PUBLIC SUMMARY DOCUMENT
Product: CETUXIMAB, solution for I.V. infusion, 100 mg in 20 mL and 500 mg in 100 mL, Erbitux®
Sponsor: Merck Serono Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought to extend the current Authority Required listing to include treatment of patients with K-RAS wild type metastatic colorectal cancer (mCRC) as monotherapy or in combination with chemotherapy following failure of chemotherapy.

2. Background

Cetuximab is currently listed on the PBS for use in squamous cell cancer of the head and neck.

This was the eighth application for listing of cetuximab for the treatment of mCRC.

At the March 2005 meeting, the PBAC rejected an application to list cetuximab for treatment of epidermal growth factor receptor (EGFR) expressing metastatic colorectal cancer in patients who have failed irinotecan based therapies, and either failed or are unsuitable for oxaliplatin based therapies, to be used in combination with irinotecan because of uncertain extent of clinical benefit and uncertain and unacceptable cost-effectiveness.

At the November 2005 meeting, the PBAC once again rejected an application for cetuximab for the treatment of mCRC where the current standard chemotherapeutic options have failed, because of uncertain clinical benefit and unacceptable and uncertain cost-effectiveness.

At the July 2006 meeting, the PBAC rejected a minor re-submission for a Section 100 listing for cetuximab for mCRC because of uncertain clinical benefit and unacceptable and uncertain cost-effectiveness.

At the November 2008 meeting, the PBAC rejected an application for third-line treatment of mCRC in patients whose tumour has the K-RAS wild type (wt) oncogene because of uncertainty about the extent of survival benefit over best supportive care (BSC) and because of the resultant high and highly uncertain cost-effectiveness ratio.

At the March 2009 meeting, the PBAC rejected a minor re-submission which provided further information to address the PBAC's concerns from the November 2008 meeting regarding the economic evaluation and K-RAS diagnostic testing, because of high and uncertain cost-effectiveness.

At the July 2009 meeting, the PBAC rejected a minor submission for cetuximab for the third-line treatment of patients with K-RAS wt metastatic colorectal cancer in combination with irinotecan on the basis of high and uncertain cost-effectiveness.

At the March 2010 meeting, the PBAC rejected the submission for cetuximab to include first line treatment of patients with K-RAS wild type metastatic colorectal cancer on the basis of uncertain clinical benefit and uncertain cost-effectiveness.

3. Registration Status

Cetuximab is TGA registered for the treatment of patients with:

- epidermal growth factor receptor (EGFR)-expressing, K-RAS wild-type metastatic colorectal cancer. In combination with chemotherapy. As a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy.
- squamous cell cancer of the head and neck. In combination with radiation therapy for locally advanced disease. In combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

4. Listing Requested and PBAC's View

Authority required

Cetuximab as monotherapy or in combination with chemotherapy following failure of chemotherapy in K-RAS wild type patients with metastatic colorectal cancer.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

It is proposed that cetuximab would be an alternative second line treatment to best supportive care, FOLFOX or FOLFIRI for patients with K-RAS wild type metastatic colorectal cancer as monotherapy or in combination with chemotherapy.

6. Comparator

As at the November 2008 and March 2009 meetings, the PBAC agreed that BSC is the appropriate comparator.

7. Clinical Trials

The resubmission uses data from trial CO17, as previously presented to the PBAC.

Trial ID / First author	Protocol title / Publication title	Publication citation
CO17 Karapetis et al, 2008	K-RAS Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer	*NEJM* 2008; 359(17): 1757-65

8. Results of Trials

The CO17 trial (Karapetis et al 2008) was presented in the previous March and July 2009 PBAC submissions. The incremental benefit from the CO17 trial in K-RAS wt patients was assumed to be 4.7 months incremental survival gain (0.39 LYG) with the addition of cetuximab. This is equivalent to a base case of quality adjusted survival of 0.25 QALYs.

The following data were presented in this submission:

- The requested listing included both cetuximab monotherapy and in combination with chemotherapy and presented ICERs for each regimen;
- A treatment algorithm was presented with weighting of treatments to be replaced by cetuximab monotherapy and in combination with chemotherapy;
- Updated drug costs were presented;
- The cost of current second line treatments, including best supportive care, were included as cost offsets; and

- The cost of K-RAS testing was included in the cost of cetuximab therapy.

The submission presented a treatment algorithm, developed in consultation with independent oncologists and members of the sponsor's Advisory Board, for K-RAS wild type patients with mCRC. The PBAC noted that from this algorithm the submission identified four treatment groups (A to D), and the percentage of patients in each treatment group, which could be replaced by cetuximab monotherapy or cetuximab in combination with chemotherapy.

9. Economic Analysis

The cost effectiveness was based on the evidence in the CO17 trial (Karapetis et al 2008) for the second line setting of mCRC as most patients would have failed two chemotherapy treatments with or without bevacizumab. The submission claimed that this was a conservative assumption as the evidence from trial CO17 is in third line patients and the requested listing is for second line patients.

The submission used the four treatment groups (A to D) to calculate the effective cost of cetuximab, the cost offsets and ICERs specific to each group.

