PUBLIC SUMMARY DOCUMENT

Product: CETUXIMAB, solution for IV 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 2010

1. Purpose of Application:

The submission sought an extension to the current Authority required listing to include first line treatment of patients with K-RAS wild type (K-RAS wt) metastatic colorectal cancer (mCRC).

2. Background:

This was the first time that 1st-line cetuximab, in combination with chemotherapy, for mCRC had been considered by the PBAC. Cetuximab is currently PBS listed for use in squamous cell cancer of the head and neck.

At the November 2008 meeting, the PBAC rejected an application for third-line treatment of mCRC in patients whose tumour has the K-RAS 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. The PBAC noted that no new clinical data were presented in this submission but additional comments on biomarker identification and revised economic evaluation sensitivity analyses were presented.

3. Registration Status:

Metastatic colorectal cancer

Cetuximab was registered by the TGA on 14 January 2010 for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, K-RAS wild-type metastatic colorectal cancer, in combination with chemotherapy, or as a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy.

4. Listing Requested and PBAC's View:

CETUXIMAB

Authority Required

Initial PBS-subsidised treatment, in combination with first line chemotherapy, of a patient with previously untreated metastatic colorectal cancer where there is evidence that the patient has KRAS wild type tumour material.

NOTE:

Cetuximab is not reimbursed for use in combination with bevacizumab.

Authority Required

Continuing PBS-subsidised treatment, in combination with first line chemotherapy, of a patient with metastatic colorectal cancer who has previously been issued with an authority prescription for cetuximab and who does not have progressive disease and who remains on first line chemotherapy.

NOTE:

Cetuximab is not reimbursed for use in combination with bevacizumab.

5. Clinical Place for the Proposed Therapy:

The submission claimed that cetuximab is an alternative to bevacizumab for use as first line treatment of patients with K-RAS wild type metastatic colorectal cancer in combination with chemotherapy.

6. Comparator:

The submission nominated bevacizumab in combination with either FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) or FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin), claiming this would be the treatment that cetuximab would be most likely to substitute.

7. Clinical Trials

The submission conducted multiple indirect comparisons, concerning progression free survival (PFS) and overall survival (OS), between cetuximab and bevacizumab. All of the studies had been published at the time of submission. The included studies including the status of the availability of a K-RAS analysis for each study are summarised in the tables below.

Summary of the trials used to conduct the indirect comparison between cetuximab and bevacizumab

Trial ID / first author	Drugs compared	Common references used	K-RAS analysis available?
Irinotecan based comparisons			
CRYSTAL	Cetuximab + FOLFIRI	FOLFIRI	Yes
AVF2107	Bevacizumab + IFL	IFL[1]	Yes
BICC-C	Bevacizumab + FOLFIRI[2]; Bevacizumab + mIFL	FOLFIRI mIFL[3]	No
FOLFOX based comparison			
OPUS	Cetuximab + FOLFOX	FOLFOX	Yes
NO16966	Bevacizumab ± FOLFOX	FOLFOX	No

Trial ID / First author	Protocol title / Publication title	Publication citation
Irinotecan based comparisons		
CRYSTAL Van Cutsem 2009	Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer."	Van Cutsem ECH et al, The New England Journal of Medicine

