PUBLIC SUMMARY DOCUMENT
Product: Panitumumab, concentrated solution for infusion, 20 mg per mL, 5 mL, Vectibix®
Sponsor: Amgen Australia Pty Ltd.
Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission sought a Section 85 Authority Required listing (and inclusion in the Chemotherapy Pharmaceuticals Access Program (CPAP)) for treatment of K-RAS wild type (WT) metastatic colorectal cancer (mCRC), after failure of treatment with a fluoropyrimidine, irinotecan and oxaliplatin.

2. Background

Panitumumab had not previously been considered by the PBAC.

3. Registration Status

Panitumumab was TGA registered on 14 May 2008 for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma in patients who have disease progression following treatment with a fluoropyrimidine, oxaliplatin- and irinotecan-based chemotherapy.

4. Listing Requested and PBAC's View

Authority required
Initial treatment of a patient with metastatic colorectal cancer that meets all of the following criteria:

- Bearing the wild-type K-RAS gene;
- With an ECOG performance status of 2 or less; and
- Who has failed treatment with a fluoropyrimidine, irinotecan and oxaliplatin.

The sponsor proposed that a written authority application be required with inclusion of a copy of the report from an Approved Pathology Authority providing evidence of the absence of mutations of the K-RAS gene in tumour material.

Duration of initial supply is 8 weeks of treatment.

Authority required
Continuing treatment of a patient with metastatic colorectal cancer who has demonstrated a lack of disease progression with previous treatment with panitumumab.

The sponsor proposed that a written statement that the patient's disease has not progressed must be provided.

Duration of continued supply is 14-week cycles.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Colorectal cancer is the second most common type of cancer and the second-leading cause of cancer-related death in Australia. Panitumumab would provide a treatment option for patients who have failed the current standard chemotherapeutic options.

6. Comparator

The submission nominated best supportive care (BSC) comprising antibiotics, analgesics, radiation therapy, corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated but excluding active chemotherapy as the comparator. The PBAC accepted this as appropriate.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented one open-label, randomised controlled trial (Study 408) as key evidence, comparing panitumumab 6mg/kg with BSC in the treatment of chemotherapy refractory mCRC. Patients were randomised to receive panitumumab plus BSC (referred to as the panitumumab arm) or BSC alone (referred to as the BSC arm).

While K-RAS had not been specifically identified at the time, the study commenced, the possibility that a biomarker may exist was foreseen and tumour tissue was prospectively collected for biomarker analysis according to the trial protocol

Details of the trial and associated reports, published at the time of the submission are presented in the table below.

Trial ID/ First author	Protocol Title/ Publication title	Publication citation
Study 408	An open-label, randomised, phase 3 clinical trial of ABX-EGF plus best supportive care versus best supportive care in subjects with metastatic colorectal cancer. 20020408 Clinical study report, 2007.	Not published
	An open-label, randomised, phase 3 clinical trial of ABX-EGF plus best supportive care versus best supportive care in subjects with metastatic colorectal cancer. 20020408 KRAS Flash Report, 2007.	Not published
Van Cutsem E *et al*.	Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer.	*Journal of Clinical Oncology*. 2007, 25(13):1658-64
Siena S *et al.*	Association of progression-free survival with patient-reported outcomes and survival: results from a randomized phase 3 trial of panitumumab.	*British Journal of Cancer*. 2007. 97(11):1469-74
Sartore-Bianchi A *et al.*	Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with panitumumab.	*Journal of Clinical Oncology*. 2007. 25(22):3238-45
Peeters M *et al.*	Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy 2009	*Cancer (in press)*
Gibson TB *et al.*	Randomized phase III trial results of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, in metastatic colorectal cancer.	*Clinical Colorectal Cancer*. 2006. 6(1):29-31

8. Results of Trials

The submission presented results for the "all enrolled" analysis set as well as the "wild-type" (non-mutated) and "mutant" K-RAS subgroups. The patients bearing the wild type K-RAS gene were the population for whom PBS listing was sought. Only the results of the comparative effectiveness of panitumumab versus BSC in patients expressing the wild-type K-RAS gene and those bearing the mutant K-RAS gene were presented.

[The results for the "all enrolled" analysis set indicated a statistically significant improvement in progression free survival (PFS) in the panitumumab arm compared to the BSC arm (median 8.0 weeks in panitumumab arm vs. 7.3 weeks BSC arm) and no difference in overall survival (OS).]

