PUBLIC SUMMARY DOCUMENT
Product: Dabrafenib; capsule, 50 mg and 75 mg, Tafinlar®
Sponsor: GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested an Authority required listing of dabrafenib for treatment of patients with BRAF V600 mutation positive advanced (unresectable stage III) or metastatic (stage IV) melanoma.

2. Background

This product had not previously been considered by the PBAC. The PBAC considered that dabrafenib is codependent on BRAF testing, and so found that the August 2012 advice from MSAC in relation to BRAF testing in the context of vemurafenib was relevant.

3. Registration Status

The submission was considered under the TGA/PBAC parallel process. There were no TGA documents available at the time of the PBAC consideration.

Dabrafenib was TGA registered on 27 August 2013 for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

4. Listing Requested and PBAC's View

Authority required
Initial treatment, as the sole PBS-subsidised therapy, of activating BRAF mutation positive advanced (unresectable stage III) or metastatic melanoma, in a patient who has a WHO performance status of 2 or less.

Note:
Patients who have developed intolerance to vemurafenib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised dabrafenib.
Patients who have progressive disease with dabrafenib are no longer eligible for PBS-subsidised dabrafenib.
Patients who have progressive disease on vemurafenib are not eligible to receive PBS-subsidised dabrafenib.
No applications for increased quantities and/or repeats will be authorised.

Authority required
Continuing treatment beyond 3 months, as the sole PBS-subsidised therapy, of advanced (unresectable stage III) or metastatic melanoma in a patient who has previously been issued with an authority prescription for dabrafenib and who has stable or responding disease according to RECIST criteria.

Note:
Patients who have developed intolerance to vemurafenib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised dabrafenib.
Patients who have progressive disease with dabrafenib are no longer eligible for PBS-subsidised dabrafenib.
Patients who have progressive disease on vemurafenib are not eligible to receive PBS-subsidised dabrafenib.

RECIST criteria are defined as follows:
- Complete response (CR) is disappearance of all target lesions;
- Partial response (PR) is a 20% increase in the sum of the longest diameter of target lesions;
- Stable disease (SD) is small changes that do not meet above criteria.

Authority required

Initial treatment, as the sole PBS-subsidised therapy, of activating BRAF mutation positive advanced (unresectable stage III) or metastatic melanoma in a patient who was receiving treatment with dabrafenib prior to [insert date].

Note:

Patients who have progressive disease with dabrafenib are no longer eligible for PBS-subsidised dabrafenib.

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 dabrafenib as a first-line treatment of advanced (unresectable stage III) or metastatic (stage IV) melanoma in patients who are BRAF V600 mutation positive with a WHO performance status ≤2.

6. Comparator

The submission nominated dacarbazine (DTIC) as the main comparator. The submission also presented an indirect comparison with vemurafenib. This was accepted by the PBAC.

7. Clinical Trials

The submission presented one head-to-head randomised open-label trial, BREAK-3, comparing dabrafenib (n=187) and dacarbazine (n=63) in BRAF mutation-positive patients with unresectable (stage III) or metastatic (stage IV) melanoma.

The submission also presented a supplementary indirect comparison with vemurafenib, based on the same trial for dabrafenib plus the pivotal clinical trial for vemurafenib, BRIM 3.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
BREAK-3 Hauschild A et al (2012)	Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomized controlled trial.	Lancet 380: 358-65.
BRIM-3 Chapman PB et al (2011).	Improved survival with vemurafenib in melanoma with BRAF V600E mutation.	NEJM 364(26) : 2507-16.

8. Results of Trials

The key results of the BREAK-3 trial are presented in the table below.

Results of BREAK-3 trial

Trial ID/outcome	Dabrafenib n/N (%)	DTIC n/N (%)	Absolute difference	Adjusted HR[a] (95% CI)
BREAK-3 as published for 19 December 2011 cut				
Progressed	77/187 (41%)	41/63 (65%)		0.30 (0.18, 0.51)
Median PFS, months	5.1 (95% CI: 4.9, 6.9)	2.7 (95% CI: 1.5, 3.2)	2.4 months	
Overall survival	NR	NR	NR	0.61 (0.25, 1.48)
Results for 25 June 2012 cut (used in modelled evaluation)				
Progressed				0.37 (0.23, 0.58)
Median PFS, months	6.9 (95% CI: 5.2, 9.0)	2.7 (95% CI: 1.5, 3.2)	4.2 months	
Overall survival	NR	NR	NR	0.75 (0.44, 1.29)

PFS=progression-free survival; DTIC=dacarbazine

[a] hazard ratio was estimated using a Pike estimator. Based on a stratified log-rank test and adjusted for disease stage at screening.

The primary outcome in BREAK-3 was progression-free survival. Overall survival was the secondary outcome.

In BREAK-3, progression-free survival was statistically significantly longer for patients treated with dabrafenib compared with DTIC (HR=0.30; 95% CI: 0.18, 0.51) at the December 2011 data cut off, with an incremental difference in median progression-free survival of 2.4 months. The difference was maintained in the June 2012 data cut-off (HR=0.37; 95% CI: 0.23, 0.58), with the incremental difference in median progression-free survival increasing to 4.2 months.

There was no statistically significant difference between dabrafenib and DTIC in overall survival. The submission acknowledged that overall survival data at the time of cut-off was not mature and median overall survival had not been reached in either the dabrafenib or DTIC arm of the trial. Therefore, no conclusions about overall survival could be drawn.