The submission estimated the cetuximab weighted drug cost across all patient groups (A to D) to be less than $15,000 across the requested indication, and a sensitivity analysis estimated the weighted ICER to be between $15,000 - $45,000 per QALY.

10. Estimated PBS Usage and Financial Implications

The submission estimated that less than 10,000 patients would be eligible for cetuximab in year 4 of listing, with an estimated total drug cost per year of between $30 and $60 million in year 4.

The submission stated that costs associated with K-RAS testing have been incorporated in the cost effectiveness calculations and assumed MBS reimbursement for the K-RAS test.

11. Recommendation and Reasons

The PBAC recommended listing cetuximab on the PBS as an Authority Required listing for the treatment of metastatic colorectal cancer in patients who meet certain criteria on the basis of high but acceptable cost-effectiveness compared with best supportive care.

This recommendation was primarily based on the evidence in the CO17 trial (Karapetis et al 2008) for the second line setting of metastatic colorectal cancer (mCRC), which demonstrated an incremental overall survival benefit of 4.7 months (0.39 LYG) with the addition of cetuximab to BSC compared to BSC alone in patients with wild-type K-RAS tumours, with a base case of quality adjusted survival of 0.25 QALYs, as presented in the March and July 2009 submissions. The PBAC accepted the QALYs as reasonable. The PBAC acknowledged that the population included in Karapetis were not entirely representative of all groups of patients that would be treated with cetuximab under the requested listing, but considered that the entire body of published evidence supported the use of cetuximab as monotherapy or in combination with irinotecan base chemotherapy.

The submission also presented a treatment algorithm which identified four treatment groups (A to D) and the percentage of patients in each treatment group, which could be replaced by

cetuximab monotherapy or cetuximab in combination with chemotherapy. In group A, cetuximab monotherapy replaced best supportive care; in group B, cetuximab monotherapy replaced FOLFOX/FOLFIRI; in group C, cetuximab plus irinotecan or oxaliplatin replaced FOLFOX/FOLFIRI, and in group D, cetuximab plus FOLFOX/FOLFIRI replaced FOLFOX/FOLFIRI.

The PBAC noted that the weighted ICER was estimated to be between $45,000 – $75,000 per QALY (base case) with an approximate upper estimate per QALY in the same range (sensitivity analysis, second-line utility, weighted result, 1/3 reduction in benefit for groups C and D). The PBAC considered that this was high but acceptable.

The PBAC noted that use of cetuximab was not associated with the same benefit when used in combination with various chemotherapy treatment regimens. The PBAC agreed that there was no clinical benefit of treatment with combination cetuximab and bevacizumab based on randomised control trial (RCT) evidence. There was also no benefit in the first-line treatment setting of combination cetuximab and FOLFOX based on evidence from the COIN Study and possibly no treatment effect modification with K-RAS. However, the BOND Study showed a benefit of 2.6 months increase in time to progression (TTP) with combination of irinotecan and cetuximab without analysis of K-RAS as a treatment effect modifier. The Crystal Study in first-line treatment with FOLFIRI/cetuximab versus FOLFIRI also showed a modest improvement in progression free survival (PFS) and treatment effect modification with K-RAS.

The PBAC noted it would be difficult to monitor a restriction which mandated monotherapy alone and considered that a pragmatic approach was to allow use of cetuximab as monotherapy or in combination with irinotecan based therapies based on clinical trial data regarding efficacy

The PBAC considered that the average duration of treatment of 12 weeks presented in the submission was reasonable.

The PBAC noted that currently the K-RAS test was not subsidised on the MBS and that the sponsor is currently funding the test for highly selected patients. The PBAC was concerned about the accuracy of this test which has not been properly assessed and inaccuracy may result in worse outcomes for patients, i.e. for those patients who had mutant type disease but treated for wild type disease. Such inappropriate use would also result in drug wastage.

The PBAC considered that the K-RAS test needed assessment for diagnostic accuracy and that this should be undertaken via the normal processes and that therefore this matter should be referred to the MSAC. As this test is likely to be undertaken at diagnosis, the PBAC considered that a model needed to be developed to ascertain costs and logistics associated with such a screening program.

The PBAC recommended the Safety Net 20 Day Rule should not apply.

Recommendation:
CETUXIMAB, solution for I.V. infusion, 100 mg in 20 mL and 500 mg in 100 mL, Erbitux®

Extend the current restriction to include:

Restriction:	Authority required Initial PBS-subsidised treatment, as monotherapy or in combination with an irinotecan based therapy, of a patient with a WHO performance status of 2 or less and with K-RAS wild type metastatic colorectal cancer after failure of first-line chemotherapy. Continuing PBS-subsidised treatment, as monotherapy or in combination with an irinotecan based therapy, of a patient with K-RAS wild type metastatic colorectal cancer who has previously been issued with an authority prescription for cetuximab and who does not have progressive disease. Cetuximab is not PBS-subsidised for use in combination with bevacizumab or oxaliplatin based therapies. NOTE: Special Pricing Arrangements apply.
Maximum quantity:	1
Repeats:	Nil

12. 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.

13. Sponsor's Comment

The sponsor had no further comment.