PUBLIC SUMMARY DOCUMENT

Product: Panitumumab, concentrate solution for infusion, 100 mg in 5mL & 400 mg in 20 mL, Vectibix®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission sought Section 100 Efficient Funding of Chemotherapy Private Hospital/Private Clinic Authority Required and Public Hospital Authority required (STREAMLINED) listings for:
1) Treatment, as monotherapy or in combination with FOLFIRI, of a patient with a WHO performance status of 2 or less and with a K-RAS wild-type metastatic colorectal cancer after failure of first-line chemotherapy; and
2) Treatment, in combination with FOLFOX, of a patient with a WHO performance status of 2 or less with previously untreated K-RAS wild-type metastatic colorectal cancer where treatment with bevacizumab is unsuitable.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This was the second submission for panitumumab considered by the PBAC.

In November 2008, PBAC considered a submission to list panitumumab as a Section 85 Authority Required listing (and inclusion in the Chemotherapy Pharmaceuticals Access Program (CPAP)), for the treatment of K-RAS wild type (WT) metastatic colorectal cancer (mCRC), after failure of treatment with a fluoropyrimidine, irinotecan and oxaliplatin.

The PBAC rejected the submission over uncertainty in the extent of the clinical benefit over the comparator, best supportive care, in progression free and overall survival, and because of the resultant high and highly uncertain cost-effectiveness ratio.

A copy of the Public Summary Document from the November 2008 meeting, is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-panitumumab-nov08

3. Registration Status

Panitumumab was TGA registered on 14 May 2008. It is indicated for the treatment of patients with wild-type K-RAS metastatic colorectal cancer (mCRC):

- As first-line therapy in combination with FOLFOX. Efficacy is influenced by patient performance status;
- As second line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Efficacy may be influenced by patient performance status; and

- As monotherapy in patients after the failure of standard chemotherapy

4. Listing Requested and PBAC's View

Section 100 (Efficient Funding of Chemotherapy)
Private Hospital/Private Clinic Authority required
Public Hospital Authority Required (STREAMLINED)

Proposed main restriction – after failure of 1st-line chemotherapy (later-line):
Initial PBS-subsidised treatment, as monotherapy or in combination with FOLFIRI, 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 FOLFIRI, of a patient with K-RAS wild-type metastatic colorectal cancer who has previously been issued with an authority prescription for panitumumab and who does not have progressive disease.

Proposed additional restriction – subset of previously untreated patients (1st-line):
Initial PBS-subsidised treatment, in combination with FOLFOX, of a patient with a WHO performance status of 2 or less and with previously untreated K-RAS wild-type metastatic colorectal cancer where treatment with bevacizumab is unsuitable.

Continuing PBS-subsidised treatment, in combination with FOLFOX, of a patient with K-RAS wild-type metastatic colorectal cancer who has previously been issued with an authority prescription for panitumumab and who does not have progressive disease.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The sponsor anticipated that panitumumab will substitute for cetuximab after failure of first-line chemotherapy and that it may be used as monotherapy or in combination with FOLFIRI.

For the proposed additional (first-line) PBS listing, it was anticipated that a small proportion of patients (deemed unsuitable for bevacizumab) may be treated with an EGFR inhibitor earlier than is currently possible within the constraints of the PBS subsidised cetuximab restriction. Panitumumab would be added to the FOLFOX chemotherapy regimen that patients would otherwise receive in the first-line setting.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated cetuximab as the main comparator in the later-line setting. The submission nominated FOLFOX alone as the main comparator in first-line setting.

The PBAC considered that the nominated comparator in each setting was reasonable.

7. Clinical Trials

Later-line setting (comparator – cetuximab):

The submission presented four randomised controlled trials for an indirect comparison between panitumumab and cetuximab.

Using a "common reference" of chemotherapy, the submission conducted an indirect comparison between: Trial 0181, comparing panitumumab + FOLFIRI with FOLFIRI; and the EPIC trial, comparing cetuximab + irinotecan with irinotecan. Using a common reference of best supportive care (BSC), an indirect comparison between; Trial 0408, comparing panitumumab + BSC with BSC, and Trial CO.17, comparing cetuximab + BSC with BSC was conducted.