		2009, 360(14): 1408-1417
Becerra C 2007	Highlights from: Annual Meeting of the American Society of Clinical Oncology - Chicago, Illinois; June 1-5, 2007.	Becerra CY et al, Clinical Colorectal Cancer, 2007, 6(8): 556-560
AVF2107 Hurwitz HL 2004	Bevacizumab plus irinotecan, fluorouracil, and folinic acid for metastatic colorectal cancer.	Hurwitz HFL, Novotny W et al, The New England Journal of Medicine, 2004;350(23): 2335-2342
Hurwitz 2005	Bevacizumab in combination with fluorouracil and folinic acid: an active regimen for first line metastatic colorectal cancer.	Hurwitz HIL et al, Journal of Clinical Oncology, 2005; 23(15): 3502-3508
Ince WL 2005	Association of K-RAS, BRAF, and p53 status with the treatment effect of bevacizumab.	Ince WL, Jubb AM et al, Journal of the National Cancer Institute, 2005; 97(13): 981-989
Kabbinavar 2008	Health-related quality of life impact of bevacizumab when combined with irinotecan, 5-fluorouracil, and folinic acid or 5-fluorouracil and folinic acid for metastatic colorectal cancer.	Kabbinavar FFW, Holmgren JF et al, Oncologist, 2008; 13(9): 1021-1029
BICC-C Fuchs 2007	Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first line treatment of metastatic colorectal cancer: results from the BICC-C Study.	Fuchs CS, Marshall J et al, Journal of Clinical Oncology. 2007; 25(30): 4779-4786
Fuchs CS 2008	Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first line treatment of metastatic colorectal cancer: updated results from the BICC-C study.	Fuchs CS, Marshall J et al, Journal of Clinical Oncology, 2008; 26(4): 689-690
Jackson N 2009	Comparing safety and efficacy of first-line irinotecan/fluoropyrimidine combinations in elderly versus nonelderly patients with metastatic colorectal cancer: findings from the bolus, infusional, or capecitabine with camptostar-celecoxib study.	Jackson N, Barrueco J et al, Cancer, 2009;115(12): 2617-29
FOLFOX based comparison		
OPUS Bokemeyer CI 2009	Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer.	Bokemeyer CI et al, Journal of Clinical Oncology, 2009; 27(5): 663-671
NO16966 Saltz LB 2008	Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study.	Saltz LBS et al, Journal of Clinical Oncology, 2008; 26(12): 2013-2019
Cassidy JS 2008	Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic	Cassidy JS et al, Journal of Clinical Oncology, 2008; 26(12): 2006-2012

	colorectal cancer.	

1. Irinotecan bolus, infusional fluorouracil and folinic acid: a different regimen to FOLFIRI.
2. Included celecoxib
3. Modified IFL

8. Results of Trials

Comparative effectiveness

The submission conducted both one-step and three-step indirect comparisons.
The submission acknowledged the high uncertainty surrounding the results from the multi-step approach and therefore considered the one-step indirect comparisons as the primary analyses in support of the listing of cetuximab on the PBS. The primary endpoint of the indirect comparison between cetuximab and bevacizumab was PFS.

The one step indirect comparison consisted of the PFS and OS results from CRYSTAL (FOLFIRI plus cetuximab compared with FOLFIRI alone) compared with the relevant results from each of the other two trials: AVF2107 (IFL plus bevacizumab compared with IFL) and BICC-C (FOLFIRI plus bevacizumab (Period 2) compared with FOLFIRI (Period 1)).

K-RAS STATUS AS AN EFFECT MODIFIER

The PBAC noted that the advice that the evidence for K-RAS as a treatment effect modifier rather than an independent prognostic factor was a major issue of contention in the literature and remained inconclusive. The PBAC considered the nature of the evidence was retrospective and there was potential for selection bias, ascertainment bias and confounding to have affected the results observed in these post hoc analyses.

The table below summarises the PFS results from AVF2107, which compared IFL + bevacizumab with IFL + placebo. Wild type patients on IFL alone had better PFS compared to mutants on IFL alone although the numbers of patients in these subgroups were small.

PFS results from AVF2107 for the ITT population and a subgroup of K-RAS evaluable patients

Outcome	IFL + Bevacizumab	IFL+placebo	Hazard ratio[a]	p-value[b]
Median PFS time, months				
ITT months 95% CI	n=402 10.6 (n.r.)	n=411 6.2 (n.r.)	 0.54 (0.45-0.66)	 <0.0001
K-RAS Subgroup months 95% CI	n=129 11.3 (n.r.)	n=101 6.3 (n.r.)	 0.44 (0.32-0.61)	 <0.0001
K-RAS wild type months 95% CI	n=85 13.5 (n.r.)	n=67 7.4 (n.r.)	 0.44 (0.3-0.7)	 <0.0001
K-RAS mutant months 95% CI	n=44 9.3 (n.r.)	n=34 5.5 (n.r.)	 0.41 (0.2-0.7)	 0.0008

[a] Hazard ratio for bevacizumab + IFL over IFL.
[b] Log-rank p-value
CI = confidence interval; IFL = irinotecan bolus fluorouracil and folinic acid;
ITT = Intention to treat; PFS = progression-free survival.

