Cost-effectiveness of dabrafenib (Tafinlar®) in combination with trametinib (Mekinist ®) for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of dabrafenib (Tafinlar®) in combination with trametinib (Mekinist®). Following the assessment of the Applicant's submission, the NCPE recommends that dabrafenib (Tafinlar®) and trametinib (Mekinist®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Novartis Ireland Ltd) dossier on the cost effectiveness of dabrafenib (Tafinlar®) and 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 **August 2020**

Summary

In September 2019, Novartis Ireland Ltd submitted a dossier of clinical, safety and economic evidence on dabrafenib and trametinib for the adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation, following complete resection. Dabrafenib and trametinib are administered orally at doses of 150mg twice daily and 2mg once daily. respectively, until disease recurrence, unacceptable toxicity, or for a duration of up to one year. A BRAF mutation test is required to determine eligibility for therapy. There are no drugs reimbursed, in Ireland, for the adjuvant treatment of melanoma. In the submission base case, dabrafenib and trametinib was compared to routine surveillance (standard of care in Ireland). A scenario analysis compared dabrafenib and trametinib to both pembrolizumab monotherapy and nivolumab monotherapy in the population of interest.

1. Comparative effectiveness of dabrafenib and trametinib

Relative efficacy of dabrafenib and trametinib versus routine surveillance was derived from phase III international, randomized, double-blinded, placebo-controlled study evaluate the efficacy and safety of dabrafenib in combination with trametinib compared with placebo (proxy for routine surveillance) in the adjuvant treatment of high-risk BRAF V600K or V600E mutation-positive stage III melanoma following complete resection. In total 18% of patients recruited to the COMBI-AD trial had stage IIIA >1mm; 41% had stage IIIB; 40% had stage IIIC melanoma and 1% were recorded as stage III unspecified. The primary efficacy endpoint was investigator assessed relapse free survival (RFS). Two separate analyses of the primary endpoint from two data cuts (June 2017, April 2018) were included in support of the Applicant's product registration. In the initial primary analysis of the intent-to-treat (ITT) population, the mean follow up was 2.5 years (median 2.8 years), investigator assessed RFS events (relapse or death) occurred in 38% (n=166/438) patients in the dabrafenib and trametinib arm compared with 57% (n=248/432) in the placebo arm. Patients in the dabrafenib and trametinib arm had a 53% lower risk of relapse or death relative to placebo (HR 0.47; 95% CI 0.39 to 0.58; p<0.001). Median RFS in the dabrafenib and trametinib arm had not been reached (95% CI 44.5 months to not reached) and was 16.6 months in the placebo arm (95% CI 12.7 to 22.1 months). In an updated analysis with an additional 10 months of follow up data (April 2018), the estimated HR was 0.49 (95% CI 0.40 to 0.59), which was consistent with the primary analysis. Overall survival (OS) and distant metastasis free

survival (DMFS) were pre-specified secondary outcomes. At the time of the primary analysis, the estimated HR for DMFS was 0.51 (95% CI 0.40 to 0.65). The updated analysis of DMFS from the April 2018 data cut estimated a HR of 0.53 (95% CI 0.42 to 0.67) which was consistent with the primary analysis. Data on OS are not sufficiently mature to evaluate and make conclusions on OS benefit.

The Applicant conducted a network meta-analysis (NMA) to inform comparisons with the PD-1 inhibitors (nivolumab monotherapy and pembrolizumab monotherapy), as no direct comparative evidence was available. However, there were systematic differences in patient populations across the different treatment comparisons in the network which rendered indirect comparisons subject to potential bias. The extent to which these differences impact the results generated from the NMA are unknown; however, the implication is that the results generated may not be representative and could therefore result in over or an underestimation of relative treatment effects in this population. The current comparative evidence provided by the Applicant cannot distinguish whether there is an additional benefit, in terms of RFS, between these treatments (dabrafenib and trametinib, nivolumab, pembrolizumab).

2. Safety of dabrafenib and trametinib

In the COMBI-AD trial, the majority of adverse events (AEs) across both arms were of grade 1 or 2 in severity. The most commonly reported treatment related AEs in the dabrafenib and trametinib arm were pyrexia (56%) and fatigue (39%). Grade 3 or 4 AEs occurred in 41% of patients in the dabrafenib and trametinib arm compared with 14% in the placebo group. Grade 3+ AEs that occurred in ≥5% of patients in the dabrafenib and trametinib arm were pyrexia (5%), and hypertension (6%). The most frequently reported AEs in the COMBI-AD trial which led to discontinuation of dabrafenib and trametinib were pyrexia (9%) and chills (4%). Other than a higher rate of discontinuations due to pyrexia and chills, the safety profile of dabrafenib and trametinib was found to be generally consistent with the established safety profile of dabrafenib and trametinib.