First-line setting (comparator - FOLFOX):

The submission presented two randomised trials to support first-line panitumumab in patients unsuitable for bevacizumab (given only in combination with chemotherapy): PRIME compared panitumumab + FOLFOX vs FOLFOX in previously untreated mCRC patients and PEAK compared panitumumab + FOLFOX vs bevacizumab + FOLFOX in previously untreated mCRC patients.

Details of the trials 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
Later-line setting- "Common reference" irinotecan based chemotherapy		
Trial 0181 Peeters et al	Randomised phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as 2nd-line treatment in patients with metastatic colorectal cancer	J*ournal of Clinical Oncology*. 2012; 28(31): 4706-4713
Price et al	Efficacy of panitumumab plus FOLFIRI versus FOLFIRI alone in patients with wild-type (WT) K-RAS metastatic colorectal cancer (mCRC) treated with prior oxaliplatin or bevacizumab regimens results from 2005181	*European Journal of Cancer*. 2011; 47: S431-S432
Bennet et al	Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first or 2nd line treatment	*British Journal of Cancer*. 2011; 105 (10): 1495-1502
Sartore-Bianchi 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): 3238-3245
Andre, et al	Panitumumab with FOLFIRI vs. FOLFIRI alone: A randomised phase 3 study for the second line treatment of patients (PTS) with metastatic colorectal cancer (mCRC)	*Annals of Oncology*, 2010; 21: i13.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Peeters, et al	Phase III study (2005181) of panitumumab (pmab) with FOLFIRI alone as 2nd-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC): Pooled safety results [abstract no. 4064]	*Journal of Clinical Oncology,* ASCO annual meeting proceedings. 2008; 26: 194
Price, et al	Randomised, open-label, phase III study of panitumumab (pmab) with FOLFIRI versus FOLFIRI alone as 2nd-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC): Efficacy by skin toxicity (ST)	*Journal of Clinical Oncology*. 2010; 28(15)
Trial 0408 Amado et al	Wild-type K-RAS is required for panitumumab efficacy in patients with metastatic colorectal cancer	*Journal of Clinical Oncology.* 2008; 26(10): 1626-1634
Van Cutsem 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): 1658-1664
Peeters, et al	Association of progression -free survival, overall survival, and patient-reported outcomes by skin toxicity and K-RAS status in patients receiving panitumumab monotherapy	*Cancer.* 2009; 115(7): 1544-1554
Siena et al	Association of progression-free survival with patient-reported outcomes and survival: Results from a randomised phase 3 trial of panitumumab	*British Journal of Cancer.* 2007;97(11): 1469-1474
Cetuximab		
EPIC Sobrero et al	EPIC: Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer	*Journal of Clinical Oncology*. 2008; 26(14): 2311-2319
Abubakr et al	Cetuximab plus irinotecan for metastatic colorectal cancer (mCRC): Safety analysis of 800 patients in a randomised phase III trial (EPIC)	*Journal of Clinical Oncology:* ASCO annual meeting proceedings. 2006l;24: 3556
Langer et al	Analysis of k-Ras mutations in patients with metastatic colorectal cancer receiving cetuximab in combination with irinotecan: Results from the EPIC trial	*Annals of Oncology.* 2008;19(S8): viii133
Sobrero et al	Cetuximab Plus Irinotecan for Metastatic Colorectal Cancer (mCRC): Safety Analysis of the first 400 Patients in a Randomised Phase III Trial (EPIC) [abstract].	*Annual Meeting Proceedings of the American Society of Clinical Oncology.* 2005;23: 266
CO 17 Karapetis, et al	K-ras mutations and benefit from cetuximab in advanced colorectal cancer	*New England Journal of Medicine.* 2008;359(17): 1757-1765
Jonker, et al	Cetuximab for the treatment of colorectal cancer	*New England Journal of Medicine.* 2007; 357(20): 2040-2048

