PUBLIC SUMMARY DOCUMENT

Product: Vemurafenib; tablet, 240 mg, Zelboraf®

Sponsor: Roche Products Pty Ltd

Date of PBAC Consideration: March 2013

1. Purpose of Application

The re-submission sought an Authority required listing of vemurafenib for the treatment of BRAF V600 mutation-positive patients with unresectable (stage IIIC) or metastatic (stage IV) melanoma and a WHO performance status of ≤2.

2. Background

At its July 2012 meeting, the PBAC deferred consideration of a submission for vemurafenib to obtain further information from the sponsor and from MSAC.

A copy of the Public Summary Document from the July 2012 meeting, is available at:http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-07/vemurafenib.

3. Registration Status

Vemurafenib was TGA registered on 10 May 2012 for the treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for a BRAF V600 mutation.

4. Listing Requested and PBAC's View

Authority required

Initial treatment of a patient with previously untreated unresectable stage IIIC or stage IV melanoma positive for the BRAF V600 mutation with a WHO performance status of less than or equal to 2.

Continuing PBS-subsidised treatment of a patient with unresectable stage IIIC or IV melanoma who has previously been issued with an authority prescription for vemurafenib and who does not have progressive disease.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Melanomas are malignant tumours derived from melanocytes. Advanced melanoma (unresectable stage III to stage IV or metastatic melanoma) is an aggressive and invasive disease, with a median survival of approximately 6 to 9 months. The strongest environmental risk factor in the development of melanoma is intermittent exposure to solar UV radiation. The geographical location of Australia, coupled with the presence of a predominantly Caucasian population results in Australia having the highest incidence per population in the world.

The aim of treatment in advanced melanoma is to optimally manage each stage of disease with a view to extending overall survival. Therapies for advanced melanoma are limited and include systemic therapy (dacarbazine, fotemustine, ipilimumab or temozolomide), palliative care/radiotherapy, palliative surgery or no treatment.

The re-submission proposed vemurafenib as first-line treatment of unresectable stage IIIc or metastatic (stage IV) melanoma in patients who are BRAF V600 mutation positive with a WHO performance status ≤2.

6. Comparator

The nominated main comparator was dacarbazine (DTIC). The original submission included fotemustine as a secondary comparator. This has been retained as a comparator in the re-submission although at a reduced proportion of use. At the request of the PBAC, best supportive care was included on the assumption that it would be the comparator for patients with a WHO performance status of 2.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The re-submission presented the BRIM 3 trial with updated results from the 1 February 2012 data cut-off, which were unavailable at the initial consideration.

Publication details of BRIM 3 have previously been reported in the July 2012 PSD.

8. Results of Trials

The co-primary outcomes in BRIM 3 were overall survival (OS) and progression-free survival (PFS).
The trial results showed vemurafenib patients had a statistically significant and clinically important advantage over dacarbazine (DTIC):

- an additional median overall survival of 3.3 months (without censoring at crossover; HR 0.76; 95% CI 0.63 to 0.93; p<0.001) to 3.9 months (with censoring at cross-over), and
- an additional median progression-free survival of 5.2 months (HR 0.38; 95% CT 0.32 to 0.46; p<0.001).

The PBAC considered "the true estimate of overall survival gain would lie between those estimated using the two approaches (of censoring or not)".

Safety data were not available from the February 2012 data cut-off, and no new safety studies were identified in the literature. However, evidence in the July 2012 submission indicated that the most common serious adverse events associated with vemurafenib were neoplasms of any type, with cutaneous squamous cell carcinomas (cuSCC) of the skin and keratocanthoma (KAs) being the most common. Of these two events, there was an absolute increase of 25% associated with vemurafenib compared to dacarbazine (RR=143.5; 95% CI 8.94, 2302.99). The PBAC concluded that vemurafenib has a different side effect profile than chemotherapy.

The re-submission provided a safety update from a Periodic Safety Update Report (PSUR) for the period 17 August 2011 to 16 February 2012 where the incidence of adverse events (AEs) was reported to be higher than in the BRIM 3 trialThere was no evidence in the re-submission to indicate new safety concerns. The PBAC concluded that vemurafenib and DTIC have different toxicity profiles, with vemurafenib being associated with manageable toxicity. The incidence of the most common AE for vemurafenib was consistent to that found in the BRIM 3 trial.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The re-submission concludes from the BRIM 3 trial, that vemurafenib for the treatment of patients with previously untreated unresectable stage IIIC or metastatic stage IV melanoma was significantly more effective than DTIC, and was associated with a different toxicity profile.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The re-submission provided a modelled economic evaluation using a cost-utility analysis based on the claim of superior effectiveness over DTIC and different toxicity profile. A stepped economic evaluation was presented, beginning with a trial-based evaluation of BRIM 3, and in response to the PBAC's request to address the unacceptably high cost per QALY in the original application, the re-submission amended its modelled evaluation, with a key change made to include non-health care costs. The base case ICER was between $75,000 and $105,000 per QALY.