3. Cost effectiveness of dabrafenib and trametinib

The Applicant submitted a cost-utility model using a semi-Markov approach to estimate the cost effectiveness of dabrafenib and trametinib in patients with BRAF mutation positive stage III melanoma following complete resection. The Applicant presented a comparison with routine surveillance as their base case, with scenario analyses for comparisons with nivolumab and pembrolizumab. The model time horizon was 50 years.

Treatment effectiveness was modelled based on RFS data from COMBI-AD trial. Outcomes for routine surveillance were assumed to be the same as the placebo arm in the COMBI-AD trial. Utilities were sourced from EQ-5D-3L data from the COMBI-AD trial and other trials in the metastatic setting. The Applicant included relevant costs. Analyses presented in this summary document are based on the list prices of all interventions included in the model (including subsequent treatments).

Relative treatment effectiveness of nivolumab and pembrolizumab were informed by a fixed effects network meta-analysis for RFS. The Applicant applied HRs generated from this NMA to RFS curves used for routine surveillance. The Review Group consider that the application of HRs as single summary measures of treatment effect may not generate a fully accurate representation of the relative effects of each treatment over time.

A key uncertainty in the cost effectiveness analysis was the choice of curves for modelling RFS beyond the trial period. Plausible extrapolations for RFS provide similar projections within the trial period and in the long term for routine surveillance; the difference is mainly in the long-term projection of additional treatment benefit for dabrafenib and trametinib. The extrapolation selected by the Applicant (unrestricted loglogistic cure) assumes that a substantially higher proportion of patients treated with dabrafenib in combination with trametinib will never experience a recurrence (compared to those patients treated with routine surveillance). The Review Group consider this may be an optimistic assumption. Given that OS data are still immature it is premature to assume a lifelong treatment benefit from dabrafenib and trametinib. Clinical opinion did not provide support for this presumption of cure. Therefore, the Review Group consider an alternative extrapolation that allows treatment effect waning. The extrapolation selected by the Review Group (restricted

lognormal cure) assumes that in the long term (after approximately 15 years) the proportion of patients who have not had a recurrence after treatment will be similar across all arms.

The NCPE adjusted a number of aspects of the model and calculated an ICER of €111,067 per QALY for dabrafenib and trametinib in comparison with routine surveillance (€109,989 incremental costs and 0.99 incremental QALYs). The Applicant had calculated an ICER of €30,252 per QALY in comparison with routine surveillance (€59,062 incremental costs and 1.95 incremental QALYs). There was little difference between probabilistic and deterministic ICERs. The probability of cost effectiveness (NCPE adjusted base case) at a threshold of €45,000/QALY was 0.8%, and at a threshold of €20,000 per QALY was 0%. The probability of cost effectiveness (Applicant base case) at a threshold of €45,000/QALY was 74.9%, and at a threshold of €20,000 per QALY was 19.3%.

4. Budget impact of dabrafenib (Tafinlar®) and trametinib (Mekinist ®)

The price to the wholesaler is €6,230 for dabrafenib (75mg capsules in a 120-pack size) and €5,628.43 for trametinib (2mg tablets in a 30-pack size). The total monthly cost to the HSE of dabrafenib is €6,448 and trametinib is €5,769 inclusive of wholesale margin, fees and rebates. No VAT applies as dabrafenib and trametinib are administered orally. All costs included in the Applicant's budget impact estimates are derived from the cost effectiveness model by setting the time horizon to one year implicitly accounting for disease progression, treatment discontinuation, the relative dose intensity (RDI) of dabrafenib (83%) and trametinib (91%) and mortality from the COMBI-AD trial. Based on the Applicant's estimate of the current eligible patient population, of 43 patients in year 1 rising to 53 patients in year 5, the projected cumulative gross budget impact over the first five years is approximately €18.9 million at an 80% market share and an annual cost per patient per year of €100,891. With the Review Group assumptions implemented in the model, the annual cost per patient is estimated to be €132,746. In the Review Group adjusted budget impact estimates the number of cycles associated with dabrafenib and trametinib was increased from 12 and 11 cycles respectively to 13 cycles to reflect the maximum one-year duration of therapy as specified in the product licence. A RDI of 100% was also applied to both dabrafenib and trametinib and a market share of 80% was also applied generating a 5-year gross budget impact of €24.8m. As dabrafenib

and trametinib are expected to displace routine surveillance no net budget impact estimates are presented. The Review Group explored the differential annual treatment costs per patient (inclusive of fees and administration costs) per year associated with dabrafenib and trametinib and compared it with nivolumab and pembrolizumab based on list prices and administration costs alone and assuming that all patients complete 12 months of treatment in line with the respective marketing authorizations. Of note dabrafenib and trametinib costs (€158,820) per patient per year are higher than both nivolumab (€107,310) and pembrolizumab (€143,991) even after accounting for costs of administration in both the community and hospital settings.

5. Patient submissions.

No patient submissions were received for this assessment.

6. Conclusion

The NCPE recommends that dabrafenib and trametinib be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.