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Asmis, et al	Comorbidity, age and overall survival in cetuximab treated patients with advanced colorectal cancer (ACRC)-results from NCIC CTG CO.17: A phase III trial of cetuximab versus best supportive care	*Annals of Oncology.* 2011; 22(1): 118-126
Au, et al	Health-related quality of life in patients with advanced colorectal cancer treated with cetuximab: Overall and K-RAS-specific results of the NCIC CTG and AGITG CO.17 Trial.	*Journal of Clinical Oncology.* 2009;27(11): 1822-1828
Karapetis, et al	Cetuximab plus BSC versus BSC alone in the treatment of metastatic EGFR-positive colorectal cancer	*Signal.* 2005;6(1): 15-17.
First-line setting direct randomised controlled trial		
PRIME Douillard, et al	Randomised, Phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) Versus FOLFOX4 alone as 1st-line treatment in patients with previously untreated metastatic colorectal cancer	*The PRIME study. Journal of Clinical Oncology.* 2010;28(31): 4697-4705.
Bennett,et al	Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first-or 2nd-line treatment.	*British Journal of Cancer.* 2011; 105 (10): 1495-1502.
Bennett,et al	Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or 2nd-line treatment.	*Journal of Clinical Oncology.* 2011; 29(15).
Douillard, et al	Effect of post-protocol anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) therapy on survival outcomes in patients with wild-type (WT) K-RAS metastatic colorectal cancer (mCRC) treated with panitumumab (pmab) plus chemotherapy	14th World Congress on Gastrointestinal Cancer, Barcelona, Spain; 27-30 June 2012

The PBAC noted that there is an ongoing direct randomised trial of panitumumab and cetuximab in the later-line setting, which will assess overall survival and is estimated to be completed later in 2013[1]. The PBAC considered that the results of this trial would be highly informative and was concerned that this study was not adequately acknowledged by the submission.

The PBAC considered that there were inadequate data on important baseline clinical variables for trials in the second-line setting. Given this, and differences in treatments in the "common reference groups", the PBAC considered the exchangeability of these trials to be weak for the purpose of valid indirect comparisons.

The PBAC considered that the results from trials relating to first-line use were not applicable for the requested listing. In PRIME, results were not presented for the population of patients

[1] http://clinicaltrials.gov/ct2/show/NCT01001377

who are unsuitable for bevacizumab, whilst in PEAK, patients who had a contraindication to receiving bevacizumab (for example patients with a significant bleeding risk) were excluded.

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

Later-line setting

PROGRESSION FREE SURVIVAL (PFS):

1) ITT analysis in the individual trials

For the irinotecan based trials, there was a statistically significant difference in PFS favouring: i) panitumumab plus FOLFIRI over FOLFIRI (Trial 0181: HR=0.80 (95%CI:0.69,0.93); p=0.0026), and ii) cetuximab plus irinotecan over irinotecan (EPIC: HR=0.69 (95%CI:0.62,0.78); p<0.0001). This trend was similar for panitumumab (Trial 0408: HR=0.54 (95%CI:0.44,0.66); p<0.001) and cetuximab (Trial CO.17: HR=0.68 (95%CI:0.57,0.80); p<0.0001) versus BSC monotherapy trials.

2) Indirect comparison between panitumumab and cetuximab (K-RAS wild type datasets). There was a statistically significant difference in PFS favouring panitumumab + FOLFIRI over FOLFIRI (Trial 0181: HR = 0.73; 95% CI: 0.60, 0.90) but not for cetuximab + irinotecan over irinotecan (EPIC: HR = 0.77; 95% CI: 0.57, 1.04) although there was a trend favouring cetuximab. K-RAS data were only available for 23% of EPIC patients so this analysis lacked statistical power. The HR indirect estimate using the "irinotecan based common reference arms" was not statistically significant (PFS HR=0.95; 95%CI:0.66,1.37).

The hazard ratio was statistically significant, favouring panitumumab over BSC (Trial 0408: HR = 0.45; 95% CI: 0.34, 0.59) and cetuximab over BSC (Trial CO.17: HR = 0.40; 95% CI: 0.30, 0.54). The indirect estimate using BSC as the common reference was not statistically significant (PFS HR = 1.13; 95% CI: 0.75, 1.68).

The PFS in the FOLFIRI arm of Trial 0181 was 3.9 months (primary analysis – Dec 2009) and 4.9 months (final analysis – May 2011) and in the irinotecan alone arm of EPIC it was 2.8 months. Thus the suitability of the comparator arms of these trials, as a common reference for the indirect comparison, was not convincing. Conversely, PFS was similar in the BSC control arms of the monotherapy trials (1.8 months for 0408 and 1.9 months for CO.17). However, for both indirect comparisons, the 95% confidence intervals are wide and do not exclude the possibility that panitumumab may be associated with a worse PFS than cetuximab. The indirect comparison presented in the submission did not specify a non-inferiority margin or a minimal clinically important difference (MCID)

Overall survival (OS):
1) Indirect comparison
The submission did not present a formal indirect comparison of OS, stating that an indirect comparison of the hazard ratios for the K-RAS wild type population was not possible for OS as survival in the control groups was confounded by the use of post-protocol anti-EGFR antibodies. The different rates of cross-over made it more difficult to conduct a valid indirect comparison.