The submission's supplementary indirect comparison of dabrafenib and vemurafenib demonstrated no statistically significant differences between the two drugs in terms of progression-free survival and overall survival. The efficacy data used for dabrafenib in this comparison was from the June 2012 cut off.

In relation to safety, the submission concluded that dabrafenib had a different but no worse safety profile compared with DTIC. Dabrafenib demonstrated greater occurrences of cutaneous squamous cell carcinomas and pyrexia. Severe neutropenia was observed in more patients treated with DTIC than dabrafenib. The submission reported that, compared to vemurafenib, dabrafenib was associated with fewer permanent discontinuations due to adverse events (3% versus 29%), with lower levels of photosensitivity (2% versus 30%) and cutaneous squamous cell carcinoma (11% versus 5%), but with more pyrexia (18% versus 28%).

For PBAC's view, see Recommendation & Reasons.

9. Clinical Claim

The submission claimed that dabrafenib is superior to DTIC with respect to efficacy and has a different but not worse safety profile. It also claimed that dabrafenib and vemurafenib are similarly effective, although the wide confidence intervals in the indirect comparison preclude a formal statistical conclusion, and have different safety profiles.

For PBAC's view, see Recommendation & Reasons.

10. Economic Analysis

The submission presented a modelled economic evaluation (cost-utility analysis) based on its claim of superior efficacy accompanied by a differing safety profile for dabrafenib compared to DTIC. The model structure did not fully reflect all aspects of the treatment of advanced or metastatic melanoma. The data presented in the submission reflected the fact that median overall survival had not yet been reached in the BREAK-3 trial. Therefore, the true size of the effect was yet to be established and the cost-effectiveness of dabrafenib was yet to be fully quantified.

The submission presented a three state 'Markov-like' model, including stable disease, progressive disease and death. The base case ICER in the submission was between $45,000 and $75,000 per QALY. However, the PBAC considered that there were a number of structural and content issues with the model that indicated the estimated ICERwas not likely to accurately represent the cost-effectiveness of dabrafenib. The PBAC considered an ICER of between $75,000 and $105,000 per QALY (excluding the adjustment for dose intensity variations) was the more likely estimate of the base case.

For PBAC's view, see Recommendation & Reasons.

11. Estimated PBS Usage and Financial Implications

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

12. Recommendation and Reasons

The PBAC deferred the submission in order to be informed of the TGA delegate's proposed registration and rationale, to enable the Department to consider an appropriate arrangement for data collection (see below) and to negotiate an appropriate price for dabrafenib, noting the following PBAC considerations:

- the estimated incremental cost per QALY gained 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 (recalling 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, and so 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 dabrafenib compared with ipilimumab:
    - ipilimumab had a more robust basis to accept the estimated extent of overall survival gain than dabrafenib
    - treatment with dabrafenib relies on access to mutation testing, which requires acceptance of some BRAF test inaccuracy (particularly false positives), which directly reduces the cost-effectiveness of dabrafenib compared with dabrafenib prescribing based on ideal BRAF test performance and ipilimumab prescribing which does not rely on mutation testing
    - there is a lack of evidence from the key trial of dabrafenib 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 dabrafenib economic evaluation which all favour dabrafenib, including a likely overestimation in extrapolating survival using the log-logistic transformation (noting the Pre-PBAC rebuttal of this concern was provided too late to be independently verified), an underestimation of dispensed drug costs by assuming dose intensity reductions can reduce the amount of drug dispensed, a likely underestimation of the utility of progressive disease, and a failure to account for adverse effects such as squamous cell carcinoma following dabrafenib
- 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 a 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, dabrafenib and vemurafenib are clinically non-inferior to each other, and so should be cost-minimised against each other with the equi-effective doses being dabrafenib 150 mg twice daily and vemurafenib 960 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 dabrafenib 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 (BREAK-3)

- the population eligible for dabrafenib 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 dabrafenib in different V600 mutation types
- the population eligible for dabrafenib 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 vemurafenib) which required its permanent cessation
- the population eligible for dabrafenib 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 dabrafenib should not exclude patients with brain metastases, recognizing the high prevalence of this type of metastasis in melanoma patients and the emerging evidence of benefit in these patients from clinical studies of dabrafenib
- the population eligible for dabrafenib could initially include grandfathered patients who have not experienced disease progression, although it was unnecessary to reference the RECIST criteria

The PBAC accepted the nominated comparators for dabrafenib.

The PBAC accepted that dabrafenib is more effective than DTIC, with a statistically and clinically significant improvement in progression-free survival (median gain of 4.2 months at the June 2012 data cut off), and that dabrafenib and DTIC have different toxicity profiles, with dabrafenib being associated with manageable toxicity. The PBAC therefore concluded that dabrafenib was better able to meet a clear clinical need than DTIC. The PBAC further accepted 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 also 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 considered that the submission's economic evaluation produced an underestimate of the likely true incremental cost per QALY for the reasons outlined in its deferral to enable a pricing negotiation, but also noted the overall lack of transparency in the submitted model. 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 dabrafenib and vemurafenib 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
- 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 dabrafenib 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

GlaxoSmithKline is committed to working closely with the PBAC to address the Committee's outstanding issues of interest to ensure that dabrafenib may be made available on the PBS for patients with V600 mutation positive unresectable or metastatic melanoma at the earliest opportunity.