PUBLIC SUMMARY DOCUMENT

Product: Panitumumab, 100 mg/5 ml and 400 mg/20 ml injection, Vectibix®
Sponsor: Amgen Australia Pty Ltd.
Date of PBAC Consideration: November 2013

1. Purpose of Application

The re-submission requested Section 100 (Efficient Funding of Chemotherapy) Authority Required (+/- Streamlined) listings for the treatment of K-RAS wild-type (WT) metastatic colorectal cancer (mCRC) in patients who have failed first-line chemotherapy.

2. Background

This was the third submission for panitumumab requesting listing for treatment of K-RAS WT mCRC after failure of first-line chemotherapy.

At its November 2008 meeting, the PBAC rejected a submission for panitumumab due to uncertainty in the extent of clinical benefit over the (then accepted) comparator, best supportive care, in terms of progression-free and overall survival, and because of the resultant high and highly uncertain cost-effectiveness ratio.

The Public Summary Document for the November 2008 meeting is available on the PBS Website.

At its March 2013 meeting, the PBAC considered a re-submission requesting listing for panitumumab in both the first- and second-line settings. The PBAC rejected the request for first-line treatment on the basis of inadequate trial data. The PBAC recommended listing of panitumumab in the later-line setting on a cost-minimisation basis compared with cetuximab, with the price of panitumumab to be lower than cetuximab's price given the lack of convincing evidence to confirm non-inferiority against cetuximab with sufficient statistical precision and a reduction from the price of cetuximab would be reasonable as a basis for the price of PBS-listed panitumumab. The sponsor did not pursue listing based on this recommendation.

The PBAC had also noted the ongoing ASPECCT trial and that the 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.

The Public Summary Document for the March 2013 meeting is available on the PBS Website.

3. Registration Status

Panitumumab is currently TGA- registered for the following indications:

- treatment of patients with wild-type RAS metastatic colorectal cancer (mCRC) as first line therapy in combination with FOLFOX (combination of folinic acid, fluorouracil and oxaliplatin) Efficacy may be influenced by patient performance status;
- treatment of patients with wild-type KRAS metastatic colorectal cancer (mCRC):
  - as second line therapy in combination with FOLFIRI (combination of folinic acid, fluorouracil, and irinotecan) for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). Efficacy may be influenced by patient performance status;
  - as monotherapy in patients after the failure of standard chemotherapy.

4. Listing Requested and PBAC's View

The re-submission requested the following revised restriction for panitumumab as second-line therapy. Changes made to the previously recommended (March 2013) restriction wording for use in the second-line setting are shown in strikethrough and italics.

Condition:	Metastatic colorectal cancer
Treatment phase:	Initial treatment
Restriction:	Section 100 (Efficient Funding of Chemotherapy Program) Private Hospital/Private Clinic Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	Patient must have K-RAS wild-type metastatic colorectal cancer Patient must have a WHO performance status of 2 or less The condition must have failed to respond to *and/or progressed following* 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:	Metastatic colorectal cancer
Treatment phase:	Continuing treatment
Restriction:	Section 100 (Efficient Funding of Chemotherapy Program) 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 K-RAS 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

Listing was requested on a cost-minimisation basis compared with cetuximab.

5. Clinical Place for the Proposed Therapy

The re-submission anticipated that panitumumab would substitute for cetuximab after failure of first-line chemotherapy and that it may be used as monotherapy or in combination with an irinotecan-based therapy.

6. Comparator

The re-submission nominated cetuximab as the comparator. This had been previously accepted by the PBAC in March 2013.

7. Clinical Trials

For use of panitumumab as monotherapy in the third-line setting, the re-submission presented one direct randomised open-label non-inferiority trial (ASPECCT) comparing panitumumab 6 mg/kg every two weeks with cetuximab 250 mg/m^2 weekly, following an initial loading dose of 400 mg/m^2. Both drugs were administered as monotherapy in K-RAS WT mCRC patients previously treated with irinotecan- and oxaliplatin-based chemotherapy. Details are presented in the table below.

