



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1207 – Testing for V600 status in patients with locally advanced or metastatic melanoma for eligibility for dabrafenib treatment***

**Sponsor/Applicant/s:** GlaxoSmithKline Australia (GSK)

**Date of MSAC consideration:** 5 April 2013

#### **1. Purpose of application**

GlaxoSmithKline Australia (GSK) lodged a major submission to the March 2013 Pharmaceutical Benefits Advisory Committee (PBAC) meeting requesting PBS listing of dabrafenib for patients with locally advanced unresectable stage III or IV melanoma.

Dabrafenib is in a class of medicines called BRAF serine-threonine kinase inhibitors. It is one of several recently developed BRAF inhibitors which have been demonstrated to display increased efficacy in BRAF mutant tumours.

The fit-for-purpose minor submission to MSAC was to complement the applicant's major submission to the PBAC for dabrafenib treatment for the related BRAF V600 mutation testing.

The determination of the BRAF mutation status of melanoma tumours is important prior to commencing treatment with a BRAF inhibitor. The relationship between BRAF mutation status and a patient's response to treatment with BRAF inhibitors (including dabrafenib) leads to a co-dependent relationship between BRAF mutation testing and BRAF inhibitor treatment.

Currently, BRAF genetic testing is not eligible for reimbursement under Medicare. However, a small number of laboratories in Australia do offer the service for a fee.

#### **2. Background**

An assessment of BRAF mutation testing associated with the BRAF inhibitor vemurafenib has been the basis of prior MSAC consideration (Application 1172).

An integrated submission to MSAC and PBAC was made for BRAF mutation testing in melanoma patients and the subsequent treatment of BRAF V600 mutation positive patients with vemurafenib. In August 2012, after considering the evidence presented in relation to BRAF V600 testing associated with vemurafenib, MSAC elected to defer its decision until it

received further advice from PBAC. However, MSAC also advised that if the PBAC recommended PBS-listing of vemurafenib then MSAC would support an expedited process for its reconsideration of BRAF V600 mutation testing in order to align its support for public funding of BRAF testing with the circumstances recommended by PBAC.

To that end MSAC foreshadowed that a MBS item descriptor for BRAF V600 mutation testing could be:

*A test of tumour tissue from a patient with unresectable stage IIIC or stage IV metastatic cutaneous melanoma requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to BRAF V600 mutation status for access to vemurafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.*

The BRAF V600 mutation testing requirements and methodologies for access to dabrafenib are consistent with those for access to vemurafenib. Consequently, a minor amendment to the provisional MBS item descriptor to include a reference to dabrafenib would fulfil the requirements BRAF mutation testing required for access to PBS-listed dabrafenib.

The applicant has taken into account the prior MSAC appraisal of BRAF V600 mutation testing conducted through MSAC application 1172. Notwithstanding a request seeking a minor modification to the patient population eligible for MBS funded testing (see Point 4 below for details), the applicant also agreed with all other aspects of MSAC's considerations and advice relating to BRAF V600 mutation testing in the context of access to vemurafenib.

### **3. Prerequisites to implementation of any funding advice**

In vitro diagnostic medical devices (IVDs) are, in general, pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management (Therapeutic Goods Administration 2009). Testing for BRAF mutations is classified as a class 3 in-house IVD. Laboratories that manufacture in-house Class 3 IVDs are required to notify the TGA of the types of IVDs manufactured in each laboratory for inclusion on a register. These laboratories must have National Association of Testing Authorities (NATA) accreditation, with demonstrated compliance with the suite of standards on the validation of in-house IVDs, as published by the National Pathology Accreditation Advisory Committee (NPAAC), for each test manufactured. The laboratory itself must meet the standard published by the International Organisation for Standardisation known as ISO 15189.

If MBS-listed, BRAF V600 mutation tests must be performed in a NATA-accredited laboratory if they are to be eligible for a rebate. NATA accreditation requires the laboratory to demonstrate, through successful participation in a suitable External Quality Assurance Program (QAP), to be proficient in the technique employed.