The PBAC noted the reports of Cejas et al (2009) on the role of K-RAS mutations in lung metastasis, which found that patients with primary tumours possessing K-RAS mutations had a shorter disease-free survival period after metastasis resection (12.0 versus 18.0 months; P = 0.035) compared to wild type patients; and Richman et al (2009) on K-RAS status as a single independent prognostic marker which found no evidence of an effect on PFS in simple or multivariable analyses (HR=1.14; 95% CI, 0.98-1.33). From Richman et al (2010), the PBAC noted that there was evidence of an independent prognostic effect on overall survival (OS) for chemotherapy alone, because patients with KRAS-mutations had poorer OS than patients with K-RAS-wild-type (HR=1.24; 95% CI, 1.06-1.46).

The PBAC noted the sponsor's claim based on four (4) published studies in mCRC that K-RAS status was not a prognostic factor independent from any drug therapy. The PBAC recalled that in March 2009 it considered B-RAF to be a marker for resistance in colorectal cancer and noted that K-RAS and B-RAF were mutually exclusive. The PBAC noted the reports by Siena et al (2009) and Azad and Tebbutt (2008) which considered the role of other potential biomarkers such as the BRAF mutation and concluded that while there is some early suggestion that the presence of BRAF mutation may predict a lack of response to EGFR inhibitors, further work is required before this could be used to guide clinical practice.

The PBAC acknowledged that the updated meta-analysis of the CRYSTAL and OPUS trials undertaken by the sponsor which evaluated the impact of K-RAS and B-RAF status on treatment response and demonstrated that the addition of cetuximab to first-line irinotecan or oxaliplatin based chemotherapy in K-RAS wild type metastatic colorectal cancer patients extended survival by 4 months. It was noted that the effect of cetuximab is not varied by BRAF mutation status but only 4 % of patients in this study were BRAF mutant.

The trials referred to above are listed in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Cejas P.	KRAS Mutations in Primary Colorectal Cancer Tumors and Related Metastases: A Potential Role in Prediction of Lung Metastasis.	PLo SONE; 2009: 4(12): e8199.
Richman SD.	KRAS and BRAF Mutations in Advanced Colorectal Cancer Are Associated With Poor Prognosis but Do Not Preclude Benefit From Oxaliplatin or Irinotecan: Results From the MRC FOCUS Trial.	J Clin Oncol; 2009: 23(35): 5931-7.
Siena S.	Biomarkers predicting clinical outcome of epidermal growth factor receptor-targeted therapy in metastatic colorectal cancer.	Journal of the National Cancer Institute; 2009; 101(19): 1308-1324.
Azad A.	Predicting the response to targeted therapy in metastatic colorectal cancer.	Asia-Pacific Journal of Clinical Oncology; 2008; 4(4): 208-217.

TRIALS WHICH INCLUDED AN IRINOTECAN BASED BACKGROUND CHEMOTHERAPY REGIMEN (IFL OR FOLFIRI).

All indirect comparisons presented in the submission were conducted for three populations:

1. Intention To Treat (ITT) comparison (ITT CRYSTAL compared with ITT AVF2107/BICC-C);
2. Mixed comparison (KRAS wild type from CRYSTAL compared with ITT from AVF2107/BICC-C); and
3. K-RAS comparison (KRAS wild type from CRYSTAL compared with KRAS wild type from AVF2107).

<u>One step indirect comparisons using the CRYSTAL and AV2107 trials:</u>
The indirect comparison included trials that examined two different background chemotherapy regimens (IFL and FOLFIRI) and thus IFL and FOLFIRI were assumed to be a common reference. The evaluation considered that this approach was flawed as these treatments were not similar and were associated with different treatment effects (the evidence suggested that FOLFIRI was superior to IFL in terms of both clinical benefit and treatment-related toxicity). In addition, the results should be interpreted with caution given that the submission did not attempt to address issues of exchangeability and a non-inferiority margin or MCID for PFS (primary outcome) was not defined.

The table below summarises the PFS results for the K-RAS wild type indirect comparison: CRYSTAL (cetuximab-K-RAS wild type) with AVF2107 (bevacizumab-K-RAS wild type).

