budget impact at €12.2 million, over 5 years. The NCPE consider that the applicant's assessment underestimates potential market share, and estimated a gross budget impact of between €22.6 and €27 million, and a net budget impact of between €16.5 and €19 million.

5. State if any patient submissions were received, and name submitting organisations.

A patient group submission was received from Melanoma Support Ireland, and was included in full in the final report to the HSE.

6. Conclusion

Following review of the company submission, trametinib in combination with dabrafenib, is not considered to be cost-effective relative to vemurafenib, dabrafenib or pembrolizumab for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation, at a threshold of €20,000 or €45,000/QALY. Reimbursement is not recommended at the submitted price.