Economic evaluation of Vemurafenib (Zelboraf) for the treatment of adult patients with BRAF V600 mutation – positive unresectable or metastatic melanoma in the Irish healthcare setting.

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1. In December 2011 Roche Pharmaceuticals submitted a completed rapid review assessment form to the National Centre for Pharmacoeconomics. A full pharmacoeconomic assessment was recommended and in May 2012 Roche submitted an economic evaluation on the cost-effectiveness of vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in the Irish healthcare setting

2. Vemurafenib is an oral tyrosine kinase inhibitor of mutated BRAF. It has marked antitumour effects against melanoma cell lines with the BRAF V600E mutation but not against cell lines with wild-type BRAF serine – threonine kinase . The submitted economic evaluation was in the form of a cost utility analysis and the perspective was that of the Irish Health Service Executive (HSE).

3. The health economic model used in this evaluation was described as a 3 health state Area Under the Curve (AUC) model with health states consisting of progression free survival, disease progression and death. The submission was based on the results from the BRIM-3 clinical trial where patients were randomly assigned to receive either vemurafenib 960 mg orally twice daily or intravenous dacarbazine 1000 mg per square meter of body surface area every three weeks. The coprimary end points of the study included overall survival and progression–free survival. Secondary endpoints included the response rate, response duration and safety. In the economic evaluation costs and consequences were discounted at 4% per annum.

4. In the basecase analysis submitted by the manufacturer the incremental cost per quality adjusted life year (QALY) gained with vemurafenib versus the comparator dacarbazine was estimated at €131,883/QALY. The incremental cost per life year gained was € 99,892/LYG.

5. The univariate sensitivity analysis indicated that the time horizon had a significant impact on the ICER e.g. a five year time horizon increased the ICER vs dacarbazine from the basecase (30 years) value of € 131,883/QALY to € 189,275/QALY. In terms of life years gained the basecase value of € 99,892/LYG increased to € 166,408/LYG. Parameters including overall survival, progression free survival utility and discount rates also impacted on the ICER and all values remained well above the threshold limits used to date. The probabilistic sensitivity analysis indicated that

vemurafenib had a 0% probability of being cost-effective for all ICER's up to €90,000/QALY

6. The Company submitted budget impact estimates in the economic dossier. The annual treatment cost for vemurafenib is calculated at € 56,727 based on the assumption of an average duration of treatment of 6 months. The gross budget impact was estimated to increase from approximately € 1.4 million in 2012 to € 2.8 million in 2016. The cumulative gross budget impact was estimated at € 12.1 million over the five year period. In a revised budget impact analysis the Company suggest that the total number of patients with the BRAF V600E mutation may be lower than expected altering the budget impact with a figure of € 211,000 for 2012 increasing to € 1.6 million by 2016 with a cumulative budget impact of € 6.6 million over the 5 year period. The review group noted the uncertainty of this revised estimate.

7. The NCPE performed an expected value of perfect information (EVPI) analysis which combines the probability of a decision error and the consequence of this error in terms of financial loss. This analysis demonstrated the 10 year population EVPI (PEVPI) at approximately € 21.96 million for a threshold ICER of € 20,000/QALY. At a threshold of € 45,000/QALY the 10 year PEVPI was in the region of € 16.98 million indicating the significant implications of the reimbursement decision.

8. The NCPE review group believe that, at the submitted price, vemurafenib (Zelboraf) is not cost-effective for the treatment of patients with BRAF V600E mutation positive unresectable or metastatic melanoma. The ICER values are well above the threshold levels of interest to the HSE i.e. € 45,000/QALY and € 20,000/QALY. Therefore we cannot recommend reimbursement of vemurafenib at the submitted price. The results of this economic evaluation will be considered by the National Cancer Control Programme (NCCP).