Cost Effectiveness of Dabrafenib (Tafinlar®) for patients with BRAF V600 mutation positive unresectable or metastatic melanoma

The NCPE has issued a recommendation regarding the use of dabrafenib(Tafinlar®) for this indication. The NCPE considers dabrafenib (Tafinlar®) to be cost effective compared to vemurafenib for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma.
The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (GlaxoSmithKline (GSK)) economic dossier on the cost effectiveness of Tafinlar ®. 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 that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence that 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 **June 2014**

Summary

GlaxoSmithKline submitted a dossier for dabrafenib(Tafinlar®) on 31 October 2013. Dabrafenib is a protein kinase inhibitor that inhibits BRAF kinases with activating V600 mutations. Dabrafenib is indicated for patients with BRAF V600 mutation positive unresectable or metastatic melanoma.

1. Comparative Effectiveness Summary

- The comparators included in the pharmacoeconomic evaluation were dacarbazine and vemurafenib. Vemurafenib was not previously demonstrated to be a cost effective treatment option in Ireland versus dacarbazine; therefore evidence versus both comparators was requested by the NCPE review group.
- Evidence from clinical trials was submitted to support the case for clinical efficacy and an indirect comparison was used to support comparative effectiveness.
- The BREAK 3 pivotal trial was a multi-national phase III randomised open-label study of dabrafenib compared with dacarbazine in previously untreated patients with BRAFV600E mutation-positive, unresectable Stage IIIc or Stage IV melanoma. Patients were randomized 3:1 to receive dabrafenib 150mg twice daily orally (n=187) or dacarbazine 1000mg/m^2 intravenously every 3 weeks (n=63). This open label trial permitted optional crossover from dacarbazine to dabrafenib upon documented progression. The primary endpoint was progression-free survival (PFS) and was analysed for the intention-to-treat (ITT) population. Efficacy analyses were conducted in the ITT and the crossover population. Assessment of progression was based on radiographic or photographic evidence and according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria. Secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response, health related quality of life (HRQOL) and safety assessments. Published results are based on a data cut-off of December 2011. The median age was 53 years in the dabrafenib arm and 50 years in

the dacarbazine arm.

- PFS and OS were estimated using the Kaplan-Meier method. At the December 2011 cut-off, the investigator assessed median PFS was 5.1 months for patients treated with dabrafenib and 2.7 months for dacarbazine (HR=0.30, 95% CI 0.18-0.51; p<0.0001). At the latest data cut-off time for PFS (June 2012), the median PFS was 6.9 months in the dabrafenib arm, and 2.7 months in the dacarbazine arm (HR=0.37, 95% CI 0.23-0.57; p<0.0001). A statistically significant improvement in OS was not observed as of the June 2012 data cut-off (HR=0.75, 95% CI 0.44, 1.29). Following adjustment for crossover, a non-statistically significant improvement in OS was observed (HR=0.55, 95% CI 0.21,1.43).
- In relation to the ORR outcome measure, 50% of patients in the dabrafenib arm achieved an ORR (95% CI 42.4, 57.1) compared to 6% in the dacarbazine arm (95%CI 1.8, 15.5).
- BREAK-MB trial

  Dabrafenib was also studied in a multi-national, open-label two-cohort Phase II study in patients with histologically confirmed BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain.

  The overall intracranial response rate (OIRR) in patients with V600E mutation positive melanoma was 39% in patients who had received prior therapy and 31% in those who had not.

- Relative efficacy

  At the time of initiation of the BREAK-3 study vemurafenib had not received regulatory approval and therefore was not used as a comparator in clinical trials. The manufacturers therefore performed an adjusted indirect treatment comparison to compare dabrafenib to vemurafenib. Data from BREAK-3 and BRIM-3, the two relevant randomised controlled trials identified through systematic review, were studied using the common comparator of dacarbazine. Little difference was found in terms of PFS (dabrafenib versus vemurafenib: HR=0.97, 95% CI: 0.60-1.57) and OS (dabrafenib versus vemurafenib: HR=0.86, 95% CI: 0.32-2.29).

2. Safety

Safety and tolerability of dabrafenib

As of the December 2012 data cut-off, patients in the dabrafenib arm of the BREAK-3 trial experienced fewer Grade 4 adverse events (AEs) than patients in the dacarbazine arm (4% versus 15%) but Grade 3 AEs were experienced more commonly in the dabrafenib arm (39% versus 27%). Grade 3 and 4 AEs which occurred in at least 5% of patients or were considered clinically important include palmar-plantar erythrodysaethesia (PPE) (2.1% dabrafenib versus 0% dacarbazine), pyrexia (3.2% dabrafenib versus 0% dacrabazine), squamous cell carcinoma (5.8% dabrafenib versus 0% dacarbazine) and neutropenia (0% dabrafenib versus 13.6% dacarbazine). Uveitis/iritis (5 cases), renal failure (<1%), neutropenia (1%), cardiovascular events (including valvular disorders) (10%) were all reported.

3. Cost-Effectiveness analysis

- A cost utility analysis comparing dabrafenib with dacarbazine and vemurafenib was submitted by the company. Health benefits were measured in QALYs and are informed by utilities from the BREAK-3 study that measured HRQoL using the EQ-5D. Costs are included from the Irish healthcare system. The population considered included the licensed population i.e. patients with stage IIIc and IV melanoma with BRAF V600E mutation. The perspective of the HSE (payer) was presented.

