



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1318 - KRAS mutation testing for panitumumab

Sponsor/Applicant/s: Amgen Australia

Date of MSAC consideration: 5 April 2013

1. Purpose of application

Amgen lodged a major submission to the March 2013 PBAC meeting requesting PBS listing of panitumumab for patients with metastatic colorectal cancer (mCRC), who have been tested for Kirsten ras (KRAS) gene mutation status and found to be the wild type. Panitumumab is in a class of medicines called epidermal growth factor receptor (EGFR) inhibitors. A very similar EGFR inhibitor, cetuximab, is already PBS listed in the second-line setting of mCRC which is shown to be KRAS wild type.

MBS Item 73330 provides for KRAS testing of tumour material from patients with mCRC to assess eligibility for cetuximab.

The purpose of the fit-for-purpose minor submission to MSAC is to request a change to the Item 73330 restriction wording to accommodate panitumumab, should it receive a positive PBAC recommendation and subsequent approval to list on the PBS.

2. Background

At its 51st meeting in December 2010, MSAC supported public funding of testing to determine tumour KRAS mutation status to contribute to the determination of eligibility for PBS-subsidised cetuximab for a patient with metastatic colorectal cancer. Testing should be performed in a National Association of Testing Authorities (NATA) accredited laboratory, and be ordered by an oncologist. It should also be supported by suitable quality standards and a quality assurance program specific to KRAS testing such as the one developed by RCPA.

This advice was implemented by the government on 1 May 2011 with the creation of MBS Item 73330 with the item descriptor:

A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to Kirsten ras (KRAS) gene mutation status for access to cetuximab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

3. Prerequisites to implementation of any funding advice

Resources required for the intervention include experienced laboratory technicians (salary); retrieval of tumour specimens (usually formalin fixed paraffin embedded tissue from the primary tumour); possible costs of repeat biopsy if a primary tumour sample is not available; KRAS gene mutation test – reagents, instrumentation – varies depending on test methodology; as well as administrative costs. Any KRAS gene mutation testing funded through the MBS should be performed in a NATA-accredited laboratory that has been demonstrated, in a suitable External Quality Assurance Program (QAP), to be proficient in the technique employed.

4. Proposal for public funding

The applicant requested PBAC to consider two separate panitumumab restrictions:

- The main restriction was for patients who have failed 1st-line chemotherapy, which is consistent with the current PBS restriction for cetuximab. This listing was proposed based on cost minimisation with cetuximab.
 - Implications for KRAS testing: the applicant claimed that this restriction for panitumumab is not anticipated to have any impact on the number of KRAS tests or the timing of testing; and
 - PBAC recommended that panitumumab be listed for this indication, therefore MSAC focused on the proposed amendment of the corresponding MBS item, noting that the tested and treated populations were identical.
- An additional restriction sought, which is not consistent with the current PBS restriction for cetuximab, for a small subset of 1st-line patients unsuitable for bevacizumab, on the basis of clinical need.
 - Implications for KRAS testing: the applicant claimed that this new restriction would not increase the number of KRAS tests, but a small proportion (< 100/year) would be done earlier than currently. However, as the MBS item descriptor does not specify that KRAS testing needs to be performed during or after first-line therapy and no change in definition of the eligible population was requested by the applicant, there is no obvious basis to indicate why these patients would be tested earlier;
 - PBAC did not recommend that panitumumab be listed for this indication, therefore MSAC did not consider advising on any amendment of the corresponding MBS item for this indication; and
 - The applicant had sought advice from the PBAC and MSAC as to whether more detailed MSAC advice is required on the proposed 1st-line listing. MSAC considered that, because this niche population had not previously been considered by either PBAC or MSAC and also involves a different line of therapy and potentially a different comparator, an integrated major submission to both PBAC and MSAC would be appropriate. This would need to address: whether the nature of the codependency varies between the existing population defined for cetuximab (and proposed for panitumumab) and this niche population; when the proposed population should best be tested, particularly whether the population to be tested should include those who present with a less advanced stage of colorectal cancer than the population already defined as eligible for testing; and whether there are any other logistical consequences for pathology laboratories that need to be considered.

5. Consumer Impact Statement

Not applicable.

6. Proposed intervention's place in clinical management

The intention for KRAS testing is to determine eligibility for panitumumab in the same population as is currently the case for cetuximab.

7. Other options for MSAC consideration

Two alternatives were considered to amend the item descriptor. One was to add the words "or panitumumab" after "cetuximab" in the existing item descriptor. The other was to describe a class of medicines that includes these two medicines.

MSAC discussed the merits of the narrow and broader options, and advised in this instance preference for the narrower option to ensure that any future competitor of these two medicines would also need to lodge a minor submission to provide supportive evidence for its request. MSAC considered that, once it develops sufficient experience in this type of situation to advise with confidence that the broader option is suitable, that would be its usual preference.

8. Comparator to the proposed intervention

There is no current equivalent comparator test listed on the MBS, therefore the comparator is "no KRAS testing before panitumumab".