2) ITT analyses from the individual trials
The difference in median OS between randomised treatment arms (anti-EGFR + chemotherapy or BSC vs. chemotherapy or BSC) was not statistically significant except for the cetuximab monotherapy trial, CO.17, which favoured cetuximab (Trial 0181: HR = 0.91 (95% CI: 0.79, 1.04), p=0.1552; EPIC: HR = 0.98 (95% CI: 0.85, 1.11), p = 0.7115; Trial 0408: HR = 1.00 (95% CI: 0.82, 1.22), p=0.9975; CO.17: HR = 0.77 (95% CI: 0.64, 0.92), p<0.0046).

The CO.17 trial had the smallest proportion of patients (7%), who crossed-over from the control arm, compared to the other trials (0181: 34%; EPIC: 47%; 0408: 76%). To add to this uncertainty, the proportion of cross-over across the trials did not necessarily represent K-RAS wild type patients (K-RAS wild type patients, not K-RAS mutants, are expected to benefit from cross-over to anti-EGFR antibodies). Thus 34% in 0181 represented K-RAS wild type patients whereas in EPIC, 47% represented the percentage of the ITT population that crossed-over to receive anti-EGFR therapy.

For the K-RAS results from the later-line trials, the trend was similar to that for the ITT analysis, with only Trial CO.17 demonstrating a statistically significant difference favouring cetuximab + BSC over BSC (approximately a 45% reduction in risk of death). The submission presented an Inverse Probability Censoring Weighted (IPCW) hazard ratio (which attempted to adjust for cross-over in the panitumumab trial, 0181). The difference in OS, adjusted for confounding, was statistically significant (HR 0.71, 95% CI: 0.53, 0.94).

<u>First-line setting</u>
PRIME – K-RAS wild-type population
The submission indicated an approximately 20% reduction in risk of progression or death, favouring the addition of panitumumab to FOLFOX vs. FOLFOX alone (HR PFS = 0.80, 95% CI: 0.66, 0.97). A non-statistically significant prolongation of OS in the panitumumab + FOLFOX arm (HR OS = 0.88, 95% CI: 0.73, 1.06) was also reported. 25% of patients in the FOLFOX only treatment arm were reported to cross over to receive anti-EGFR antibodies as post-protocol therapy.

Using an inverse probability censored weighting (IPCW) analysis, the adjusted HR indicated a statistically significant 26% reduction in risk of death (HR = 0.74, 95% CI: 0.56, 0.97).

K-RAS mutant subgroup
There was a statistically significant reduction in PFS in the panitumumab + FOLFOX arm vs. the FOLFOX arm (HR = 1.29; 95% CI: 1.04 to 1.62; p=0.02). The observed median OS was 15.5 months vs. 19.3 months, respectively (HR = 1.24; 95% CI: 0.98 to 1.57; p=0.068).

PEAK

The HRs (panitumumab vs. bevacizumab) for PFS (HR = 0.87, 95% CI: 0.65, 1.17) and OS (HR = 0.72, 95% CI: 0.47, 1.11) were not statistically significant. The sponsor noted that the proportion of patients in the bevacizumab arm that crossed-over to receive anti-EGFR therapy (31%) was similar to the proportion of patients in the panitumumab arm that crossed-over to receive anti-VEGF therapy (30%). At the time of the analysis, the estimated median OS was 25.4 months in the bevacizumab arm, whilst the estimated median OS was not reached in the panitumumab arm.

For PBAC's view, see Recommendation and Reasons.

