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: November 2008

1. Purpose of Application

The submission sought 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. Background

Cetuximab is currently listed on the PBS for use in squamous cell cancer of the head and neck. This is the fourth 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 because of uncertain clinical benefit and unacceptable and uncertain cost-effectiveness. The PBAC considered that the proposed continuation rule would not be enforceable and that an element of clinical judgement was required when distinguishing between partial response and stable disease. The Committee considered there was likelihood of misclassifications when assessing patient eligibility under the continuation rule. The PBAC considered that uncertainty still existed as to the extent of incremental survival gain with cetuximab. The submission claimed that cetuximab plus irinotecan was of similar or less toxicity than "usual care". The PBAC noted that a comparison across the single-arm studies provided showed that the proportion of patients with grades 3 and 4 adverse events of cetuximab plus irinotecan was greater than those of the components of usual care. The PBAC considered that there remained uncertainty over the comparative toxicity of cetuximab plus irinotecan and usual care. The PBAC also considered that the submission's assumed utility prior to progression, and the incremental cost per QALY gained were biased in favour of cetuximab (See also Public Summary Document of November 2005).

At the July 2006 meeting, the PBAC considered a minor re-submission for a Section 100 listing for cetuximab for treatment of mCRC. The PBAC considered the proposed continuation rule requiring patients to have regular scans in the last weeks of life to be too onerous. It was not clear whether the cost of scanning had been included in the cost-effectiveness ratios. The application was rejected because of uncertain clinical benefit and unacceptable and uncertain cost-effectiveness.

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

Initial and Continuing

PBS-subsidised treatment of patients with metastatic colorectal cancer with a WHO performance status of 2 or less 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

Usual Care (UC) defined as best supportive care (BSC) plus active chemotherapy. The PBAC considered that the appropriate current comparator in the setting of metastatic colorectal cancer (mCRC) was best supportive care, as there was no evidence that patients with mCRC whose disease had progressed despite treatment with oxaliplatin, irinotecan and 5-fluorouracil will benefit from further treatment with the currently available chemotherapeutic agents. This was a change from the Committee's finding in November 2005 that usual care, a composite of active chemotherapy and best supportive care, was the appropriate comparator and reflected recent advances in knowledge in this area. This also meant that no costs for chemotherapy can be validly included in the comparator arm of the economic evaluation.

For PBAC's view see Recommendation and Reasons.

7. Clinical Trials

The re-submission used the two open-label randomised trials (BOND and CO-17) to conduct an indirect comparison between cetuximab plus irinotecan and "Usual Care" on the whole mCRC population via cetuximab as the common reference. The re-submission also conducted an indirect comparison on the PBS eligible population (K-RAS wild type) between cetuximab plus irinotecan (using data from the retrospective studies De Roock/Lievre) and "Usual Care" (using data from a retrospective analysis of Study CO-17).

The trials published at the time of the submission were:

Trial ID	Protocol/Publication title	Publication citation

Study 007 (BOND)	Open, randomised, multicentre, Phase II study of cetuximab alone or in combination with irinotecan in patients with metastatic colorectal adenocarcinoma expressing the epidermal growth factor receptor (EGFR) and progressing on a defined irinotecan-based regimen. November 27 2006.	Cunningham, DHY., Siena, S., et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *New England Journal of Medicine* 2004; 351:337-345.
CO-17 Jonker DJ et al	Cetuximab for the treatment of colorectal cancer.	*New England Journal of Medicine* 2007; 357(20):2040-8.
Karapetis C et al	Cetuximab plus BSC versus BSC alone in the treatment of metastatic EGFR-positive colorectal cancer.	*Signal* 2005;6 (1): 15-7.
De Roock et al	KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab.	*Annals of Oncology* 2008:19(3); 508-515
Lievre et al	KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab.	Journal of Clinical Oncology 2008:26(3);374-379

8. Results of Trials

Whole mCRC population

For progression free survival (PFS), there was a statistically significant difference favouring (1) cetuximab plus irinotecan over cetuximab monotherapy in BOND [4.1 vs. 1.5 months, HR=0.54 (95%CI: 0.42, 0.71; p<0.0001)] and (2) cetuximab monotherapy over best supportive care in Study CO-17 [1.9 vs. 1.8 months, HR=0.68 (95%CI: 0.57, 0.80; p<0.0001)]. For overall survival (OS), there was no statistically significant difference for cetuximab plus irinotecan over cetuximab monotherapy in BOND [8.6 vs. 6.9 months, HR=0.91 (95%CI: 0.68, 1.21; p=0.48). There was a statistically significant difference favouring cetuximab monotherapy over best supportive care in Study CO-17 [6.1 vs. 4.6 months, HR=0.77 (95%CI: 0.64, 0.92; p=0.0046)]. It was possible that the results for overall survival in BOND were indicative of confounding by cross-over (56 of 111 (50.5%) patients received cetuximab plus irinotecan combination therapy upon documented disease progression with cetuximab monotherapy). The usefulness of PFS where there was a relatively short interval between recurrence and death was uncertain and its interpretation as a composite clinical endpoint (the definition of which can be inconsistent across different trials) can be problematic. There appeared to be important differences in treatment survival effects (in weeks) between the cetuximab monotherapy arms across the studies. An examination of the Kaplan-Meier plots also suggested that the assumption on which the calculation of hazard ratios was based did not hold in the current context, i.e. the curves indicated that the ratio of the hazards was not constant over time or the individual hazard functions were not proportional to each other – an assumption that underpins the log-rank statistical test that has been used.