Trial (population)	**Group 1 PFS (months)** Median (95%CI)	**Group 2 PFS (months)** Median (95%CI)	**Hazard ratio (95% CI)**	**Log-rank p-value**	**Indirect comparison Cetux vs beva HR (95% CI) p-value**
Cetuximab					
CRYSTAL (K-RAS wild type)	**FOLFIRI + cetux,** n=316 9.90 (n.r.)	**FOLFIRI alone,** n=350 8.40 (n.r.)	0.69 (0.56, 0.87)	0.0012	
Bevacizumab					
AVF2107 (K-RAS wild type)	**IFL +beva** n=85 13.5 (n.r.)	**IFL+ placebo** n=67 7.4 (n.r.)	0.44 (0.30,0.70)	<0.0001	**1.58 (0.98, 2.55)** **P=0.06**

Cetux = cetuximab; beva = bevacizumab; HR = hazard ratio; CI = confidence interval;
FOLFIRI = irinotecan infusional fluorouracil and folinic acid; ITT = Intention to treat;
IFL = modified bolus irinotecan fluorouracil and folinic acid, n.r. = not reported;
PFS = progression-free survival.

The evaluation considered that the populations included in this comparison (that is, K-RAS wild type patients) represented the relevant population for whom PBS listing of cetuximab was sought. The PBAC noted, however, that a substantial proportion (more than 80 %) of the study population in AV2107 was not available for K-RAS testing. The median PFS in the individual treatment arms were presented without confidence

intervals. No absolute differences in PFS between the treatment arms and their confidence intervals were provided.

The submission noted that there was no difference in PFS between cetuximab and bevacizumab (p=0.06). The hazard ratio point estimate derived from the indirect comparison, as well as the upper limit of the confidence interval, suggested that in terms of clinical benefit (PFS), the balance of probability favoured bevacizumab over cetuximab in a K-RAS wild type mCRC population, i.e. point estimate suggested 1.58 times the risk of progression with cetuximab as opposed to bevacizumab. The width of the confidence interval suggested the analysis was slightly under-powered, hence the non-significant p value.

Overall Survival

For the overall survival (OS) results for the K-RAS wild type indirect comparison – CRYSTAL (cetuximab-K-RAS wild type) and AVF2107 (bevacizumab-K-RAS wild type, the submission noted that there was no difference in OS between cetuximab and bevacizumab (p=0.27). The evaluation considered the wide confidence interval for the (indirect) hazard ratio suggested a lack of power to determine statistically significant differences between the groups in terms of overall survival. The (indirect) hazard ratio point estimate also suggested that cetuximab might reduce overall survival in comparison to bevacizumab. Absolute differences in median survival and confidence intervals for the difference in median survival times were not presented, and no minimal clinically important difference (MCID) was selected, so on the basis of the information presented in the submission, the difference in overall survival between cetuximab and bevacizumab in a K-RAS wild-type mCRC population was unknown.

<u>One step indirect comparison using the CRYSTAL and BICC-C trials:</u>

An indirect comparison was presented using the CRYSTAL and BICC-C trials with FOLFIRI alone as the common reference. However, this indirect comparison was also unsound as the relative treatment effect between FOLFIRI + bevacizumab and FOLFIRI alone was derived from a non-randomised comparison (across 2 periods). Furthermore, no indirect comparison of K-RAS wild type populations using the CRYSTAL and BICC-C trials was conducted because there were no K-RAS data available for the BICC-C trial. The evaluation considered that the submission's assumption that the ITT bevacizumab population was equivalent to a K-RAS wild type population (and hence that a mixed comparison is relevant) was unconvincing, given the common finding in K-RAS trials that K-RAS wild type patients had a better prognosis than K-RAS mutant patients, irrespective of treatment or potential treatment modifying effect. This likely prognostic effect also meant that this 'mixed' comparison would be biased in cetuximab's favour.

TRIALS WHICH INCLUDED FOLFOX AS A BACKGROUND CHEMOTHERAPY REGIMEN.

Results of the indirect comparison:
Progression Free Survival:

Although effectiveness data stratified by K-RAS status were available from the OPUS cetuximab trial, there were no such data available from the NO16966 bevacizumab trial; thus the indirect comparison used data from patients who are not strictly the population for whom PBS listing of cetuximab was sought. The evaluation considered that a likely better prognosis for K-RAS wild type patients meant that such a 'mixed' comparison would be biased in favour of cetuximab. A comparison of ITT populations alone

suggested that PFS was not statistically significantly different between cetuximab plus FOLFOX and bevacizumab plus FOLFOX.

Overall Survival:
The results from the indirect comparison indicated that there were no significant differences in OS between cetuximab + FOLFOX compared with bevacizumab + FOLFOX. These results should be interpreted with caution given the nature of the indirect comparison and potential confounding of the OS endpoint by post-progression treatment.