The sponsor stated panitumumab and cetuximab were comparable with respect to adverse event rates. However, no direct comparative safety data were provided to assess the relative safety profiles of panitumumab and cetuximab. Relative safety conclusions were drawn using naïve indirect comparisons of adverse events (AEs) from trials that have apparently different event rates in their respective 'common reference' control arms. The PBAC noted that the dose of irinotecan, given as a single agent, in the cetuximab EPIC trial (350mg/m^2 every 3 weeks) was much higher than the dose of irinotecan within the FOLFIRI regimen given in the panitumumab 0181 trial (180mg/m^2 every two weeks).

The most common AEs across all trials were diarrhoea, dermatitis acneiform, rash, nausea, fatigue, vomiting and neutropenia.

Safety data from the PEAK trial suggested that the proportion of Grade 3/4 AEs (with the exception of hypertension) was higher in the panitumumab than the bevacizumab treatment arm.

9. Clinical Claim

Later-line setting

The submission described panitumumab as equivalent in terms of comparative effectiveness and equivalent in terms of comparative safety compared to cetuximab. The submission also noted that panitumumab was associated with a much lower incidence of infusion reactions and requires less frequent administration, which provides an imperative to list a second EGFR inhibitor on the PBS.

First-line setting

The submission described panitumumab, when added to FOLFOX, as superior in terms of comparative effectiveness over FOLFOX alone, but "adds a manageable level of toxicity" (i.e. is inferior in terms of safety).

The trial evidence demonstrated that panitumumab added some clinical benefit as well as some adverse events when given in combination with FOLFOX compared to FOLFOX alone. However, the claim made in the submission was not specifically supported for the relevant PBS population for whom listing of first-line panitumumab is sought, that is, patients unsuitable for bevacizumab.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis between panitumumab and cetuximab, consistent with the submission's clinical claim that panitumumab is non-inferior to cetuximab in the later-line setting.

The equi-effective doses were estimated as panitumumab 6 mg/kg administered every 2 weeks until progression and cetuximab 400 mg/m2 for a loading dose in Week 1 and then 250 mg/m2 administered every week from the second week onwards until progression. These doses were consistent with the registered doses of both panitumumab and cetuximab and the doses used in the clinical trials.

The cost-minimisation analysis considered only drug costs. Administration costs were not included.

The submission also claimed that, in the first-line setting, panitumumab plus FOLFOX is superior to FOLFOX alone, in terms of comparative effectiveness, but inferior to FOLFOX alone, in terms of comparative safety. No economic evaluation was provided in the submission for this comparison.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year receiving panitumumab in the later-line setting was estimated in the submission to be less than 10,000 in Year 5, assuming a market share of 30% in the first year of the proposed and up to 50% in Year 5. The PBAC considered that this was a likely underestimate, as given the less frequent administration and possibly fewer infusion reactions of panitumumab compared with cetuximab, panitumumab may take a larger market share.

The submission estimated listing of panitumumab in the later-line setting would be roughly cost neutral to the PBS, given substitution of cetuximab.

The likely number of patients per year receiving panitumumab in the first-line setting was estimated in the submission to be less than 10,000 in Year 5. The cost per year to the PBS of listing panitumumab in the first line setting was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC rejected the request for first line treatment on the basis of inadequate clinical trial data to support listing for the intended patient population.

The PBAC recommended the listing of panitumumab in the later-line setting as a monotherapy or in combination with an irinotecan based therapy. Listing was recommended on the basis of the comparison presented against cetuximab, but with the price for panitumumab to be lower than cetuximab's price given the lack of convincing evidence to confirm that panitumumab is non-inferior to cetuximab.

With reference to the request to list panitumumab in the first-line setting, the PBAC considered that use of the term "unsuitable" for treatment with bevacizumab would be open

to wide interpretation and would require greater clarity for Medicare to be able to administer such a restriction in practice.

With respect to panitumumab's use in the later/second line setting, the PBAC noted that the requested restriction specified panitumumab's use as monotherapy or in combination with FOLFIRI but that the current PBS restriction for the comparator, cetuximab, specifies use of cetuximab as monotherapy or in combination with an irinotecan based therapy. The PBAC considered that there would be an inconsistency between the two restrictions arising from cetuximab's seemingly broader restriction, and recommended that panitumumab's restriction specify 'an irinotecan based therapy' as opposed to 'FOLFIRI'.

Regarding the clinical place in therapy, the PBAC considered that the use of EGFR inhibitors in addition to oxaliplatin-based chemotherapy in the first line setting, had not been established in light of a recently published meta-analysis review[2] that suggested adding EGFR inhibitors to oxaliplatin-based chemotherapy does not increase survival benefit.

