PUBLIC SUMMARY DOCUMENT
Product: Vemurafenib, tablet, 240 mg, Zelboraf®
Sponsor: Roche Products Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

To seek an Authority Required listing for initial and continuing treatment of previously untreated unresectable stage IIIC or stage IV melanoma in patients positive for the serine/ threonine-protein kinase B-raf (BRAF) V600 mutation, or alternatively BRAF V600 mutation with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, who do not have progressive disease.

2. Background

Vemurafenib for metastatic melanoma and BRAF mutation testing were considered by the PBAC and the Medical Services Advisory Committee (MSAC) respectively under the pilot co-dependent technology assessment process.

3. Registration Status

Vemurafenib was registered on 10 May 2012 for the indication:

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
For the treatment of previously untreated unresectable stage IIIC or stage IV melanoma positive for the BRAF V600 mutation.

Or

Authority Required
Initial PBS-subsidised treatment of a patient with previously untreated unresectable stage IIIC or stage IV melanoma positive for the BRAF V600 mutation with an ECOG performance status of 0 or 1.

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.

Grandfather clause
Initial PBS-subsidised supply for continuing treatment with vemurafenib for a patient with:

1. advanced melanoma harbouring the BRAF V600 mutation
2. receiving treatment with vemurafenib prior to [date of PBS listing]

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 submission proposed that the place in therapy of vemurafenib is for first-line treatment of BRAF V600 mutation positive, unresectable stage IIIC or stage IV melanoma. The PBAC accepted that there is a high clinical need for melanoma therapies.

6. Comparator

The submission nominated dacarbazine as the main comparator, with fotemustine as a secondary comparator. The PBAC considered that best supportive care should be considered as a secondary comparator as most patients do not get dacarbazine or fotemustine, because these chemotherapies are generally accepted as not being very effective but cause substantial symptomatic toxicity.

7. Clinical Trials

The following table shows the direct randomised trials (and associated reports) presented in the submission.

Trial	Description	Reports
NO25026 (BRIM 3)	Randomised, open-label	Clinical Study Report – NO25026 – BRIM 3: A randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or dacarbazine. Research Report No. 1039652. April 2011. Chapman PB, Hauschild A, Robert C et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New England Journal of Medicine* 2011;364(26):2507-2516.

8. Results of Trials

The BRIM 3 trial was a multicentre international open label, phase III, randomised study that involved 104 sites in 12 countries, including 11 centres in Australia and 4 centres in New Zealand. Patients (n = 675) with no previous treatment for metastatic melanoma were randomised to receive vemurafenib versus dacarbazine. Patients that participated in this trial were diagnosed with metastatic melanoma a mean of 9 months prior to treatment. A total of 77 patients from Australia and New Zealand were recruited, representing 11.4% of patients enrolled in the trial. The PBAC noted that less than 10% of trial participants had Stage IIIC disease compared with metastatic disease.

The BRIM 3 trial provides evidence of the treatment effectiveness of vemurafenib compared with dacarbazine in a biomarker positive metastatic melanoma population based on the Roche cobas® test.

Patients that participated in this trial were diagnosed with metastatic melanoma a mean of 9 months prior to treatment. In the clinical setting, these patients would be treated much earlier as the median survival time is 6.2 months. This suggests that patients in BRIM 3 may have been inherently healthier than usual patients. In considering this, the PBAC noted that, compared to regular clinical practice, the BRIM3 trial participants experienced a delay between diagnosis of metastatic melanoma and start of treatment (median of 3 months, mean of 9 months, 70% within 6 months, and a range of 0 months to 184 months). Although it is difficult to judge whether, compared to the trial results, the extent of benefit in regular clinical practice would decrease (because the trial participants may have had less aggressive disease) or increase (because the disease in trial participants may have already worsened between diagnosis and start of treatment), the PBAC judged that the extent of delay overall was not sufficient to expect that either possibility would substantially modify the interpretation of the results.

Dose modifications were required in 38% of patients receiving 960 mg twice daily vemurafenib, compared to only 16% of patients receiving 1,000 mg/m^2 dacarbazine requiring dose modification.