Monotherapy – Direct randomised trial presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
ASPECCT	Amgen Inc. (2013). Flash Memo: 20080763. A randomised, multicentre, open-label, Phase 3 study to compare the efficacy and safety of panitumumab and cetuximab in subjects with previously treated, wild-type K-RAS, metastatic colorectal cancer. Data cut-off date: 05 Feb 2013. Report Date: 06 May 2013.	NA

NA = Not available in re-submission.

No new data for use of panitumumab in combination with irinotecan-based therapy in the second-line setting were presented in the re-submission. The basis of the March 2013 re-submission was an indirect comparison between panitumumab and cetuximab using four randomised controlled trials:

- Using a "common reference" of chemotherapy, the re-submission conducted an indirect comparison between Study 0180, which compared panitumumab plus FOLFIRI versus FOLFIRI, and the EPIC trial, which compared cetuximab plus irinotecan versus irinotecan; and
- Using a common reference of best supportive care (BSC), the re-submission conducted an indirect comparison between Study 0408, which compared panitumumab plus BSC versus BSC, and Study CO.17, which compared cetuximab plus BSC versus BSC. Details of the studies have been previously reported in the March 2013 Public Summary Document for panitumumab.

8. Results of Trials

With regard to comparative effectiveness, the results of the indirect comparison of panitumumab versus cetuximab in the second-line setting have been previously reported in the March 2013 Public Summary Document.

The results from the direct ASPECCT trial (monotherapy in third-line patients) for overall survival (OS) and progression-free survival (PFS) from the primary analysis set are presented in the table below.

ASPECCT results of overall survival (OS) and progression-free survival (PFS) results – Primary analysis set[§]

Outcome	Panitumumab N = 499	Cetuximab N = 500
OS		
Subjects with events, n (%)	383 (76.8)	392 (78.4)
Median OS, months (95% CI)	10.4 (9.4, 11.6)	10.0 (9.3, 11.0)
HR, panitumumab vs cetuximab (95% CI) p-value (non-inferiority)[◊]	0.966 (0.839, 1.113)[β] 0.0007	
PFS		
Subjects with events, n (%)	477 (95.6)	477 (95.4)
Median PFS, months (95% CI)	4.1 (3.2, 4.8)	4.4 (3.2, 4.8)
HR (95% CI)	1.002 (0.882, 1.138)	

[§]The primary analysis set includes all subjects who are randomised and who received at least one dose of protocol-specified therapy (panitumumab or cetuximab). This was pre-specified in the protocol. This set consisted of approximately 99% of the true ITT population for both panitumumab (499/506) and cetuximab 500/504) – p51 of the ASPECCT synopsis report (Version 4).
[β]Cox proportional hazards model stratified by randomisation factors: Geographic region (North America, Western Europe and Australia vs rest of world) and ECOG performance status (0 or 1 vs 2).
[◊]Primary Analysis to test null hypothesis (H_0): Panitumumab preserves <50% of the cetuximab OS effect over best supportive care (BSC). This level of clinical effect was sourced from a historical trial of cetuximab vs BSC (CO.17, considered at the March 2013 meeting for the recommendation of panitumumab and at the July 2010 meeting for the recommendation of cetuximab). A synthesis approach with an asymptotic standard normal test statistic is used to test non-inferiority.

The PBAC noted that there was no statistically significant difference in OS, between panitumumab and cetuximab, with either drug given as monotherapy in third-line patients (HR= 0.97; 95% CI: 0.84, 1.11). Non-inferiority was demonstrated because the lower margin of the 95% CI for the retention rate was 81.9%, which exceeded the protocol-defined criterion for non-inferiority of at least 50%. This approach of assessing non-inferiority primarily depended on the constancy assumption, i.e. that a similar relative cetuximab treatment effect (over BSC) as that observed in the historical CO.17 trial, would be observed had a BSC arm been included in the ASPECCT trial.