The primary end point of the trial was PFS, with key secondary end points including OS and best objective response defined as the best disease status from randomisation through to the end of the study which included complete response, partial response, stable disease and progressive disease. The key results of the analysis of PFS for the K-RAS analysis set are presented in the table below. The analysis of the K-RAS subgroups (mutant and wild type) in the trial was post hoc.

Summary of the analysis of progression free survival (K-RAS efficacy analysis set)

	Wild-type K-RAS efficacy analysis set		**Mutant K-RAS efficacy analysis set**	
	Panitumumab (n = 124)	**BSC (n = 119)**	**Panitumumab (n = 84)**	**BSC (n = 100)**
	n (%)	n (%)	n (%)	n (%)
Subjects with events	115 (93)	114 (96)	76 (90)	95 (95)
Disease progression	93 (75)	103 (87)	65 (77)	78 (78)
Death, any cause	22 (18)	11 (9)	11 (13)	17 (17)
Subjects censored	9 (7)	5 (4)	8 (10)	5 (5)
Kaplan-Meier (weeks)				
Median (95% CI)	12.3 (8.3, 16.1)	7.3 (7.0, 7.7)	7.4 (7.3, 7.9)	7.3 (6.3, 7.9)
Hazard ratio (95% CI)	0.45 (0.34, 0.59)		0.99 (0.73, 1.36)	
P-value	<.0001		0.9732	

A quantitative interaction test at 5% significance level was used to compare the magnitude of the relative treatment effect on PFS between the wild type and mutant K-RAS subgroups. This test was significant (P<0.0001).

A statistically significant improvement in PFS was observed favouring the panitumumab group compared with the BSC group in patients with tumours expressing wild type K-RAS. The median PFS was significantly longer, at 12.3 weeks, in patients with wild type K-RAS treated with panitumumab than those with mutant K-RAS (7.4 weeks). This can be compared with 7.3 weeks in both K-RAS subgroups treated with BSC.

The PBAC noted that there were more deaths in the K-RAS wild type panitumumab treated group than in the wild type BSC group (18% vs. 9%), despite improved progression free survival in the former group

The analysis of overall survival showed that, although more patients were deemed progression free with panitumumab compared to BSC, this did not translate into differences in OS (median overall survival: 8.1 months panitumumab wild type vs. 7.6 months BSC wild type). The submission claimed that this is due to the effect of early cross over of patients from BSC to panitumumab treatment and the magnitude of this cross-over (76%). The PBAC acknowledged this was a possibility but that it was also possible that PFS is not a valid surrogate for OS, and thus no effect of panitumumab on OS had been demonstrated.

The PBAC considered that K-RAS status may be an effect modifier but that considerable uncertainty remains around the circumstances in which K-RAS status will accurately predict outcome, and the extent of benefit conferred by it.

For PBAC's comments on these results, see Recommendation and Reasons.

The PBAC noted that the analysis of the toxicity profile of panitumumab, comparing wild type and mutant subgroups suggested that, relative to BSC, panitumumab is associated with additional toxicities. The risk of several adverse events, particularly erythema, pruritus and dermatitis acneiform was found to be elevated following the addition of panitumumab to BSC. The PBAC further noted an increased risk of adverse events in patients receiving panitumumab who have the wild type K-RAS gene. However, until comparable data emerge from prospective pre-planned analyses, it was difficult to confidently conclude whether there is a K-RAS modifying effect for toxicity (in addition to PFS and best objective response) in mCRC patients.

9. Clinical Claim

The submission described panitumumab as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC. According to the analysis of K-RAS subgroups, the submission further claimed that the treatment effect associated with panitumumab is exclusively confined to patients expressing the wild type K-RAS gene. The PBAC considered that the evidence provided did not adequately support these descriptions.

10. Economic Analysis

A stepped modelled economic evaluation was presented in the form of cost-effectiveness and cost-utility analyses. Patients were modelled using a decision tree approach. Modelling was based upon the differential survival observed within the various best objective response categories (complete response, partial response, stable disease, and progressive disease).

The estimated base case incremental cost per Quality Adjusted Life Year (QALY) fell in the range of $45,000 to $75,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated a cost per year to the PBS of between $10-30 million in Year 5. The PBAC considered this uncertain.