The PBAC noted that the inclusion of non-health care cost in the base case analysis rather than supplementary analysis was inconsistent with the PBAC guidelines. Without non-health care costs, the ICER was higher, but within the same range.

The PBAC noted that the corresponding ICERs, taking into account the rebate offered in the Pre-Sub Committee Response, were reduced to between $45,000 and $75,000 (including non-health care costs) and between $75,000 and $105,000 (without non-health care costs).

For PBAC's view see Recommendations and Reasons

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of $30-60 million in Year 5.

The re-submission proposed a risk share arrangement which reduced this cost.

12. Recommendation and Reasons

The PBAC deferred the submission again in order for the Department to consider an appropriate arrangement for data collection (see below), and to enable the Department to negotiate an appropriate price for vemurafenib noting the following PBAC considerations:

- the estimated incremental cost per QALY gained of between $75-105, 000 (with the rebate offered in the Pre-Sub Committee Response, but not including non-health care costs, see below) was unacceptably high and uncertain;

- the PBAC's November 2012 recommendation of ipilimumab in melanoma at a base case incremental cost per QALY in the range of $45,000 to $75,000 provides the closest contextual similarity to serve as a benchmark. The PBAC recalled that this was also high and uncertain, but acceptable if the modelled survival gain is observed in clinical practice,

because the ICER was highly dependent on the duration of survival. The PBAC had also recommended the implementation of a mechanism within a risk-share arrangement to verify the anticipated overall survival benefits of ipilimumab after two years in Australian clinical practice, but the pricing negotiations also need to factor in the following disadvantages of vemurafenib compared with ipilimumab:

- treatment with vemurafenib relies on access to mutation testing, which requires acceptance of some BRAF test inaccuracy (particularly false positives) which directly reduces the cost-effectiveness of vemurafenib compared with vemurafenib prescribing based on ideal BRAF test performance and ipilimumab prescribing which does not rely on mutation testing;
- because only a few patients with V600K cross-reacted with the COBAS 4800 assay used in the key trial of vemurafenib, there is a paucity of evidence to support its effectiveness (and therefore its price) in the treatment of any BRAF V600 mutation other than V600E, and non-V600E mutations represent 27% (Menzies et al, 2012) of the population eligible for treatment under the proposed restriction;
- there are other concerns with the vemurafenib economic evaluation which favour vemurafenib as noted by ESC, including a likely overestimate of the overall survival gain (comparing the results of the model to the corresponding results observed in the key trial);

- there is a need to clarify the expected utilisation and costs to the MBS and PBS of BRAF testing and BRAF inhibitor therapy (see below), and thus the basis for the proposed risk share arrangement to share the risk of continued BRAF inhibitor therapy beyond disease progression and possibly the use of a BRAF inhibitor in a patient with a non-V600E mutation;

- the PBAC intends to conclude that, on balance, vemurafenib and dabrafenib are clinically non-inferior to each other (see below), and so should be cost-minimised against each other with the equi-effective doses being vemurafenib 960 mg twice daily and dabrafenib 150 mg twice daily (see below).

In relation to the foreshadowed restriction, the PBAC advised:

- the population eligible for mutation testing, and, if BRAF V600 positive, for treatment with vemurafenib should include unresectable Stage III (ie Stage IIIA and IIIB as well as IIIC), noting that this is consistent with the recommended eligible population for ipilimumab, but only a small number of patients with Stage III disease were included in the key trial (BRIM 3);

- the population eligible for vemurafenib should include any BRAF V600 mutation rather than be restricted to V600E only. The PBAC considered that the broader restriction would need to be supported by a process for data collection investigating the prevalence of V600 mutations in Australia and the efficacy of vemurafenib in different V600 mutation types;

- the population eligible for vemurafenib should be previously untreated for their Stage III or IV melanoma, with the probable exception of a patient developing an

intolerance to another BRAF inhibitor (such as dabrafenib) which required its permanent cessation;

- the population eligible for vemurafenib should include patients with a WHO performance status of 2 as well as 0 or 1, despite the weak evidence for effectiveness in the expected small proportion of this WHO 2 subgroup being based on observational studies, but recognising the potential for favourable response and the manageable toxicity profile across all WHO subgroups;

- the population eligible for vemurafenib should not exclude patients with brain metastases;

- the population eligible for vemurafenib could initially include grandfathered patients who have not experienced disease progression;

- PBS-subsidised vemurafenib treatment should not continue beyond disease progression.

The PBAC accepted the nominated comparators for vemurafenib, but also considered that dabrafenib, another BRAF inhibitor and thus a pharmacological analogue of vemurafenib, is also an acceptable comparator, noting that a submission for dabrafenib had been lodged for consideration at the March 2013 PBAC meeting.