Despite no additional data being presented specific to the combination use of panitumumab with an irinotecan-based therapy in the second-line setting, the PBAC considered that the data from the ASPECCT trial in the third-line setting, when considered alongside the previously presented indirect comparison, provided adequate support for the claim of non-inferiority of panitumumab compared with cetuximab after the first-line setting.

However, the PBAC noted with concern the emerging data on variable treatment effect of panitumumab (and cetuximab) associated with a broader range of RAS mutations than the

exon 2 mutations currently detected with K-RAS testing. The PBAC noted the recent publication of a retrospective biomarker analysis of tumour samples from the randomised phase III PRIME trial of the first-line use of panitumumab in mCRC (Douillard, NEJM, 2013, 369:11). This analysis showed a detrimental effect for patients treated with panitumumab/FOLFOX4, where tumour samples showed a wild type K-RAS exon 2 but mutations elsewhere in RAS. In fact the overall survival was 15.5 months with panitumumab and chemotherapy compared with 19.2 months in patients treated with chemotherapy alone. The issue of reduced efficacy of cetuximab with FOLFIRI in people with a broader range of RAS mutations was also raised by similar results for similar subgroups of the FIRE-3 trial reported at the 2013 European Cancer Congress. The PBAC acknowledged that this is a rapidly moving issue for the consideration of regulatory authorities and the Medical Services Advisory Committee (MSAC) as well as the PBAC. The Therapeutic Goods Administration (TGA) and the European Committee for Medicinal Products for Human Use have modified the contraindication in the panitumumab Product Information (PI) to 'The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant RAS mCRC or for whom RAS mCRC status is unknown.' The TGA-approved PI for panitumumab differentiates between the RAS and K-RAS genes: treatment of patients with wild-type RAS mCRC in first line therapy and wild-type K-RAS mCRC in second line therapy. The PBAC considered that there was potential for harm associated with the use of panitumumab (and cetuximab) in those patients who do not have true K-RAS WT mCRC due to inaccuracies in the current test.

On this basis, the PBAC sought advice from MSAC and the sponsor companies (Amgen and Merck Serono) regarding the need for wider RAS mutation testing (and other mutation testing) to better select patients. This was considered important to define those who may benefit from epidermal growth factor receptor (EGFR) directed therapy, but also to identify those who are harmed by exposure to combination EGFR therapy/chemotherapy in place of standard care. The advice on biomarker testing needs to consider both panitumumab and cetuximab and the implications of the use of these agents as monotherapy or in combination with other agents.

With regard to comparative harms, from the results of the ASPECCT trial, the PBAC noted that, compared with cetuximab, panitumumab was associated with a higher incidence of any drug-related adverse event grade 3 or higher, any adverse event of interest of grade 3 or higher, hypomagnesaemia and hypokalaemia. Cetuximab was associated with a higher incidence of infusion reactions (IRs), pyrexia, constipation and abdominal pain.

The re-submission provided additional data on IRs associated with panitumumab and cetuximab, summarising the results from a recent systematic review of the literature on IRs associated with chemotherapies and monoclonal antibodies for mCRC by Song et al, 2011. The re-submission concluded that the incidence of IRs is much lower with panitumumab compared with cetuximab.

The PBAC considered that it was unlikely that the difference in IRs favouring panitumumab over cetuximab would materially affect the healthcare resources provided to patients, as most would still require administration of other weekly medications.

9. Clinical Claim

The re-submission described panitumumab as non-inferior in terms of effectiveness and non-inferior in terms of safety compared to cetuximab.

The PBAC considered that this claim was reasonable in the third-line setting where both drugs were used as monotherapy in the ASPECCT trial. When the results of the ASPECCT trial were considered together with the previously presented indirect comparison of panitumumab and cetuximab in the second-line setting, the PBAC considered there to be sufficient support for the claims of non-inferiority in the more generalised 'later-line' combination therapy setting (that is, after first-line therapy of mCRC).