12. Recommendation and Reasons

The Committee agreed that there is no evidence that patients with metastatic colorectal cancer (mCRC) whose disease has progressed despite treatment with oxaliplatin, irinotecan and 5-fluorouracil will benefit from further treatment with the currently available chemotherapeutic agents. Thus, best supportive care (BSC) is an appropriate comparator in this setting.

The Committee noted that although K-RAS had not been identified a-priori as a predictive marker in the key trial (Study 408), the possibility that biomarkers might exist was predicted and tumour tissues were prospectively collected according to the trial protocol with about 90 % of patients having samples analysed for K-RAS mutations. The Committee considered that K-RAS status might be an effect modifier but that considerable uncertainty remains around the circumstances in which K-RAS status will accurately predict outcome, and of the extent of benefit conferred by it. For example, the available evidence does not allow discernment of whether K-RAS status is a prognostic factor in its own right or a predictor of responsiveness to treatment. In trial 408, there were more deaths in the K-RAS wild type panitumumab treated group than in the wild type BSC group (18 % vs. 9 %) despite improved progression free survival in the former group. Additionally data from the CAIRO2 cetuximab trial are not supportive of K-RAS status as a predictive indicator of responsiveness to treatment.

However the largest area of concern to the PBAC was the inadequacy of the evidence from trial 408 to support the claim of a better therapeutic effect for panitumumab over BSC, with the Committee agreeing with its Economic Sub-Committee that the large proportion of patients in the BSC arm (76 %) that crossed over to panitumumab made the endpoints difficult to interpret for a number of reasons.

Firstly, the primary outcome of progression free survival is likely to be highly confounded by this crossover and other aspects of the trial design. For example, the open label design together with the possibility for patients in the BSC arm to switch to active treatment upon progression, and for all patients receiving active treatment to cease that treatment upon (further) progression, is likely to have biased patients and investigators to making an earlier determination of progression in the BSC arm (thus allowing patients to switch to active treatment) and a later determination of progression in the panitumumab arm (thus allowing patients to continue on active treatment for longer). This is particularly so as the determination of disease status, (assessment of progression using radiographic and clinical data) treatment and withdrawal from the study was as the discretion of the investigator and even though the assessment of disease progression was undertaken by a blinded independent review committee, the decision to make an assessment was unblinded. It is also probable that it was the sickest patients with the most rapidly progressing disease in the BSC arm that would not have crossed over to active treatment. The cumulative effect of these factors will be to overestimate the extent of progression free survival which can be attributed to panitumumab.

Secondly, because the majority of "BSC" patients were on panitumumab for almost all the study period, this group of patients is likely to have derived similar benefits, if any, to active treatment as the group initially randomised to panitumumab. This is reflected in the lack of difference in overall survival between the two groups (median overall survival: 8.1 months

panitumumab wild type vs. 7.6 months BSC wild type). The submission attempts to deal with the uncertainty introduced by the cross-over design by censoring all the cross-over patients from the overall survival estimate, however the implication of this censoring is that the BSC arm is shrinking both by deaths as well as by censoring after progression. This results in a much smaller sample size in the BSC arm for the time from progression to death, so the mean overall survival value in the BSC arm is highly uncertain.

Consequently, the PBAC concluded that there is considerable uncertainty around the extrapolated survival data in the modelled economic evaluation, with survival in the BSC arm likely to be underestimated and that in the panitumumab arm likely to be overestimated.

Further, the Committee also did not accept the use of the mean progression free survival (PFS) rather than median PFS in the modelled economic evaluation, given the likely reason for treatment effect was cross-over at progression and the sample size is smaller and thus the mean value is more likely to be affected by outliers. The Committee furthermore agreed with ESC that step 4 of the economic evaluation is very dependent on the mix of outcomes in the Australian population being the same as in the pivotal trial. This is highly unlikely due to the issues of cross over and the treatment pathways which will change with the listing of bevacizumab.

The PBAC considered the subjective nature of the assessment upon which the decision to cease treatment is based, means that in practice, not all patients with progressive disease will cease treatment after 8 weeks. This uncertainty, together with those described above and with uncertainties around the estimation of eligible patients results in high uncertainty in the total financial cost.

Thus, overall the PBAC rejected the application because of uncertainty about the extent of clinical benefit over best supportive care, both in terms of progression free and overall survival, 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

The sponsor has no comments.