Comparative toxicity
The submission did not adjust the safety data for different treatment exposures across the trials. The submission conducted multiple statistical analyses using relative risks and risk differences to compare each adverse event (there was no indication from the submission that the level of significance had been adjusted for such multiple analyses). Interpretation of these results should acknowledge the fact that non-significance, in a statistical sense, does not necessarily surmise lack of clinical importance, but more likely reflects lack of statistical power where the number of events is small.

The adverse event profiles for the different background chemotherapies are well established. As there were no available data from direct trials comparing cetuximab with bevacizumab, a robust comparative assessment of their toxicity profiles was difficult. However, these monoclonal antibodies are associated with some adverse events that appear to be specific to the relevant antibody. Overall, bevacizumab appeared to be associated with a significant increased risk of hypertension whilst cetuximab appeared to be associated with significantly more skin reactions e.g. rash and mucositis. Both drugs appeared to increase the risk of thromboembolic events/pulmonary embolism.
Thus cetuximab and bevacizumab appeared to have different adverse event profiles.

9. Clinical Claim

The submission claimed cetuximab plus chemotherapy (FOLFIRI/FOLFOX) as 'not different' from bevacizumab plus chemotherapy (FOLFIRI/FOLFOX) in terms of comparative effectiveness for the treatment of patients with K-RAS wild type mCRC and has a different safety profile.

10. Economic Analysis

The submission presented a cost minimisation analysis. In the K-RAS wild type group, the median treatment exposure (weeks) for the cetuximab + FOLFIRI treatment arm was 32 weeks, which was considered to underestimate the cetuximab costs overall.

The justification for a cost-minimisation approach was not well supported by the evidence of non-inferiority or equivalence presented in the submission. The adverse events selected for the cost comparison were based on statistically significant differences versus chemotherapy. All adverse events that involved non-trivial resource usage should be included in a cost comparison.

The median number of cycles was used to estimate duration of cetuximab treatment (and attendant costs) whilst Progression Free Survival (PFS) was used to estimate duration and cost of bevacizumab treatment. Median PFS did not reflect dose reductions and compliance. The costs associated with K-RAS testing were inadequately addressed in the

submission. The downstream costs associated with false positive and false negative diagnoses needed to be identified.

11. Estimated PBS Usage and Financial Implications:

The submission estimated that the requested listing would be a financial net savings to the PBS less than $10 million per year, and assumed all patients would undergo K-RAS status testing.

12. Recommendation and Reasons:

The PBAC considered that bevacizumab was not the appropriate comparator and that it was unlikely that cetuximab would substitute for bevacizumab because the K-RAS status of most mCRC patients is unknown at the time treatment commences. Therefore, bevacizumab would be used as first-line treatment in combination with chemotherapy. Even if the K-RAS status is known, clinicians are more likely to commence treatment with bevacizumab and only use cetuximab subsequently. The PBAC also considered that since bevacizumab is only available for first line therapy it was noted that the use of cetuximab as first line therapy would preclude patients from receiving bevacizumab.

The PBAC noted the results of the CRYSTAL – Progression Free Survival (PFS) Updated Analysis. For the mutant group, although the results were not statistically significant, the point estimates (7.4 months) and 95 % confidence interval of the HR (1.171 (0.887-1.544)) included worsening of PFS treatment effects as a result of the addition of cetuximab to FOLFIRI. The OPUS results - PFS (Updated Analysis) demonstrated that for mutants, the addition of cetuximab to FOLFOX resulted in significantly worse PFS (5.5 months) compared with FOLFOX alone (8.6 months). The PBAC considered that this may have important implications for patients who are false positive (false wild types) on K-RAS testing who go on to receive cetuximab. Whilst conclusive data are not available, this issue remains an important concern particularly given the high uncertainty surrounding the type of tests to be used for K-RAS testing as well as their diagnostic accuracy.

However, the PBAC acknowledged that the updated meta-analysis of the CRYSTAL and OPUS trials in the sponsor's Pre-PBAC response which evaluated the impact of K-RAS and B-RAF status on treatment response demonstrated that the addition of cetuximab to first-line irinotecan or oxaliplatin based chemotherapy in K-RAS wild type metastatic colorectal cancer patients extended survival by 4 months. It was noted that the effect of cetuximab is not varied by BRAF mutation status but only 4 % of patients in this study were BRAF mutant.