10. Economic Analysis

The re-submission presented a cost-minimisation analysis of panitumumab and cetuximab, consistent with the claim of non-inferiority. The equi-effective doses were estimated as panitumumab 6 mg/kg every 2 weeks until progression and cetuximab 400 mg/m^2 for a loading dose in week 1 followed by 250 mg/m^2 every week until progression. The PBAC noted that these doses were unchanged from the previous re-submission and were consistent with the doses used in the ASPECCT trial. The PBAC considered the cost-minimisation approach and the equi-effective doses were appropriate based on the evidence presented supporting non-inferiority.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of patients treated with panitumumab to be less than $10,000 in Year 5 of listing, at a cost to the R/PBS of between $10-30 million in Year 5. The cost to the R/PBS was revised during the evaluation and was higher, (but within the same range) in Year 5, reflecting changes to the Efficient Funding of Chemotherapy arrangements fee structure. The re-submission estimated the net impact to the R/PBS, accounting for the cost-offsets of cetuximab, resulted in cost savings of less than $10,000 in Year 5 (revised during the evaluation).

The re-submission also claimed cost-savings to other government health budgets due to a reduced number of chemotherapy administrations. The PBAC noted that the cost-savings to other government budgets may be overestimated, as the re-submission estimated the proportion of public patients based on chemotherapy Australian Refined-Diagnosis related Groups (AR-DRG) data, rather than cetuximab utilisation data. Further, the PBAC agreed with the Economic Sub-Committee (ESC) that as freed resources in the public hospital system are typically redeployed, apparent cost savings to other government health budgets are unlikely to be realised as true financial savings. The PBAC also noted that the re-submission did not consider chemotherapy administrations and associated professional attendances that occur in the outpatient setting and accrue costs to the Medical Benefits Scheme (MBS). The PBAC therefore considered that the re-submission's estimate of net cost-savings to government health budgets of less than $10 million in Year 5 (revised during the evaluation) would not be fully realised.

The PBAC noted the sponsor's willingness to enter into a special pricing arrangement. The PBAC recalled and reaffirmed its March 2013 recommendation that it was reasonable for panitumumab to join the corresponding cetuximab risk sharing arrangement should listing occur.

12. Recommendation and Reasons

The PBAC recommended listing of panitumumab under the Section 100 Efficient Funding of Chemotherapy Program for the later-line treatment of K-RAS WT mCRC on a cost-minimisation basis compared with cetuximab. The PBAC considered that this recommendation should replace the recommendation made at its meeting in March 2013. The equi-effective doses are panitumumab 6 mg/kg every two weeks and cetuximab 250 mg/m^2 weekly, following an initial loading dose of 400 mg/m^2.

The PBAC considered that the restriction wording for panitumumab should be consistent with the current restriction wording for cetuximab in mCRC. The PBAC recommended that the restriction include wording to not allow simultaneous use of panitumumab and cetuximab, or switching from one agent to the other following disease progression, except where patients experience intolerance necessitating permanent treatment withdrawal. Consistent wording should also be included in the current restriction for cetuximab for mCRC.

The PBAC noted that the maximum amount for listings under the Efficient Funding of Chemotherapy program is calculated to provide sufficient for a single infusion based on the recommended dose and using a patient body weight of 120 kg or a patient body surface area of 2.2 m^2. The PBAC therefore recommended that the maximum amount for the listing of panitumumab should be 720 mg, (6 mg/kg x 120 kg) consistent with the usual EFC program protocol.

As in March 2013, the PBAC accepted cetuximab as the appropriate comparator for panitumumab in the second-line setting.

Despite no additional data being presented specific to the combination use of panitumumab with an irinotecan-based therapy in the second-line setting, the PBAC considered that the data from the ASPECCT trial in the third-line setting, when considered alongside the previously presented indirect comparison, provided adequate support for the claim of non-inferiority of panitumumab compared with cetuximab after the first-line setting.