The clinical evaluation of cetuximab plus irinotecan versus Usual Care for the population for whom PBS listing was sought (K-RAS wild type) was based on indirect comparisons across retrospective studies of combined data from single arm studies.

K-RAS status as a treatment effect modifier

The data from the studies indicated that K-RAS status was a treatment effect modifier; however these results were interpreted with caution given that the data were derived from

post hoc retrospective analyses of single arm studies and the approach of combining the response data was uncertain. There was considerable potential for selection bias, ascertainment bias and confounding to have affected the results.

The results from De Roock indicated that the majority of the clinical benefit in K-RAS wild type patients (for example in terms of median OS) was derived from the addition of irinotecan to cetuximab (difference between cetuximab plus irinotecan and cetuximab monotherapy approximates 20 weeks). There were no important differences between the mutant groups regardless of treatment type; however, the wild type patients demonstrated important clinical benefit upon addition of irinotecan.

The inconsistency of treatment effect in the 'common reference' group (cetuximab monotherapy) across the studies made the interpretation of the results problematic. Median overall survival appeared to be different between the K-RAS wild type cetuximab monotherapy 'arms'.

K-RAS wild type population: indirect comparison between cetuximab plus irinotecan and BSC via cetuximab monotherapy as the common reference

The re-submission concluded that in the all patient group the incremental survival comparing cetuximab plus irinotecan to Usual Care was approximately 25 weeks. This increased to approximately 40 weeks in the WT patients. The use of absolute differences in treatment effect rather than relative treatment effects across studies, to conduct an indirect comparison, was problematic. Relative effects were 'more stable' across different studies and more appropriate for use in an indirect comparison context where there were differences between the treatment effects of the common reference arms. However, an indirect comparison in the current setting was difficult. The median and mean estimates did not describe the whole survival experience and it was uncertain whether the difference in treatment effects was constant across the different studies.

The re-submission did not present any uncertainty around the estimates of incremental survival gain. The survival data were derived using simple weighting by size of sub-group. The survival data for the cetuximab plus irinotecan were also obtained by combining data from single arm open-label studies. These did not form an evidentiary basis adequate enough to provide support for the re-submission's claim.

Therefore considerable uncertainty surrounded the extent of incremental survival benefit of cetuximab plus irinotecan compared to Usual Care for use in the stepped economic evaluation. Furthermore, the assumption that the BSC arm from Study CO-17 was equivalent to "Usual Care" in terms of effectiveness was not adequately justified in the re-submission.

Cetuximab in combination with irinotecan tended to have more serious adverse events (AEs) and Grade 3/4 AEs compared to cetuximab monotherapy. The most common treatment related grade 3 or 4 AEs were diarrhoea, neutropenia, asthenia and rash in the combination therapy group compared to asthenia, dyspnea, rash and abdominal pain in the cetuximab monotherapy group. These AEs were expected to be less in the BSC group. Cetuximab monotherapy had a greater incidence of any adverse event of grade 3 or higher compared to the BSC group ($p<0.001$). Patients in the cetuximab monotherapy group had a higher incidence of rash, infection without neutropenia, confusion and other pain as well as hypomagnesemia and infusion reactions. Many of these reactions were known and expected reactions of cetuximab.

9. Clinical Claim

The re-submission described cetuximab plus irinotecan as superior in terms of comparative effectiveness compared to cetuximab monotherapy which was in turn superior compared to best supportive care (considered equivalent to Usual Care) but associated with more toxicity. Based on the supporting data the PBAC did not accept this claim.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented in the re-submission. The incremental cost per extra QALY gained was in the range of $45,000 - $75,000 for the base case K-RAS wild-type patients and in the range of $105,000 - $200,000 for all patients.

The results of the sensitivity analyses indicated that the incremental cost effectiveness ratio (ICER) values were most sensitive to clinical benefit in terms of survival. The magnitude of survival benefit associated with cetuximab plus irinotecan over 'Usual Care' used in the stepped economic evaluation was derived from absolute rather than relative treatment effects in an indirect comparison across single arm studies. The economic evaluation also failed to examine any overall impact of the reliability, sensitivity and specificity and accessibility of K-RAS testing. The PBAC was of the opinion that the above aspects of the economic evaluation tended to bias the clinical benefit in favour of the proposed drug combination.

11. Estimated PBS Usage and Financial Implications

The likely number of prescriptions per year was estimated to be < 10,000 and the financial cost to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated to be between $10 million - $30 million in Year 5.