The PBAC noted that the COIN Study (Continuous versus Intermittent oxaliplatin-based combination chemotherapy in patients with advanced colorectal cancer) was excluded because effectiveness data were not available. However recently, data emerging from the COIN trial were discussed at the joint 15th Congress of the European Cancer Organisation (ECCO) and 34th Congress of the European Society for Medical Oncology (ESMO) in Berlin, Germany. The investigators determined K-RAS status in 80 % of patients, finding wild-type K-RAS in 56 % and K-RAS mutations in 44 %. The PBAC noted that in patients with K-RAS wild-type mCRC disease, the median overall survival (OS) was not significantly improved with the addition of cetuximab to chemotherapy (oxaliplatin + 5-fluorouracil + folinic acid) 17.0 months versus 17.9 months (chemotherapy alone). Median two-year survival was 36 % and 34 %, respectively, and

progression-free survival (PFS) was 8.6 months in both arms. Overall survival in patients with KRAS mutations was 13.6 months with the addition of cetuximab to chemotherapy and 14.8 months with chemotherapy alone.

The PBAC concluded that the clinical effect was at most modest and very little benefit was demonstrated from the COIN study. There was also the potential for harm in patients who are false positive (false wild types) on K-RAS testing who go on to receive cetuximab as survival has been shown to be worse in patients who are K-RAS mutant and receive chemotherapy with cetuximab.

The PBAC noted that the evidentiary basis of the submission to support the claim of equi-effectiveness between cetuximab and bevacizumab is based on an indirect comparison approach. The PBAC agreed that the main area of clinical uncertainty was problems with the indirect comparison as identified by the ESC as follows:

- lack of exchangeability across the trials, and therefore the results of the indirect comparison were highly uncertain, and were difficult to interpret;
- indirect comparison based on limited bevacizumab effectiveness data in the intended population, that is, the K-RAS wild type population;
- for the irinotecan based chemotherapy trials, the 'common reference' is not common (IFL and FOLFIRI);
- for the CRYSTAL versus BICC comparison, there is a loss of randomisation across the two periods of the BICC-C trial;
- No non-inferiority margin or MCID in terms of the primary outcome (PFS) is considered or defined in the submission;
- For mutants, the addition of cetuximab to FOLFOX results in significantly worse PFS.

The PBAC agreed that cetuximab plus chemotherapy compared with bevacizumab plus chemotherapy has a different safety profile. However, the PBAC also agreed with the ESC that non-inferiority of cetuximab compared to bevacizumab had not been conclusively established due to the high uncertainty regarding the validity of the presented indirect comparisons, the lack of a specified minimal clinically important difference (MCID) for the primary outcome of PFS and the lack of adequate K-RAS data for the comparator, bevacizumab.

The PBAC noted that the duration of treatment from the CRYSTAL trial, used to calculate the costs of cetuximab, was sourced from the ITT population (22 weeks) rather than the K-RAS wild type population (32 weeks). The PBAC agreed that the cetuximab costs may be considerably underestimated. If the treatment exposure in K-RAS wild type patients in CRYSTAL is considered a more reasonable duration, the net financial implications for listing cetuximab on the PBS would increase from an approximate claimed savings of less than $10 million per year to an approximate cost per year in the range of $10 to $30 million. The PBAC also noted that the submission's estimates were based on cetuximab substituting bevacizumab and did not account for the costs of using cetuximab after bevacizumab.

The PBAC noted that if cetuximab was listed for first-line treatment of metastatic colorectal cancer, patients treated with cetuximab would not be able to access bevacizumab after failure of cetuximab under the circumstances requested in the submission. However, the PBAC considered that cetuximab may have a role for first-line

treatment in combination with FOLFOX or FOLFIRI in patients who have metastatic disease confined to the liver, which is unresectable, as recommended by NICE.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit and uncertain cost-effectiveness.

However, the PBAC recalled that cetuximab was considered to be an active agent in the treatment of metastatic colorectal cancer when given as monotherapy in the third-line setting. In the November 2008 submission, results derived from study 017 in which the group with wild type K-RAS mCRC was treated with cetuximab monotherapy, demonstrated a statistically significant improvement in overall survival of around 20 weeks over the same group treated with BSC. The PBAC noted that due to problems with the modelled evaluation and the drug price proposed the submission was rejected on the basis of high and highly uncertain incremental cost-effectiveness.

The PBAC noted that the submission meets criteria for independent review.

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

The sponsor has no comment.