### **4. Proposal for public funding**

In MSAC's consideration of application 1172 (BRAF genetic testing in patients with melanoma for access to proposed PBS vemurafenib) the following MBS item descriptor was foreshadowed:

*A test of tumour tissue from a patient with unresectable stage IIIC or stage IV metastatic cutaneous melanoma requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to BRAF V600 mutation status for access to vemurafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.*

The applicant requested minor amendments (shown below in bold) to this MBS item descriptor in order to facilitate the public reimbursement of BRAF mutation testing for PBS-subsidised melanoma BRAF inhibitors vemurafenib and dabrafenib. The proposed

amendments to the MBS-item descriptor were presented as part of the PBAC submission for dabrafenib:

*A test of tumour tissue from a patient with unresectable stage IIIC or stage IV metastatic cutaneous melanoma requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to BRAF V600 mutation status for access to **BRAF inhibitors vemurafenib or dabrafenib** under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.*

The rationale for the inclusion of vemurafenib and dabrafenib in the same MBS item descriptor is that the identification of a BRAF V600 mutation in a patient does not determine treatment with a specific BRAF inhibitor; rather it is indicative that they will respond to treatment using any BRAF inhibitor. The addition of dabrafenib to the MBS item descriptor foreshadowed by MSAC will allow final treatment decisions to be made by clinicians in consideration of individual patient circumstances, a situation that more accurately represents clinical practice.

In circumstances where a clinician decides to change patient management, e.g. as a result of experiencing side-effects with their current treatment, references to all PBS-listed BRAF inhibitors in the MBS item descriptor would also serve to overcome the potential need for repeat BRAF testing in order to access PBS-subsidised treatment with an alternative BRAF inhibitor. In these instances repeated testing would result in additional costs to the MBS and the conduct of repeat BRAF V600 mutation testing with no additional clinical benefit.

The rationale for removal of the restriction for access to BRAF V600 mutation testing for patients with stage IIIC or stage IV melanoma to include any stage III or stage IV disease is that this patient population reflects that enrolled in the clinical trials of dabrafenib and the patient population for which PBS listing is sought. The applicant acknowledged the previous MSAC proposal to restrict the eligible patient population for MBS-funded BRAF V600 mutation testing to patients with unresectable stage IIIC and stage IV melanoma. An assessment of the impact of expanding this patient population to include any patient with unresectable stage III or stage IV disease is presented in the fit-for-purpose minor submission.

A summary of the applicant's proposed PBS restriction for dabrafenib for consideration at the March 2013 PBAC meeting is as follows:

#### 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.

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

#### **5. Consumer Impact Statement**

Not applicable.

#### **6. Proposed intervention's place in clinical management**

The applicant proposed that all patients diagnosed with unresectable stage III or metastatic (stage IV) melanoma would undergo BRAF testing. Only patients testing positive for BRAF V600 mutations would be eligible to receive dabrafenib. This is not consistent with the

proposed PBS restriction, which more broadly refers to testing positive to an activating BRAF mutation. Patients testing negative for a V600 mutation would be eligible to receive dacarbazine (or fotemustine) as a first line therapy followed by ipilimumab as a second line therapy (chemotherapy is offered on the basis that the patient's health status is considered satisfactory to receive that treatment). Patients testing positive for a V600 mutation would be eligible to receive dabrafenib.

## **7. Other options for MSAC consideration**

### Whom to test:

MSAC/PBAC previously recommended Stage IIIC; TGA was still considering Stage III for dabrafenib. In the resubmission, the testing population was identified to be patients with "advanced (unresectable Stage III) or metastatic melanoma". The difference in the number of patients between "unresectable Stage IIIC" disease and all "unresectable Stage III" disease is likely to be small.

MSAC noted that dabrafenib was considered at the March 2013 PBAC meeting, which agreed to broaden the treated population to encompass unresectable Stage IIIA and Stage IIIB as well as unresectable Stage IIIC and Stage IV (metastatic) melanoma in any PBAC recommended PBS restriction. MSAC therefore similarly supported a broadening of the population of eligible patients for testing in alignment with this proposal.

### What to test and whom to treat?

The MBS item descriptor needs to define the biomarker to be tested; the PBS restriction needs to define the threshold for biomarker positivity to be eligible for treatment. MSAC previously recommended "BRAF V600 mutation", but the submission to PBAC proposed "activating BRAF mutation positive".

The submission to MSAC presented response rates from the single arm Phase II BREAK-2 study. It stated these results provide evidence that patients whose tumours harbour non-V600E (including BRAF V600K) mutations derive clinical benefit from dabrafenib consistent with that observed in patients with BRAF V600E-mutated melanomas.