The PBAC accepted that vemurafenib is more effective than DTIC, with a statistically and clinically significant improvement in progression-free survival (median gain of 5.2 months at the most recent data cut off available) and overall survival (median gain between 3.3 and 3.9 months), and that vemurafenib and DTIC have different toxicity profiles, with vemurafenib being associated with manageable toxicity. The PBAC therefore concluded that vemurafenib was better able to meet a clear clinical need than DTIC. The PBAC further concluded that, on balance, dabrafenib and vemurafenib are clinically non-inferior to each other. This conclusion was based mainly on similar gains in progression-free survival over DTIC. However, the PBAC also noted that dabrafenib has a preferable toxicity profile as evidenced by fewer and less extensive dose intensity reductions and by favourable differences in rates for adverse events such as photosensitivity, cutaneous squamous cell carcinoma – but not pyrexia. Countering this, dabrafenib, unlike vemurafenib, has not demonstrated an unequivocal overall survival advantage over DTIC.

The PBAC noted that the most recent overall survival results for both key trials (BRIM 3 (vemurafenib) and BREAK-3 (dabrafenib)) were based on similar durations of follow- up, suggesting that the BREAK-3 results for dabrafenib were not premature compared with the BRIM 3 results for vemurafenib. The PBAC also noted that the divergence in the overall survival curves occurred early in BRIM 3 for vemurafenib compared with DTIC, but any divergence in the overall survival curves occurred much later in BREAK-3 for dabrafenib compared with DTIC. It was postulated that this difference in results of overall survival might be due to the wider availability of second-line treatments, but the PBAC noted that the trials were conducted within a year of each other. The PBAC noted that the study protocols for BRIM 3 and BREAK-3 differed with respect to their approach to crossover in that this was not originally permitted in the BRIM-3 trial. As a consequence, a lesser proportion of patients crossed over in the vemurafenib trial than in the dabrafenib trial and this may have contributed to the apparent difference in overall survival outcomes.

The PBAC disagreed with the submission's base case economic evaluation including non-health care costs because this was inconsistent with the approach requested in its guidelines for submissions. This produced an incremental cost per QALY that favoured vemurafenib. The PBAC did not accept that the references made by the applicant to analogous overseas appraisals of economic evaluations of vemurafenib were relevant, noting that differences in prevalences of melanoma and BRAF mutation sub-types have consequences for the overall opportunity cost of the request being considered by the PBAC which outweigh the parallels being drawn by the applicant. The PBAC also noted that the modelled gain in mean overall survival overestimated the gain in mean overall survival observed in the clinical trial, which favoured vemurafenib. Overall, PBAC did not consider that vemurafenib was acceptably cost-effective compared with DTIC on the basis of its assessment of the modelled economic evaluation provided for vemurafenib at the greater rebate offered.

The PBAC also noted that the structure of the modelled economic evaluations differed across the two BRAF inhibitor submissions, which contributed to differences in their results beyond those explained by the differences in prices requested for the two BRAF inhibitors. The PBAC determined the equi-effective doses of vemurafenib and dabrafenib on the basis of the doses used in their respective key trials without adjusting for any variations in dose intensity.

The PBAC noted discrepancies in the estimated utilisation and net costs to PBS across the submissions for the two BRAF inhibitors. These arose from differences in:

- the epidemiological basis for estimating the numbers of patients eligible for BRAF testing (and which should not be adjusted for trial enrolment);
- the estimated duration of BRAF inhibitor therapy;
- the proposed cost per day for the two BRAF inhibitors.

The PBAC also advised that:

- there should be a consolidated epidemiological approach to calculations of the numbers of patients with melanoma tested and treated;
- the prevalence of BRAF V600 test positivity is 44.5% based on the recently updated Australian data published by Menzies et al, 2012;
- the estimate of the duration of BRAF inhibitor therapy should be appropriately aligned with the trial-based duration of progression-free survival, which is similar across the two BRAF inhibitors, but should also account for treatment cessations due to intolerance;
- the cost per day of the BRAF inhibitors should be updated to reflect the outcome of the Department's pricing negotiations.

Given the uncertainty over the extent of any effectiveness of vemurafenib in non-V600E mutations and consistent with MSAC's August 2012 advice in relation to BRAF testing for a review after two years of any MBS listing, the PBAC requested that the Department investigate the opportunity, in the event of MBS and PBS listing, for prospective data collection of:

- the frequency of BRAF testing;
- the V600 test results (eg prevalences of V600 sub-types) of the population eligible for BRAF testing;

- linked to the health outcomes (eg response, progression-free survival and/or overall survival) following treatment with a BRAF inhibitor across patients with different V600 mutation sub-types.

This might be facilitated by requiring the specific V600 mutation to be reported when seeking PBS authorisation to prescribe the BRAF inhibitor. Such pharmacogenetics data would help inform any future review of the proposal to allow any V600 mutation sub-type to be eligible for a PBS-subsidised BRAF inhibitor.

Recommendation:
Deferred

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Roche is extremely disappointed with the PBAC's decision, and regrettably will not be making another submission for the PBS listing of vemurafenib at this time.