In the intention to treat (ITT) analysis for trials examining the combination of EGFR antibodies with irinotecan, there was a statistically significant difference in progression free survival (PFS) favouring the combination of EGFR inhibitor with irinotecan over irinotecan alone. Trial 0181 comparing panitumumab + FOLFIRI with FOLFIRI reported a HR of 0.80 (95% CI 0.69, 0.93) and EPIC comparing cetuximab + irinotecan with cetuximab and reported a HR of 0.69 (95% CI: 0.62, 0.78). For trials examining the effect of monotherapy with EGFR inhibitors compared with BSC, the hazard ratio favoured panitumumab over BSC (Trial 0408) and cetuximab over BSC (Trial CO.17).

The indirect comparisons between panitumumab and cetuximab using the K-RAS wild type subgroups from the trials of combination therapy (EGFR antibody and irinotecan) and monotherapy did not indicate statistically significant differences. The indirect estimate of PFS of panitumumab compared to cetuximab using the "irinotecan based common reference arms" and the primary analysis of Trial 0181 was a HR of 0.95 (95%CI: 0.66, 1.37) tended to favour panitumumab. However, the PBAC noted that, based on the final analysis of Trial 0181, the indirect estimate of the HR of 1.06 (95% CI: not calculated) tended to favour cetuximab. Similarly, the indirect estimate of the HR of 1.13 (95% CI: 0.75, 1.68) comparison using BSC arms as the common reference also tended to favour cetuximab.

The PBAC considered that, for both indirect comparisons, the 95% confidence intervals were wide and did not exclude the possibility that panitumumab may be associated with a worse PFS than cetuximab. The PBAC was therefore unconvinced that panitumumab is non-inferior to cetuximab based on indirect comparison.

The safety data were also considered inadequate given the different event rates in the common reference arms in the trials. The PBAC noted the dose of irinotecan was much higher in the cetuximab trial than the panitumumab trial.

[2] Zhou S-w, Huang Y-y, Wei Y, Jiang Z-m, Zhang Y-d, et al. (2012) No Survival Benefit from Adding Cetuximab or Panitumumab to Oxaliplatin-Based Chemotherapy in the First-Line Treatment of Metastatic Colorectal Cancer in KRAS Wild Type Patients: A Meta-Analysis. PLoS ONE 7(11): e50925. doi:10.1371/journal.pone.0050925

The PBAC considered that the results of the trials presented in the submission for the later line setting did not convincingly demonstrate non-inferiority. The PBAC considered that the claim of equivalent effectiveness and equivalent safety was not well supported given the indirect nature of the comparison and lack of exchangeability between the trials. The PBAC also noted that less frequent infusions is unlikely to affect patients as they would be likely to still require other medicines weekly.

The PBAC noted the ongoing direct randomised trial of panitumumab and cetuximab in third line monotherapy, which will assess overall survival is expected later in 2013 and noted these results may clarify whether panitumumab is non-inferior to cetuximab. The PBAC further considered that the results of this study may be informative on whether price parity between panitumumab and cetuximab would be justified.

Recommendation:
Recommended

Section 100 Efficient Funding of Chemotherapy Program

Condition/Indication:	Metastatic colorectal cancer
Treatment phase:	Initial treatment
Restriction:	Private Hospital/Private Clinic Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	Patient must have KRAS wild-type metastatic colorectal cancer Patient must have a WHO performance status of 2 or less
	The condition must have failed to respond to first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) The treatment must be as monotherapy; OR The treatment must be in combination with an irinotecan based therapy.

Condition/Indication:	Metastatic colorectal cancer
Treatment phase:	Continuing treatment
Restriction:	Private Hospital/Private Clinic Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	Patient must have received an initial authority prescription for panitumumab for treatment of KRAS wild-type metastatic colorectal cancer after failure of first-line chemotherapy. Patient must not have progressive disease The treatment must be as monotherapy; OR The treatment must be in combination with an irinotecan based therapy.

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

Amgen acknowledges the PBAC's positive recommendation for panitumumab in the later-line setting. Amgen believes there is a role for panitumumab in first line and will continue to work with the PBAC towards an eventual listing in this setting.