



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No.1207 – BRAF V600 mutation testing associated with access to PBS-listed dabrafenib

Sponsor/Applicant/s: GlaxoSmithKline Australia Pty Ltd

Date of MSAC consideration: 1 August 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. GSK also submitted a complementary fit-for-purpose minor submission to the April 2013 MSAC meeting for the related BRAF V600 mutation testing.

Both submissions were deferred by the respective Committees. MSAC deferred the application for BRAF V600 mutation testing until PBAC reconsidered the PBS listing of dabrafenib.

GSK lodged a minor resubmission for dabrafenib to the July 2013 PBAC meeting. To ensure coordination of advice to the Minister from MSAC and PBAC, the Department prepared a short paper to enable the August 2013 MSAC meeting to reconsider 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

BRAF V600 mutation testing for dabrafenib

A fit-for-purpose minor submission was submitted to the April 2013 MSAC meeting for BRAF mutation testing in melanoma patients to complement a major submission to the March 2013 PBAC meeting for the subsequent treatment of BRAF V600 mutation positive patients with dabrafenib. Both submissions were deferred by the respective Committees.

At its April 2013 meeting, MSAC deferred the application for BRAF V600 mutation testing to help determine eligibility for proposed PBS-subsidised dabrafenib in unresectable Stage III or Stage IV metastatic cutaneous melanoma until PBAC reconsidered 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.

BRAF V600 mutation testing for vemurafenib

An integrated submission to MSAC and PBAC (August and July 2012, respectively) 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 PBAC recommends 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 V600 mutation testing with the circumstances recommended by PBAC.

Subsequently, the applicant lodged a major re-submission to the March 2013 PBAC meeting and complementary fit-for-purpose minor re-submission to the April 2013 MSAC meeting. Both submissions were deferred by the respective Committees. MSAC deferred the application until PBAC reconsidered the PBS listing of vemurafenib. MSAC noted that this might be associated with a PBAC reconsideration of dabrafenib, an alternative BRAF inhibitor.

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, all BRAF V600 mutation tests must be performed in NATA accredited laboratories to be eligible for a rebate.

4. Proposal for public funding

In April 2013, MSAC foreshadowed the following MBS descriptor:

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.

The proposed MBS descriptor for BRAF V600 mutation testing in support of dabrafenib reflects the patient population that was enrolled in the clinical trials of dabrafenib and is consistent with the patient population for which PBS listing is sought.

The proposed PBS listing for dabrafenib in the minor submission to the July 2013 PBAC meeting was for an Authority Required listing for treatment of BRAF V600 mutation positive advanced (unresectable stage III) or metastatic (stage IV) melanoma in a patient with a WHO performance status of 2 or less.

5. Consumer Impact Statement

Not applicable.

6. Proposed intervention's place in clinical management

It is proposed that all patients diagnosed with unresectable stage III or metastatic (stage IV) melanoma would undergo BRAF V600 mutation testing. Only patients testing positive for BRAF V600 mutations would be eligible to receive dabrafenib. Patients testing negative for a BRAF 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).

7. Other options for MSAC consideration

Whom to test:

MSAC/PBAC previously agreed that the eligible patient population was patients with unresectable Stage III and Stage IV (metastatic) melanoma.

What to test and whom to treat?

The proposed MBS item descriptor defines BRAF V600 mutation status as the biomarker to be tested; the proposed PBS restriction defines the threshold for biomarker positivity to be eligible for treatment with dabrafenib, i.e. patients must have a positive BRAF V600 mutation test result.

8. Comparator to the proposed intervention

The main 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 guiding subsequent vemurafenib therapy or usual care.

9. Comparative safety

At its August 2012 meeting, MSAC noted that the retest rate for BRAF V600 mutation testing is up to 9.4%. It is possible that for some patients, another biopsy may be required solely for the purpose of BRAF V600 mutation 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.

11. Economic evaluation

At its August 2012 meeting, MSAC noted the overall integrated submission addressed comparative cost-effectiveness and that this was the subject of PBAC consideration.

12. Financial/budgetary impacts

At its April 2013 meeting, MSAC advised that the complexity of BRAF V600 mutation 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 V600 mutation testing item be benchmarked against this item at \$230.95.

MSAC confirmed 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. The lower prevalence estimate of BRAF V600 positive melanoma patients is accepted at 44.5%; based on an updated study (Menzies et al, 2012).

The submission to MSAC proposed that the number of patients tested (unresectable stage III and IV) would be less than 10,000 per year. The submission estimated that the net cost to MBS (at 75% of the \$305 proposed schedule fee) of testing would be less than \$1 million per year. No other costs to MBS were provided.

13. Key issues from ESC to MSAC

Not applicable

14. Other significant factors

Nil

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

MSAC noted that the July 2013 PBAC meeting had recommended dabrafenib for listing on the PBS, and had recommended it be restricted to unresectable Stage III and Stage IV (metastatic) melanoma in patients who test positive for a BRAF V600 mutation. MSAC reaffirmed the importance of aligning the population of patients eligible for testing with this restriction.

MSAC reaffirmed its April 2013 advice that the MBS fee for a BRAF mutation testing item be \$230.95 because the complexity of the testing and the extent of consumables such as reagents were similar to the benchmark MBS item 73330 for KRAS mutation testing. MSAC

noted that this would slightly reduce the applicant's estimates of financial implications to the MBS of about \$0.5 million per year.

MSAC noted that representatives of the National Health and Medical Research Council, MSAC, PBAC and the Department had met to discuss targeted data collection relating to BRAF mutation testing and BRAF inhibitor treatment as proposed by PBAC in March 2013 and supported by MSAC in April 2013.

MSAC foreshadowed it would advise that the words "dabrafenib or vemurafenib" be substituted for "dabrafenib" in the wording of an MBS item for BRAF mutation testing in the event of a PBAC recommendation to list vemurafenib on the PBS. MSAC did not prefer the alternative of trying to find a broader way of describing the consequent treatment options because it wanted to be able to review each new co-dependent linkage at this early stage of considering co-dependent test and medicine technologies. For example, it would want to consider the "evidentiary standard" test for each new treatment option (the test used to identify the BRAF V600 mutation status in the key trials supporting the new treatment option) and to consider the means through which the treatment option achieves its effect.

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 mutation testing to help determine eligibility for proposed PBS-subsidised dabrafenib in unresectable Stage III or Stage IV metastatic cutaneous melanoma, MSAC supports its public funding via a new MBS item, with an MBS fee of \$230.95 and an item descriptor of:

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 dabrafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC also reaffirmed its April 2013 advice that, as part of implementing coordinated MBS and PBS listing of these co-dependent health technologies, appropriate data be collected prospectively to be reviewed two years after listing.

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

GlaxoSmithKline welcomes the MSAC recommendation which will enable access to dabrafenib for Australian persons with BRAF mutation positive metastatic melanoma.

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.