PUBLIC SUMMARY DOCUMENT
Product: Cetuximab, solution for I.V. infusion, 100 mg in 20 mL, 100 mg in 50 mL and 500 mg in 100 mL, Erbitux®
Sponsor: Merck Serono Australia Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

1) To request an Authority required listing (and inclusion in the Chemotherapy Pharmaceuticals Access Program (CPAP)) of cetuximab for the treatment of patients with metastatic colorectal cancer following failure of irinotecan and failure of or intolerance to oxaliplatin.
2) To provide further information to address the PBAC's concerns from the November 2008 meeting regarding the economic evaluation and KRAS diagnostic testing.

2. Background

Cetuximab is currently listed on the PBS for use in squamous cell cancer of the head and neck. This is the fifth application for listing of cetuximab for the treatment of metastatic colorectal cancer (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 but unacceptable cost-effectiveness.

At the November 2005 meeting, the PBAC once again rejected an application for cetuximab for the treatment of metastatic colorectal cancer (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 treatment of 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 wild type KRAS because of uncertainty about the extent of survival benefit over best supportive care and because of the resultant high and highly uncertain cost effectiveness ratio.

3. Registration Status

Cetuximab solution for I.V. infusion 2 mg/mL was TGA registered on 4 February 2005. Additional strengths (50 mg/10 mL, 100 mg/20 mL, 250 mg/50 mL and 500 mg/100 mL) were TGA registered on 25 September 2007.

All strengths are registered for the following indications:

- Treatment of patients with metastatic colorectal cancer that has been demonstrated to express epidermal growth factor receptor (EGFR) and whose disease has progressed or is refractory to irinotecan based therapy. Cetuximab can be used at the doses recommended either in combination with irinotecan or as a single agent;

- In combination with radiation therapy, for the treatment of patients with locally advanced squamous cell cancer of the head and neck.

4. Listing Requested and PBAC's View

Authority required

PBS-subsidised treatment of patients with metastatic colorectal cancer with a WHO performance status of 2 or less, in combination with irinotecan, where:

a) Patients have received and failed 5-fluorouracil or capecitabine, received and failed an irinotecan based therapy and received and failed or are unsuitable for an oxaliplatin based therapy.
b) There is evidence that the patient has KRAS wild type in the tumour material.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Cetuximab provides a treatment option for patients with metastatic colorectal cancer who have failed the current standard chemotherapeutic options.

6. Comparator

The submission nominated best supportive care (BSC) as the comparator.

At the November 2008 meeting, the PBAC agreed that BSC is the appropriate comparator, as there was no evidence that patients with metastatic colorectal cancer (mCRC), whose disease had progressed despite treatment with oxaliplatin, irinotecan and 5-fluorouracil, would benefit from further treatment with the currently available chemotherapeutic agents.

7. Clinical Trials

No new clinical data were presented in this submission compared to the November 2008 submission. See November 2008 Public Summary Document (PSD) for details.

8. Results of Trials

For the key results, see November 2008 PSD.

In this submission, the treatment effect (overall survival) was derived using data from Study C017, as reported by Karapetis (2008), for KRAS wild type patients receiving cetuximab plus best supportive care versus best supportive care alone.

The overall survival curve from Karapetis et al. (2008), for cetuximab plus BSC and BSC alone, was used to calculate the area under extrapolated survival curves and derive a mean overall survival, which was between 5 – 6 months in the BSC arm and 10-11 months for the cetuximab plus BSC arm.

For PBAC's view, see Recommendation and Reasons.

9. Economic Analysis

A modelled economic evaluation was presented in the form of a cost-effectiveness analysis.

The submission presented a "worse case" scenario analysis as part of the modelled economic evaluation for the KRAS sub-group in which the treatment effect came from the CO17 study cetuximab versus BSC but the costs are those of cetuximab and irinotecan.

The sensitivity analyses showed that the economic model is sensitive to the overall survival time and that varying the cost of the KRAS test has only a minor impact on the incremental cost-effectiveness ratio (ICER) but that the inclusion of costs for irinotecan substantially increases the ICER.

In the November 2008 submission, the cost for irinotecan per patient was derived from a progression-free survival period of approximately 35.3 weeks sourced from Lievre et al. 2008. The cost for irinotecan in the present submission is less as the mean progression-free survival from Study C017 for cetuximab monotherapy is used to derive a time on treatment.

The "worst case" ICER is estimated to be in the range of $75,000 - $200,000 (evaluation calculation) per QALY. No adverse events or cost of adverse events for irinotecan treatment are factored into the ICERs and therefore the new cost of irinotecan therapy may be underestimated.

For PBAC's view, see Recommendation and Reasons.

10. Estimated PBS Usage and Financial Implications

The likely number of prescriptions per year for cetuximab was estimated to be less than 10,000 in year 5.

11. Other Relevant Factors

KRAS diagnostic test

The submission presented updated information relating to the accuracy of the KRAS test.

The submission also claimed a retrospective KRAS analysis of tumour samples from Study C017 (Karapetis et al.), as evidence for the predictive value of KRAS testing to determine which patients would best benefit from cetuximab therapy.