- A three state 'Area under the Curve' (AUC) model was developed in Microsoft Excel® to model the clinical and economic outcomes based on PFS and OS survival functions. Patients enter the model in the progression health state; upon progression, patients move to the post progression health state. At any time in the model, patients can die and enter the absorbing death state. It is a lifetime model, the time horizon is set at 30 years.

- The model reflects the clinical pathway of patients in Ireland, for first and second line treatment. The model does not capture the costs of any third line treatments. Post second line therapy, patients receive non-systemic therapy and end of life care.

- HRQoL was measured in the clinical trial. The questionnaire was administered at screening, week 6, week 12, week 15, at disease progression and approximately 30 days after progression. Forty nine per cent of dabrafenib and 21% of dacarbazine patients completed all assessments. It was not clear why more data was missing for the dacarbazine arm. The HRQoL utility assigned for the progression free health state was 0.767 for BRAF inhibitors (dabrafenib and vemurafenib) and 0.750 for dacarbazine. The post progression health state was 0.677.

- The total cost to the HSE per pack of dabrafenib (120 x 75mg) is €6,479.20 including 8% wholesaler margin and 4% rebate. Assuming a mean treatment duration of 12 cycles, this yields €78,494.76 per treatment course (including patient care fee). Weight based treatments are estimated based on 80kg or $1.8m^2$. Resource use depending on treatment was based on a Canadian Physician survey validated by Irish oncologists with Irish unit costs associated to resources. A once off cost for post first line treatment was applied. The proportion of patients receiving an active second line treatment was taken from the clinical trial (14.4% for dabrafenib versus 18.6% for dacarbazine patients). There is uncertainty whether second line treatment reflects standard practice in Ireland.

Results

- An incremental analysis was conducted. The evaluation reported Quality Adjusted Life Years (QALYs) gained. Life Years Gained (LYG) was also presented.

  <u>Compared to dacarbazine</u>

  Compared to dacarbazine, dabrafenib results in an incremental cost of

€113,613 and a QALY gain of 1.345. This yields a deterministic ICER of €84,473/QALY.

The cost/LYG was €61,152/LYG (incremental costs €113,613 and incremental LYG 1.858).

The company incorporated a number of changes the NCPE requested, mainly in relation to the survival modelling. The above results are based on the revised submission.

Compared to vemurafenib

Dabrafenib was less costly (-€43,380) and slightly more effective (+0.363 QALYs) than vemurafenib and therefore dominates vemurafenib.

Dabrafenib produced slightly more LYG (0.528) and was less costly -€43,380 (dominates vemurafenib).

Sensitivity analysis

- In a one-way sensitivity analysis the following parameters were varied for both the dabrafenib vs. dacarbazine and the dabrafenib vs. vemurafenib analyses. In the case of dabrafenib vs. dacarbazine the parameters which had most impact were efficacy (HR for OS and PFS), model time horizon and using alternative parametric models for PFS extrapolation; other parameters which influenced the ICER were the cost of dabrafenib, and further parametric models for PFS. In the case of dabrafenib vs. vemurafenib the parameters which had most impact were efficacy (HR for PFS) and dabrafenib costs (+50%).
- At a threshold of €45,000 per QALY, the probability of dabrafenib being cost effective was 81% compared to vemurafenib. The probability of being cost effective was 11% when compared to dacarbazine.

4. Budget Impact Analysis

- Based on data from the NCRI, the company projected that the number patients eligible for treatment with dabrafenib will increase from 61 patients in 2014 to 71 patients in 2018. The company estimates the market share of dabrafenib to be 10% in 2014 rising to 38% in 2016 and settling back to

30% in 2018. This rise and fall of market share is based on the assumption that interest in dabrafenib will initially increase due to its potential use in combination with the MEK inhibitor currently being developed by GSK, and then fall again due to other agents entering the market. The assumption that the number of patients will decrease is considered by the NCPE review group to be an assumption not supported with relevant evidence.

- The gross budget impact (BI) is estimated to increase from €0.47 million in 2014 (6 patients), €1.3 million in 2015 (17 patients), €1.9 million in 2016 (25 patients), €1.7 million (22 patients) in 2017 and to €1.6 million in 2018 (21 patients); a cumulative 5 year gross budget impact of €7.1 million. When the NCPE review group maintained an increase in market share for 2017 (40%) and 2018 (45%) and in this case the gross BI would be €8.4 million.
- In the base case, the company has presented the cumulative net BI of dabrafenib (minus monthly care fee) of €7,075,286. The NCPE review group considers that this could be an overestimation of the net budget impact as the cost offsets of other treatments were not accounted for in the calculations.

5. Conclusion

For the evaluation presented by the company two comparators were presented; dacarbazine and vemurafenib. Previously vemurafenib was not found to be cost effective at the list price submitted but a subsequent Patient Access Scheme (PAS) has allowed reimbursement on the High Technology Drugs Scheme. Dabrafenib is not considered cost effective in comparison to dacarbazine at a threshold of €45,000/QALY but is considered cost effective versus vemurafenib at €45,000/QALY. As BRAF inhibitors are now reported to be used first line in Ireland, the comparison with vemurafenib may be reasonable.