12. Recommendation and Reasons

The Committee considered that the appropriate current comparator in the setting of metastatic colorectal cancer (mCRC) was best supportive care, as there was no evidence that patients with mCRC whose disease had progressed despite treatment with oxaliplatin, irinotecan and 5-fluorouracil will benefit from further treatment with the currently available chemotherapeutic agents. This was a change from the Committee's finding in November 2005 that usual care, a composite of active chemotherapy and best supportive care, was the appropriate comparator and reflected recent advances in knowledge in this area. This also meant that no costs for chemotherapy can be validly included in the comparator arm of the economic evaluation.

The PBAC noted that, although not made explicit by the requested restriction, the relevant comparison for this application was that of cetuximab plus irinotecan against best supportive care, and that if this was the intent of the restriction and the evidence base used to justify the listing then the restriction should be amended to specify that cetuximab must be used in combination with irinotecan. The Committee also noted that, in an update to the last submission for cetuximab in mCRC, the restriction now sought to limit treatment to patients whose tumour had wild type K-RAS. Although PBAC considered that it was quite possible that K-RAS status was likely to be an effect modifier, considerable uncertainty remains around the circumstances in which K-RAS status will predict outcome, and the extent of benefit conferred by it. It was possible that K-RAS status might predict the natural course of mCRC independent of treatment with cetuximab, in addition to being an effect-modifier for

cetuximab. Data from the CAIRO2 cetuximab trial were not supportive of K-RAS status as a predictive indicator of responsiveness to treatment. Furthermore there are likely to be other molecular markers which predict response to cetuximab and the use of K-RAS alone requires further justification. Garassino et al. (2008) and Lievre et al. (2008) proposed that a randomised, controlled study, specifically aimed to examine the possible predictive and prognostic role of K-RAS mutations, was needed to definitively resolve whether K-RAS mutations were an independent prognostic factor for cetuximab treatment[1,2].

The Committee noted that there were no direct comparative studies of cetuximab plus irinotecan against best supportive care in mCRC patients with wild type K-RAS and that the evidentiary basis for the K-RAS population was based on analyses of retrospective data extracted from four studies. The indirect comparison between cetuximab plus irinotecan and best supportive care using the results from the open-label randomised BOND and CO-17 trials was considered by the Committee to have limited relevance to this population, primarily because no information on K-RAS status was available for the BOND study.

In the absence of evidence from a proper randomised comparison, PBAC considered that the claim of an overall survival benefit of approximately 40 weeks was not well substantiated, as was based on non-experimental evidence that was likely to be subject to selection bias (confounding). The Committee considered the response rate from study CO17 likely to be more reliable as it was collected, albeit retrospectively, from an RCT, whereas the De Roock result was derived from a retrospective analysis of mCRC patient K-RAS data that were lumped from four different trials, and was likely to overestimate the benefit of cetuximab treatment.

The modelled economic evaluation presented thus relied upon an estimate of overall survival that was highly uncertain. The most reliable results were those derived from study CO17 in which the group with wild type K-RAS mCRC treated with cetuximab monotherapy demonstrated a statistically significant improvement in overall survival of around 20 weeks over the same group treated with BSC. However, the modelled evaluation assumed a benefit of approximately 40 weeks for the combination of cetuximab with irinotecan; thus most of the uncertainty arose from the additional benefit assumed to accrue from the addition of irinotecan to cetuximab. This, together with the drug price proposed in the submission, resulted in an incremental cost effectiveness ratio (ICER) that was both high and highly uncertain.

The PBAC also identified the model's inclusion of the costs but not the clinical benefit of active chemotherapy for 60 % of patients in the BSC arm as favouring cetuximab. The use of the QoL estimates derived from the MABEL[3] study and Petrou and Campbell[4] were considered to add to the uncertainty in the ICER. Although quality of life were collected in Study CO-17, these were not used in the economic evaluation as the interpretation of QoL data was complicated by differences in compliance rates between the cetuximab monotherapy

[1] Garassino et al. Should KRAS mutations be considered an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab? J Clin Oncol 2008 DOI:10.1200/JCO.2008.16.8195.
[2] Lievre et al. (2008) KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008; 26:374-379.
[3] Monoclonal Antibody Erbitux in a European Pre-License Study.
[4] The utility values obtained by Petrou and Campbell (1997) were used in the July 2005 PBAC submission; the utility values by Petrou and Campbell have also been used in NICE reviews for irinotecan, oxaliplatin and raltitrexed for the treatment of advanced mCRC (Jones, L et al 2001).

and best supportive arms. Lastly, the submission failed to assess the impact of the accuracy of K-RAS testing on the incremental cost-effectiveness of treatment.

Thus, overall the PBAC rejected the application 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.

Recommendation:
Reject

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

Merck Serono Australia is disappointed with this recommendation and will continue to work with the PBAC to ensure access to this targeted therapy for patients with metastatic colorectal cancer.