The test is already MBS-listed to enable patient access to cetuximab, which is only beneficial and cost-effective in patients with responsive tumours.

9. Comparative safety

At its December 2010 meeting, MSAC agreed that the KRAS test is safe for patients as it uses a sample already collected for histological assessment from patients diagnosed with mCRC. Test safety is unlikely to be a cause for concern if there are processes in place to efficiently store and retrieve archived tumour samples and if the tests used to determine KRAS gene mutation status are highly sensitive.

10. Comparative effectiveness

In December 2010, MSAC noted that if the KRAS test is not listed on the MBS, this could potentially mean that 60-65% of patients with mCRC who have wild type KRAS would remain ineligible to receive cetuximab resulting in reduced disease-free survival; or if patients chose to pay for the test themselves, this could result in inequity of care/access to treatment issues.

MSAC considered that the following information would have further assisted its ability to advise on the comparative effectiveness of KRAS testing for panitumumab as well as cetuximab:

- a comparison of the detailed methods and tests used for KRAS testing in the key trials supporting panitumumab in the proposed population with those in the key trials supporting cetuximab in the same population and those used in contemporary Australian pathology practice
- a comparison of the in vitro studies showing the biomarker's ability to differentiate panitumumab's effectiveness as well as cetuximab's effectiveness.

MSAC requested this type of information be provided in future minor submissions to MSAC addressing the codependency between a MBS-listed testing strategy (or MSAC-supported testing strategy) when the same testing strategy is proposed to help determine PBS eligibility for a different medicine of the same mechanism of action to treat the same population.

11. Economic evaluation

The minor submission to MSAC inferred that there are no economic consequences for the MBS of its proposals (see below).

12. Financial/budgetary impacts

The minor submission to MSAC agreed with the December 2010 MSAC estimate of the number receiving a KRAS test as being 7000 per year. This estimate is not expected to vary as a result of listing panitumumab as a treatment alternative to cetuximab.

The MBS item fee for 73330 is \$230.95, with no suggested change in fee should the existing item related to cetuximab be extended to include panitumumab for the same population. This addition would not increase costs to the MBS for KRAS testing.

13. Key issues from ESC to MSAC

Not applicable.

14. Other significant factors

MSAC noted that laboratory issues with KRAS testing – NATA/RCPA accreditation, QAP membership, block preparation, storage and block retrieval would remain unchanged following implementation of this request.

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

MSAC noted PBAC's recommended restriction for panitumumab and considered that it would be appropriate to ensure that the population eligible for KRAS testing should be identical to the population tested to determine eligibility for cetuximab. MSAC discussed the merits of adding panitumumab as an alternative to cetuximab in the item descriptor or replace both medicines with a name for the class of medicines, and advised in this instance its preference for the narrower option to ensure that any future competitor of these two medicines would also need to lodge a minor submission to provide supportive evidence for its request.

MSAC noted the minor resubmission from the applicant and considered that this was a fit-for-purpose approach in the circumstances that it had previously supported the same testing strategy in the same tested population for treatment by another medicine with the same mechanism of action in the same treated population. MSAC considered that a full integrated co-dependent submission would be required if the proposed medicine had a different mechanism of action or the proposed test or treated population were different.

MSAC considered that there was no need to revise the MBS fee and noted that the minor submission did not identify any financial implications to the MBS.

MSAC considered that the following information would have further assisted its ability to advise on the comparative effectiveness of KRAS testing for panitumumab as well as cetuximab:

- a comparison of the detailed methods and tests used for KRAS testing in the key trials supporting panitumumab in the proposed population with those in the key trials supporting cetuximab in the same population and those used in contemporary Australian pathology practice; and
- a comparison of the *in-vitro* studies showing the biomarker's ability to differentiate panitumumab's effectiveness as well as cetuximab's effectiveness (noting that this information is likely to form part of the dossier submitted to the TGA, but would also be relevant for MSAC purposes).

MSAC requested this type of information be provided in future minor submissions to MSAC addressing the co-dependency between a MBS-listed testing strategy (or MSAC-supported testing strategy) when the same testing strategy is proposed to help determine PBS eligibility for a different medicine of the same mechanism of action to treat the same population.

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 KRAS mutation testing for panitumumab, MSAC supports the extension of the current MBS item for KRAS testing to include panitumumab as well as cetuximab when testing tumour tissue from a patient with metastatic colorectal cancer to determine if the requirements for access under the PBS are fulfilled. MSAC further advised that there was no need to consider changing the MBS fee and that no consequential changes should be expected to the MBS costs of KRAS testing.

MSAC advised that the MBS item descriptor be amended by inserting "or panitumumab" as follows:

CATEGORY 6 – PATHOLOGY SERVICES
73330 A test of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to Kirsten ras (KRAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

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

Amgen is pleased that MSAC supports the extension of MBS item 73330 for KRAS testing to include panitumumab.

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.