The sponsor has set up a national KRAS testing program.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC noted that the submission nominated best supportive care as the comparator, agreed by the PBAC as appropriate at the November 2008 meeting, as there was no evidence that patients with metastatic colorectal cancer (mCRC), whose disease had progressed despite treatment with oxaliplatin, irinotecan and 5-fluorouracil, would benefit from further treatment with the currently available chemotherapeutic agents. However, the PBAC noted that the requested restriction in the current re-submission includes use of cetuximab with irinotecan.

The PBAC noted that no new clinical data were presented in the re-submission but additional information in relation to KRAS mutation testing; a revised economic evaluation; and a revised risk sharing arrangement with the Department was presented. The treatment effect (overall survival) was derived using data from Study C017, as reported by Karapetis (2008),

for KRAS wild type patients receiving cetuximab plus best supportive care versus best supportive care alone. However, because the BOND trial appears to suggest that cetuximab + irinotecan is superior to cetuximab alone in the whole mCRC population, a "worse case" scenario analysis was presented as part of the modelled economic evaluation for the KRAS sub-group in which the treatment effect came from the CO17 study cetuximab versus BSC but the costs are those of cetuximab and irinotecan.

The PBAC noted that using a Weibull extrapolation over a time horizon of five years, fitted to the Karapetis et al. (2008) data, mean overall survival estimated during the evaluation was 7.3 months (31.6 weeks) for the BSC arm and 10.9 months (47.6 weeks) for the cetuximab plus BSC arm. The PBAC also noted that the difference in mean overall survival presented in the submission was approximately 22 weeks compared to the evaluation's estimate of 16 weeks. The PBAC considered that the submission's estimate likely overestimated the overall survival and that the very small number of patients alive by 14 months suggested that there may not be a need to extrapolate the treatment effect beyond the duration of the trial.

Therefore, the PBAC considered that the extent of overall survival benefit of cetuximab over best supportive care in the KRAS sub-group remained uncertain as it is based on a post-hoc analysis; and the method of extrapolation of the treatment effect beyond the trial period (14 months to 5 years) is uncertain. The PBAC noted that the Pre-PBAC response estimated the mean survival for KRAS wild type patients receiving BSC using the Kaplan-Meier curve to be approximately 24 weeks and that the ICERs were estimated to be in the range of $45,000 - $75,000 per QALY, depending on whether the estimate was trial based, submission based or evaluation based.

The PBAC noted that the modelled economic evaluation presented a cost-effectiveness analysis, and that the "worst case" (cost is cetuximab and irinotecan and BSC but effectiveness is cetuximab and BSC versus BSC) assumes a treatment period based on progression-free survival data for cetuximab monotherapy KRAS wild-type group from Study CO17. The PBAC also noted that the economic model is sensitive to the overall survival time and that varying the cost of the KRAS test has only a minor impact on the ICER but the inclusion of costs for irinotecan substantially increases the ICER.

In the November 2008 submission the cost for irinotecan per patient was based on an estimated time on treatment derived from a progression-free survival period of approximately 35.3 weeks sourced from Lievre et al. 2008. The PBAC noted that the cost for irinotecan in the present submission is less as the mean progression-free survival from Study C017 for cetuximab monotherapy is used to derive a time on treatment. The PBAC noted that the "worst case" ICER is estimated to be in the range of $75,000 to $200,000 (evaluation calculation) per QALY and that no adverse events or cost of adverse events for irinotecan treatment are factored into these ICERs and therefore the cost of irinotecan therapy is underestimated.

The PBAC noted that data on the sensitivity and specificity of the available KRAS tests was not available and considered that the potential impact of false positive and false negative outcomes to the economic evaluation is unknown and remains an area of uncertainty. The criteria for entry into the trial was EGFR positivity and the PBAC considered that the effect of patients being treated with cetuximab on the PBS without this pre-requisite is unknown as the requested restriction does not select for EGFR positive patients alone. The trial based

ICER of between $45,000 - $75,000 per QALY as calculated in the Pre-PBAC response includes only patients that are EGFR positive and therefore the PBAC considered this ICER to be uncertain.

The PBAC noted that the presence of the V600E B-RAF mutation may also be a marker for resistance in colorectal cancer as per the published paper by Di Nicolantonio, F et al in the *Journal of Clinical Oncology, Dec 10 2008, 5705-5712*, and noted that KRAS and B-RAF are mutually exclusive. The PBAC considered that the inclusion of these and other molecular markers may lead to better targeting of patients.

Therefore, the PBAC rejected the submission for cetuximab on the basis of high and uncertain cost-effectiveness. Without further information, the PBAC considered that a price decrease would be necessary to alleviate the uncertainty of the cost-effectiveness and to protect against the high cost of use with irinotecan.

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

The identification of the K-Ras oncogene represents an important advancement in personalised medicine. Merck Serono Australia remains committed to working together with the PBAC to address their remaining uncertainties and ensure that patients with metastatic colorectal cancer will have appropriate access to treatment with cetuximab.