The results for the BRIM 3 30th December 2010, 31st March 2011 and 3rd October 2011 data-cuts are shown in the table below. The hazard ratios for overall survival and progression-free survival are statistically significantly favouring vemurafenib and the confidence intervals include only clinically important effect sizes. The submission claimed that patients being treated with vemurafenib had a significantly longer time period before progression of disease or death. Vemurafenib is also more effective at inducing a statistically significant and clinically important complete or partial response to treatment, with shorter times for both time to response and duration of response. However, the number of complete responders was very low; only 6 out of 219 patients had responded completely to vemurafenib treatment by the 31st March 2011. The analysis of best overall response rate and number of complete or partial responders was not ITT for the 31st March 2011 data-cut.

The difference in overall survival, progression-free survival and overall response rate between groups decreased for each data-cut even though they were still statistically significant. Progression-free survival and overall response rate were not reported for the 3rd October 2011 data-cut. There was little difference in the absolute proportion of patients surviving after using either treatment by the 3rd October 2011 data-cut. Overall, patients treated with vemurafenib lived for an extra median three and a half months compared to those treated with dacarbazine.

The following table shows the results of primary and secondary outcomes in BRAF V600 positive patients.

Outcome from BRIM 3 Trial	Vemurafenib n with event/N (%) or median [95% CI] or (range)	Dacarbazine n with event/N (%)or median [95% CI] or mean ± SD	Absolute difference RD (95% CI)	Hazard ratio HR Relative risk RR (95% CI) or p value
30th December, 2010 data cut				
Overall survival				HR = 0.37 (0.26, 0.55)
Mortality rate	43/336 (12.8%)	75/336 (22.3%)	–9.52%	RR = 0.57

Outcome from BRIM 3 Trial	Vemurafenib n with event/N (%) or median [95% CI] or (range)	Dacarbazine n with event/N (%)or median [95% CI] or mean ± SD	Absolute difference RD (95% CI)	Hazard ratio HR Relative risk RR (95% CI) or p value
			(–3.82, –15.23)	(0.41, 0.81)
Median time to event	9.23 months [8.05, NR]	7.75 months [6.28, 10.28]	1.48 months	p < 0.0001
Progression-free survival				
Median time to event	5.32 months [4.86, 6.57]	1.61 months [1.58, 1.74]	3.71 months	p < 0.0001
Best overall response rate	106/219 (48.4%)	12/220 (5.5%)	42.95% (35.68, 50.21)	RR = 8.874 (5.034, 15.642)
Responders:	n = 106	n = 12		
Duration of response	5.49 months [3.98, 5.72]	NR [4.60, NR]		p = 0.36
Time to overall response	1.45 months (1.0-5.5)	2.72 months (1.6-5.8)	1.27 months	
Complete response	2/219 (0.9%)	0/220 (0%)	0.91% (–0.35, 2.17)	RR = 4.018 (0.182, 88.609)
Partial response	104/219 (47.5%)	12/220 (5.5%)	42.03% (34.77, 49.30)	RR = 8.706 (4.936, 15.357)
Stable disease	81/219 (37.0%)	53/220 (24.1%)	12.90% (4.36, 21.43)	RR = 1.535 (1.147, 2.055)
Progressive disease	23/219 (10.5%)	103/220 (46.8%)	–36.32% (–44.06, –28.57)	RR = 0.224 (0.149, 0.339)
31st March, 2011 data cut				
Censored at cross-over:				
Overall survival				HR = 0.44 (0.33, 0.59)
Mortality rate	78/337 (23.2%)	121/338 (35.8%)	–12.65% (–5.84, –19.47)	RR = 0.65 (0.51, 0.82)
Median time to event	NR [9.59, NR]	7.89 months [7.26, 9.63]		
Not censored at cross-over:				
Overall survival				HR = 0.47 (0.35, 0.62)
Mortality rate	78/337 (23.2%)	122/338 (36.1%)	–12.95% (–6.13, –19.77)	RR = 0.64 (0.50, 0.82)
3rd October, 2011 data cut				
Censored at cross-over:				
Overall survival				HR = 0.62 (0.49, 0.77)
Mortality rate	159/337 (47.2%)	152/338 (45.0%)	+2.2%	*RR = 1.05 (0.89, 1.24)*
Median time to event	13.21 months [11.96, 14.98]	9.63 months [7.92, 11.79]	3.58 months	p < 0.0001
Not censored at cross-over:				
Overall survival				HR = 0.67 (0.54, 0.84)
Mortality rate	159/337 (47.2%)	175/338 (51.8%)	–4.6%	*RR = 0.91 (0.78, 1.06)*
Median time to event	13.21 months [11.96, 14.98]	9.92 months [9.07, 12.22]	3.29 months	p = 0.0003