MSAC reaffirmed its previous advice, when considering BRAF testing in the context of vemurafenib in August 2012, that the biomarker be defined as 'BRAF V600 mutation status'.

### Comparing the "evidentiary standard" with likely Australian BRAF testing

The issue of comparing test strategies across the trials relied upon as evidence for a codependency (the "evidentiary standards") was not specified in the August 2012 MSAC minutes relating to BRAF testing because MSAC did not anticipate that its minutes would subsequently be relied as the basis for a codependency for dabrafenib as well as vemurafenib.

The Department's request of the applicant to provide a minor submission to MSAC did not specifically ask for the testing strategy adopted in the key BREAK-3 randomised trial of dabrafenib. Section 4.6.1 of the 1748-page Clinical Study Report (CSR) for the BREAK-3 trial is entitled: "Baseline Confirmation of BRAF Mutation Positive Melanoma" and states:

"Formalin fixed paraffin embedded tumor tissue from a biopsy was obtained from subjects prior to the first dosing day. Tissue was collected from skin, lymph nodes and other organs for:

- to determine the presence of a BRAF V600E mutation prior to study entry as determined by central testing in a Clinical Laboratory Improvement Amendments-laboratory using their investigational use only (IUO) assay.

- Development and validation of a BRAF mutation-companion diagnostic assay for regulatory approval to determine the specific BRAF mutational status in subjects with metastatic melanoma who may benefit from treatment with GSK2118436 [dabrafenib]. Details are provided in Section 6.6 of Protocol Amendment 5.”

From Section 4.6.6 of the CSR, the assay is further described as “the Response Genetics, Inc [RGI] BRAF IUO assay”; from Section 10.1 of the CSR, it is also described as an allele specific polymerase chain reaction (ASPCR) assay.

The CSR stated that the eligible population was limited to those with BRAF V600E mutation positive melanoma. This limitation to V600E only is reinforced by the fact that a participant was withdrawn from the dacarbazine (DTIC) arm of the trial due to “investigator discretion”. The footnote to this entry in Table 6 of the CSR states “Subject 1390 had BRAF V600K mutation positive melanoma and was randomized in error. The subject discontinued the study prior to the start of study treatment.”

MSAC noted that the applicant confirmed this description. The committee indicated that it needed detailed information on the test strategy(ies) in the trial(s) relied upon as evidence for a codependency (the “evidentiary standards”) when the claim is extended beyond the initial codependent medicine to include subsequent medicines of the same mechanism of action.

## **8. Comparator to the proposed intervention**

The comparator for this assessment was ‘no testing with usual care’ for melanoma patients. Usual care consists of standard chemotherapy (dacarbazine, or less commonly fotemustine) as a first line therapy, and ipilimumab may be offered as a second line treatment.

An alternative comparator would be BRAF V600 mutation testing with vemurafenib therapy or usual care.

## **9. Comparative safety**

At its August 2012 meeting, MSAC noted that the retest rate for BRAF testing is up to 9.4%. It is possible that for some patients, another biopsy may be required solely for the purpose of BRAF testing due to an inadequate amount of tumour tissue, poor quality of the first sample, or a need to test a new metastasis because of possible biomarker differences from the primary tumour. There is a small risk associated with this extra medical procedure that will vary according to the site of the primary tumour or metastasis.

## **10. Comparative effectiveness**

At its August 2012 meeting, MSAC concluded that the BRAF test concordance data, and the BRAF test analytical validity data against the constructed reference standard (of Sanger sequencing with confirmatory pyrosequencing) suggests likely low levels of false positive and false negative test results from across the likely test options. MSAC noted that the TGA-approved COBAS test has comparatively poor performance in detecting the rarer V600 mutations, including V600K, but affirmed that this was not sufficiently important to limit the test options in any MBS item descriptor. MSAC also noted that it would have a stronger basis to consider the broadening of the definition of the biomarker to any V600 mutation if appropriate in vitro data were presented.

MSAC noted that a more complete assessment of BRAF status as a possible prognostic factor as differentiated from its claimed role as a predictor of variation in the treatment effect of dabrafenib.

## **11. Economic evaluation**

At its August 2012 meeting, MSAC noted the overall integrated submission addressed comparative cost-effectiveness as mediated through vemurafenib in patients testing positive for BRAF, and that this was the subject of PBAC consideration. A similar approach was assumed by this applicant to apply to the codependency between BRAF testing and dabrafenib.