The PBAC considered the cost-minimisation approach and the equi-effective doses were appropriate based on the evidence presented supporting non-inferiority in terms of comparative efficacy and comparative safety.

The PBAC noted that MSAC, at its April 2013 meeting, supported the extension of the current MBS item for K-RAS testing to include panitumumab as well as cetuximab when testing tumour tissue from a patient with metastatic colorectal cancer to determine if the requirements for access under the PBS are fulfilled. However, the PBAC noted the recent publication of a retrospective biomarker analysis of tumour samples from the randomised phase III PRIME trial. This analysis showed a detrimental effect for patients treated with

panitumumab/FOLFOX4 where tumour samples showed wild type K-RAS at exon 2 but mutations elsewhere in RAS. In fact the overall survival was 15.5 months with panitumumab and chemotherapy compared with 19.2 months in patients treated with chemotherapy alone. On this basis, the PBAC sought advice from MSAC and the sponsor companies (Amgen and Merck Serono) regarding the need for wider RAS mutation testing (and other mutation testing) to better select patients. This was considered important to define those who may benefit from EGFR directed therapy but also to identify those who are harmed by exposure to combination EGFR therapy/chemotherapy in place of standard care. The advice on biomarker testing needs to consider both panitumumab and cetuximab and the implications of the use of these agents as monotherapy or in combination with other agents.

The PBAC advised that panitumumab is not suitable for inclusion in the list of PBS medicines for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.

The Safety Net 20 Day Rule should not apply.

In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of the material available to it at its November 2013 meeting, panitumumab should not be treated as interchangeable on an individual patient basis with cetuximab.

Outcome:

Recommended

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Proprietary Name and Manufacturer
PANITUMUMAB			Vectibix® AN
panitumumab 100 mg/5 mL injection, 1 x 5 mL vial	720 mg	5	
panitumumab 400 mg/20 mL injection, 1 x 20 mL vial			

Severity:	Metastatic
Condition:	Colorectal cancer
Treatment phase:	Initial treatment
Restriction:	Section 100 – Efficient Funding of Chemotherapy Program Private Hospital/Private Clinic Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	Patient must have K-RAS wild-type metastatic colorectal cancer *AND* Patient must have a WHO performance status of 2 or less *AND* The condition must have failed to respond to first-line chemotherapy *AND* The treatment must be as monotherapy; OR The treatment must be in combination with an irinotecan-based therapy *AND*

	The treatment must be the sole PBS-subsidised anti-EGFR antibody therapy for this condition
Prescriber instructions	Patients who have progressive disease on cetuximab are not eligible to received PBS-subsidised panitumumab. Patients who have developed intolerance to cetuximab of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised panitumumab. Panitumumab is not PBS-subsidised for use in combination with oxaliplatin-based therapies.
Administrative advice	Note Special Pricing Arrangements apply.

Severity:	Metastatic
Condition:	Colorectal cancer
Treatment phase:	Continuing treatment
Restriction:	Section 100 – Efficient Funding of Chemotherapy Program 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 K-RAS wild-type metastatic colorectal cancer after failure of first-line chemotherapy *AND* Patient must not have progressive disease *AND* The treatment must be as monotherapy; OR The treatment must be in combination with an irinotecan-based therapy *AND* The treatment must be the sole PBS-subsidised anti-EGFR antibody therapy for this condition
Prescriber instructions	Patients who have progressive disease on cetuximab are not eligible to received PBS-subsidised panitumumab. Patients who have developed intolerance to cetuximab of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised panitumumab. Panitumumab is not PBS-subsidised for use in combination with oxaliplatin-based therapies.
Administrative advice	Note Special Pricing Arrangements apply.

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 is pleased that panitumumab will be available on the PBS for metastatic colorectal cancer patients.