NR = not reached; SD = standard deviation

The PBAC also considered results from the 1 February 2012 data cut from this trial which were provided after the submission was initially lodged, in which vemurafenib demonstrated a statistically significant and clinically important benefit in terms of an additional median overall survival of 3.3 months (without censoring at cross-over) to 3.9 months (with censoring at cross-over), and an additional median progression-free survival of 5.2 months. The PBAC accepted that the true estimate of overall survival gain would lie between those estimated using these two approaches of censoring or not, and that the use of modified WHO criteria rather than RECIST criteria and the use of independent assessors did not raise difficulties in interpreting the trial results related to disease progression. The PBAC noted that long-term benefit is limited by the inevitable development of resistance at a median onset of about 7 months. The advice of MSAC was therefore also sought on the current or future role of testing for vemurafenib resistance mutations.

Comparative treatment safety

The submission reported that serious drug-related adverse events were statistically significantly higher in the vemurafenib arm than the dacarbazine arm of the BRIM 3 trial. Twice as many patients discontinued vemurafenib treatment compared to those that discontinued dacarbazine treatment due to an adverse event, but this difference did not reach statistical significance. There were significantly more dose modifications in the vemurafenib arm (129/336; 38%) than the dacarbazine arm (44/282; 16%) at the 30th December 2011 data-cut (RR = 2.46 [95% CI 1.82, 3.33]).

The most common serious adverse events that were significantly higher in the vemurafenib arm than the dacarbazine arm of the BRIM 3 trial were neoplasms of any type, with cutaneous squamous cell carcinoma (cuSCC) of the skin and keratoacanthoma (KA) being the most common. There was an absolute increase of 25% (RR = 143.50; 95% CI 8.94, 2302.99.

Blood and lymphatic adverse events were the most common adverse events occurring in the dacarbazine arm of the BRIM 3 trial, especially thrombocytopenia, neutropenia and decreased neutrophil count. The difference between the dacarbazine arm (16%) and the vemurafenib arm (6%) was statistically significant.

Monitoring ECG and electrolytes for QT elongation is recommended in the vemurafenib draft product information. However, patients with mean QTc interval ≥ 450 msec at screening and with serious arrhythmia or cardiac problems were excluded from the BRIM 3 trial. These patients would not be excluded in a clinical setting and would require monitoring. The submission claimed clinicians are unlikely to monitor for long QT and therefore it was excluded from the economic model.

The key adverse events of interest for dacarbazine were those highlighted in the dacarbazine Product Information.

The submission concluded that vemurafenib was associated with an increased incidence of adverse events compared with dacarbazine, but that this did not lead to an increase in the rate of treatment discontinuations. 97% of patients treated with vemurafenib had at least one adverse event compared to 90% of patients treated with dacarbazine. This resulted in 6% and 4% of patients discontinuing treatment, respectively.

The submission also concluded that, with the exception of cuSCCs managed with surgical excision, the other common adverse events were predominantly mild-to-moderate in severity.

On balance vemurafenib appears to have a different drug-related adverse event profile than dacarbazine as well as a worse serious drug-related event profile. Some of these adverse events may be mitigated by the active monitoring of patients and prophylaxis; however, this would need to be weighed against the effectiveness of BRAF mutation targeted vemurafenib treatment, resistance to treatment, and the cost implications of adverse events and the associated mitigation efforts.

The PBAC concluded that vemurafenib has a different profile of side-effects to chemotherapy. The Committee focussed firstly on the rapid development of squamous cell carcinomas (typically harbouring *HRAS* mutations) with vemurafenib that illustrates the potential for BRAF blockade to enhance tumorigenesis in BRAF wild/*RAS* mutant cells. Although of lesser relevance in the setting of metastatic disease, there may be a future need to screen potentially eligible patients for *RAS* mutations in some sites (e.g. colorectum, head and neck, skin lesions) before exposing patients to a *BRAF* inhibitor. In the meantime, PBAC was somewhat reassured that there has been no report of a squamous cell carcinoma emerging during vemurafenib therapy that subsequently progressed to metastatic disease or resulted in death. The advice of MSAC was therefore also sought on the potential use of *RAS* testing following introduction of *BRAF* inhibitors into clinical practice.