## **12. Financial/budgetary impacts**

The proposed MBS item fee was \$285-\$325 (and the submission to MSAC reasonably used 75% of \$305 as the unit cost of BRAF testing in its estimates of costs to the MBS). MSAC noted that the complexity of the testing and the extent of consumables such as reagents were similar to KRAS testing (MBS item 73330), and so instead advised that the MBS fee for the proposed BRAF testing item be benchmarked against this item at \$230.95. This does not include the cost of retrieving archived samples from other laboratories.

At its August 2012 meeting, MSAC advised that the best estimate of the prevalence of BRAF V600 mutations for patients with metastatic melanoma in Australia is 45.8% (range 43.3% to 48.2%) based on two studies totalling 227 patients. Consistent with the March 2013 PBAC consideration, MSAC accepted the lower prevalence estimate of BRAF V600 positive melanoma patients of 44.5%, because it is based on an update (Menzies et al, 2012) of the study previously relied upon by MSAC with a larger sample size.

The submission to MSAC proposed that the number of patients tested (unresectable stage III and IV) would be less than 10,000 in Year 5. The submission estimated that the net cost to MBS (at 75% schedule fee) of testing would be less than \$1 million in Year 5. No other costs to MBS were provided.

MSAC noted that these estimates might change following the PBAC consideration of the co-dependent submission for dabrafenib.

## **13. Key issues from ESC to MSAC**

Not applicable.

## **14. Other significant factors**

Not applicable.

## **15. Summary of consideration and rationale for MSAC's advice**

MSAC noted that dabrafenib was considered at the March 2013 PBAC meeting, which agreed to broaden the treated population to encompass unresectable Stage IIIA and unresectable Stage IIIB as well as unresectable Stage IIIC and Stage IV (metastatic) melanoma in any PBAC-recommended PBS restriction. MSAC therefore proposed to similarly broaden the population of eligible patients for testing in alignment with this proposal.

MSAC reaffirmed its previous proposal to define the biomarker as 'BRAF V600 mutation status'.

MSAC noted that the complexity of the testing and the extent of consumables such as reagents were similar to KRAS testing (MBS item 73330), and advised that the MBS fee for the proposed BRAF testing item be benchmarked against this item at \$230.95.

Consistent with the PBAC consideration, MSAC accepted the lower prevalence estimate of BRAF V600 positive melanoma patients of 44.5%, because it is based on an update (Menzies et al, 2012) of the study previously relied upon by MSAC with a larger sample size. MSAC noted that the estimates of financial implications to the MBS might change following the PBAC consideration of the co-dependent submission for vemurafenib.

## **16. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of BRAF testing to help determine eligibility for proposed PBS-subsidised dabrafenib in unresectable Stage III or Stage IV metastatic cutaneous melanoma, MSAC deferred the application until PBAC reconsiders the PBS listing of dabrafenib. MSAC noted that this might be associated with a PBAC reconsideration of vemurafenib, an alternative BRAF inhibitor.

In that event, MSAC foreshadowed that the MBS fee could be expected to be \$230.95 and the item descriptor could be expected to be:

*A test of tumour tissue from a patient with unresectable stage III or stage IV metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to BRAF V600 mutation status for access to vemurafenib or dabrafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.*

MSAC also advised that it supported PBAC's request for the Department to investigate the possibility, in the event of MBS and PBS listing, for prospective data collection to be reviewed two years after any listing. In addition to the aspects of data collection identified by PBAC, MSAC also suggested:

- what test was performed on each occasion;
- what methodology was used;
- concordance data to compare test performance; and
- basic patient demographics.

MSAC advised that developing this request would require engagement with the Pathology Services Advisory Committee (PSAC), National Association Testing Authorities (NATA), key laboratories and relevant professional organisations such as the Royal College of Pathologists of Australasia. The data collection would be improved by adequate funding and independent oversight (i.e. who collects the data; who are the data custodians; who has access to the data; who analyses the data).

## **17. Applicant's comments on MSAC's Public Summary Document**

GlaxoSmithKline welcomes the MSAC recommendation.

## **18. Context for decision**

This advice was made under the MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;

- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role.

MSAC may delegate some of its functions to its Executive sub-committee.

### **19. Linkages to other documents**

MSAC's processes are detailed on the MSAC Website at: [www.msac.gov.au](http://www.msac.gov.au).