9. Clinical Claim

The submission described BRAF V600 mutation testing and treatment of mutation positive patients with vemurafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety for patients with BRAF V600 mutation positive metastatic melanoma over treatment with usual care (no testing and treatment with dacarbazine).

For PBAC's view, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a cost utility analysis (CUA) based on the claim that vemurafenib increases progression-free survival and overall survival, and is associated with a quality of life benefit.

The proposed scenario of 'BRAF mutation testing in unresectable Stage IIIC and Stage IV melanoma patients and vemurafenib treatment in mutation positive patients (and conventional chemotherapy in mutation negative patients)' was compared to the existing scenario where testing is not undertaken and all patients receive chemotherapy.

The submission presented an ICER in the range of $105,000-200,000 based on taking improved progression free survival outcomes from the BRIM 3 trial and applying these to an Australian BRAF V600 mutation positive metastatic melanoma population, extrapolating to 5 years duration (from the average follow up of 5.52 months in the trial) and selectively applying externally estimated utility weights from a published study. The sponsor proposed a risk share arrangement, which reduced the ICER in the range $75,000-105,000. The evaluation considered this an underestimate. The ICER increased to $105,000-200,000 per QALY with the inclusion of changes in assumptions recommended in the commentary.

For PBAC's views 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 Government of 30 – 60 million in Year 5 once pricing rebate considered.

For PBAC's views see Recommendations and Reasons

12. Recommendation and Reasons

The PBAC deferred consideration of this application to obtain further information from the applicant and from MSAC.

The information needed from the applicant involves confirmation from the applicant that it is prepared to:

(a) address the unacceptable cost-effectiveness of vemurafenib (with an incremental cost per extra QALY gained between $105,000 - $200,000 in the Pre-Sub-Committee Response) by offering a substantially lower effective price than achieved by the reduction offered in its proposed rebating arrangement noting that other new oral anti-cancer drugs recently listed on the basis of a similar clinical improvement are cheaper on both a per patient basis and an annual cost to PBS basis.

(b) agree that the proposed risk share arrangement will account for Australian prevalence of *BRAF* mutation positive melanoma and use of vemurafenib beyond progression of melanoma.

(c) address the following components of or changes to the requested restriction:

   a. the inclusion of patients with WHO performance status 2. Their exclusion is consistent with the trial population, but, given reports of substantial response in patients with performance status of 2, it is important for the applicant to address the impact of including this group.
   b. the inclusion of patients with active CNS disease (an important type of metastasis in melanoma with 20% of patients presenting with metastatic melanoma having metastases in the brain and 45% of patients with metastatic melanoma developing metastases in the brain during the course of their disease). The incremental benefit of vemurafenib in this patient group needs to be addressed.
   c. the definition of the biomarker being any V600 mutation, rather than V600E only or limited to V600E and V600K (which seems acceptable due to the large proportion of V600E overall and the underpowered evidence available which suggests that the other V600 mutations predict a similar treatment effect).
   d. the possibility that PBS-subsidised vemurafenib will continue after disease progression in patients who undergo successful resection of sites of progressive disease.
   e. limiting vemurafenib use to monotherapy and clarifying the place of this medication in relation to ipilimumab. The impact of pre-exposure to ipilimumab on the effectiveness of vemurafenib also needs to be addressed.

(d) clarify the model's estimate of 5-year discounted overall survival and the reasons for why the ICER became less favourable in the Pre-SubCommittee Response.

(e) confirm whether or not the concerns raised in the Joint ESC advice and in the evaluation that most modelling assumptions favour vemurafenib result in a substantially improved ICER in favour of vemurafenib overall (these assumptions include the difference in the duration of costing cycles across vemurafenib and

chemotherapy, the ratio of use of dacarbazine and fotemustine, the underestimate of dacarbazine dose).

(f) provide all models electronically to enable full independent evaluation before PBAC re-consideration.

The advice needed from MSAC was identified in the Joint ESC advice, especially the disease stage at which subsidised testing should occur, the total number of tests, the number of tests per patient reflecting the frequency of repeat testing, the costs of testing per patient treated with vemurafenib, and the cost of testing for resistance. The prevalence of BRAF mutations in melanoma patients in Australia may be particularly important given the relatively high prevalence of melanoma in Australia compared to other countries. The advice from MSAC on these issues is important to reduce uncertainty in the proposed risk share arrangements.

The PBAC noted that there is emerging evidence that vemurafenib may be harmful in patients who have preneoplastic lesions with *RAS* mutations but wild-type BRAF, because it may promote malignancy. Thus the consequences of false positive test results are important. The PBAC also noted the potentially important omission in the submission of a model that was capable of examining the consequences of varying test accuracy. Therefore the advice of MSAC was also sought on the extent of discordance across the various BRAF test options.

The PBAC accepted that there is a high clinical need for melanoma therapies. The PBAC considered that best supportive care should be considered as a secondary comparator as most patients do not get dacarbazine or fotemustine, because these chemotherapies are generally accepted as not being very effective but cause substantial symptomatic toxicity.

The PBAC noted that, compared to regular clinical practice, the BRIM3 trial participants experienced a delay between diagnosis of metastatic melanoma and start of treatment (median of 3 months, mean of 9 months, 70% within 6 months, and a range of 0 months to 184 months). Although it is difficult to judge whether, compared to the trial results, the extent of benefit in regular clinical practice would decrease (because the trial participants may have had less aggressive disease) or increase (because the disease in trial participants may have already worsened between diagnosis and start of treatment), the PBAC judged that the extent of delay overall was not sufficient to expect that either possibility would substantially modify the interpretation of the results.

In the 1 February 2012 cut-off of the key BRIM3 trial with dacarbazine as the comparator, vemurafenib has demonstrated a statistically significant and clinically important benefit in terms of an additional median overall survival of 3.3 months (without censoring at cross-over) to 3.9 months (with censoring at cross-over), and an additional median progression-free survival of 5.2 months. The PBAC accepted that the true estimate of overall survival gain would lie between those estimated using these two approaches of censoring or not, and that the use of modified WHO criteria rather than RECIST criteria and the use of independent assessors did not raise difficulties in interpreting the trial results related to disease progression. The PBAC noted that long-term benefit is limited by the inevitable development of resistance at a median onset of about 7 months. The advice of MSAC was therefore also sought on the current or future role of testing for vemurafenib resistance mutations.

The PBAC also accepted that vemurafenib has a different profile of side-effects to chemotherapy. The rapid development of squamous cell carcinomas (typically harbouring

HRAS mutations) with vemurafenib illustrates the potential for BRAF blockade to enhance tumorigenesis in BRAF wild/*RAS* mutant cells. Although of lesser relevance in the setting of metastatic disease, there may be a future need to screen potentially eligible patients for *RAS* mutations in some sites (eg colorectum, head and neck, skin lesions) before exposing patients to a *BRAF* inhibitor. In the meantime, PBAC was somewhat reassured that there has been no report of a squamous cell carcinoma emerging during vemurafenib therapy that subsequently progressed to metastatic disease or resulted in death. The advice of MSAC was therefore also sought on the potential use of *RAS* testing following introduction of *BRAF* inhibitors into clinical practice.

The PBAC would have preferred a stronger evidentiary basis to support the submission's claim of a utility advantage for vemurafenib over dacarbazine in the modelled progression-free health states across the two drugs. The PBAC accepted that this utility advantage reflects an impression that dacarbazine has a greater rate of some symptomatic side-effects such as nausea and vomiting, and that anecdotal evidence supports an improvement in disease symptoms in some patients on vemurafenib therapy. However, this utility advantage is not consistent with the fact that no quality of life difference was detected by the BRIM3 trial's limited application of the Functional Assessment of Cancer Therapy – Melanoma questionnaire. Related to this, the PBAC also noted that other aspects of using vemurafenib, such as advantages of oral administration including reduced IV line complications, the potential for reduced hospital care, and the greater potential to return to productivity (to be measured as quality of life changes) were not captured in the model, but were relevant to its considerations.

The PBAC also acknowledged and noted the consumer comments on this item.

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

The PBAC accepted that there is a high clinical need for melanoma therapies. Roche is committed to addressing the outstanding issues of concern in a resubmission to the earliest available PBAC meeting.