PUBLIC SUMMARY DOCUMENT
Product: Bevacizumab, solution for I.V. infusion, 100 mg in 4 mL, 400 mg in 16 mL, Avastin®
Sponsor: Roche Products Pty Ltd
Date of PBAC consideration: March 2008

1. Purpose of Application
To seek a Section 100 (Special Authority Program) listing for bevacizumab for the treatment of metastatic colorectal cancer.

2. Background
This drug has not previously been considered by the PBAC.

3. Registration status
The TGA has registered bevacizumab for use in combination with fluorouracil, folinic acid and irinotecan or fluorouracil and folinic acid, for the treatment of patients with metastatic colorectal cancer.

4. Listing Requested and PBAC's views
Section 100 Special Authority Program
Authority required
Treatment of metastatic colorectal cancer in previously untreated patients with a WHO performance status of 0 or 1 in combination with:

(1) 5-fluorouracil and folinic acid; or
(2) irinotecan, 5-fluorouracil and folinic acid

Treatment of metastatic colorectal cancer in patients with a WHO performance status of 0 or 1 in combination with chemotherapy where disease progression has occurred following first-line treatment which includes bevacizumab.

For PBAC's comments on the requested restriction see Recommendations and Reasons.

5. Clinical place for the proposed therapy:
Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth. Bevacizumab would provide an additional treatment for patients being treated with chemotherapy for colorectal cancer.

6. Comparator:
The submission nominated placebo (for standard medical management) as the main comparator.

For PBAC's comments on the comparator see Recommendations and Reasons.

7. Clinical trials
The submission presented three randomised trials comparing bevacizumab 5mg/kg with placebo in the treatment of previously untreated metastatic colorectal cancer in combination with either 5-fluorouracil (FU)/leucovorin (LV) or irinotecan plus 5-FU/LV (IFL).

The submission also presented a supporting observational study comparing bevacizumab 5mg/kg plus chemotherapy to chemotherapy alone in the second-line treatment of metastatic colorectal cancer following first-line treatment involving the use of bevacizumab.

The trials and study as published at the time of submission are listed below.

Trial/Author	Publication title	Publication citation
AVF2107g Hurwitz H, et al. Hurwitz HI, et al	Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer.	New England Journal of Medicine 2004; 350(23):2335-42 Journal of Clinical Oncology 2005; 23(15):3502-8
AVF0780g Kabbinavar F, et al.	Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.	Journal of Clinical Oncology 2003; 21(1):60-5
AVF2192g Kabbinavar FF, et al.	Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial.	Journal of Clinical Oncology 2005; 23(16):3697-3705
BRiTE Grothey A, et al. Kozloff M, et al.	Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (MCRC): Results from a large observational study (BRiTE). Survival of patients (pts) with mCRC treated with bevacizumab in combination with chemotherapy: results from the BRiTE registry.	ASCO 2007, Poster 4036 ASCO 2007, Gastrointestinal Cancers Symposium, Poster 66

8. Results of trials

The key results showed that the addition of bevacizumab to first-line chemotherapy was associated with a significant increase in progression free survival in all three of the randomised trials. The addition of bevacizumab to first-line chemotherapy also led to an increase in overall survival, although the differences were not statistically significant in two of the three randomised trials.

The results from the observational study (BRiTE) used to support second-line treatment with bevacizumab reported significant benefits associated with second-line treatment with bevacizumab (in terms of overall survival and survival beyond disease progression). However, the PBAC was advised the interpretation of results was problematic given the potential for serious confounding and bias in the study.

Based on the data submitted, relative to placebo, bevacizumab was associated with additional toxicities.

In Study AVF2107g, hypertension and diarrhoea were the only Grade 3/4 adverse events that occurred with significant increased incidence among patients receiving bevacizumab in combination with IFL chemotherapy (Arm 2), compared with patients receiving placebo in combination with IFL (Arm 1). Arterial thromboembolic events occurred with significant increased incidence in Arm 2, compared with Arm 1.

In Study AVF0780g, asthenia was the only Grade 3/4 adverse event that occurred with significant increased incidence among patients treated with bevacizumab in combination with 5-FU/LV (Arm 2), compared with patients with 5-FU/LV alone (Arm 1). Diarrhoea was the only treatment-related adverse event that occurred with significant increased incidence in Arm 2, compared with Arm 1.

In Study AVF2192g, hypertension was the only Grade 3/4 adverse event that occurred with significant increased incidence among patients treated with bevacizumab in combination with 5-FU/LV (Arm 2), compared with patients treated with placebo in combination with 5-FU/LV (Arm 1).

Overall, the risk of several adverse events, particularly hypertension, proteinuria and arterial thromboembolic events, was found to be elevated following the addition of bevacizumab to chemotherapy.

9. Clinical claim

The submission described bevacizumab as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo in the treatment of previously untreated metastatic colorectal cancer in combination with 5-FU/LV or irinotecan plus 5-FU/LV.

The submission described bevacizumab as superior in terms of comparative effectiveness over placebo in the treatment of metastatic colorectal cancer in combination with chemotherapy where disease progression has occurred following first-line treatment involving the use of bevacizumab.

For PBAC's views see Recommendations and Reasons.

10. Economic analysis

A cost-effectiveness approach was presented.

The preliminary trial based economic evaluation results showed an incremental cost per extra life-year gained when bevacizumab was compared to placebo (bolus irinotecan/5-fluorouracil/leucovorin (IFL)) of between $105,000 to $200,000.

The results of the stepped modelled economic evaluation gave an incremental cost per extra QALY gained in first-line use of between $105,000 to $200,000 when bevacizumab was compared to placebo (various chemotherapy regimens).

In first- and second-line use, the base case discounted incremental cost per extra QALY gained was less than in first line use alone, but still more than $105,000.

The sensitivity analyses performed indicated the model was somewhat sensitive to the time horizon, treatment effects and uptake rates, but not in the extreme.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost to the PBS of more than $100 million per year from year three of listing for the first-line and second-line indications combined.

12. Recommendation and Reasons

The PBAC considered that the requested listing was highly ambiguous and expressed concern about leakage of bevacizumab to patients with poor performance status (i.e. WHO 2 and not just 0 and 1), into second line therapy when bevacizumab has not been used first line, and as single agent bevacizumab. The Committee considered these issues could be best addressed through a cap on expenditure and through including a NOTE stating "not for use as monotherapy" in the restriction.

The PBAC also considered it would be poor clinical practice to endorse a restriction which might encourage use of the irinotecan/Saltz regimen (IFL - Trial AVF2107) given the toxicity and efficacy profile of this protocol, which was no longer accepted as best practice in Australia or the USA.

The PBAC noted that placebo (standard medical management) was nominated as the comparator. However, if the treatment algorithm as proposed in the restriction is accepted, then FOLFIRI (folinic acid/fluorouracil/irinotecan)/bevacizumab would replace FOLFOX (folinic acid/fluorouracil/oxaliplatin) as the current most widely used oxaliplatin-based regimen and therefore the appropriate main comparator would be FOLFOX. The committee noted that, according to the sponsor's survey, the most commonly prescribed first line regimen in Australia contained oxaliplatin (85% of treatments).

The PBAC noted that in the first-line setting, the addition of bevacizumab to first-line chemotherapy (5FU/LV) was associated with a significant increase in progression free survival in all three of the randomised trials presented. The addition of bevacizumab to first-line chemotherapy also led to an increase in overall survival, although the differences were not statistically significant in two of the three randomised trials. The Committee agreed that overall, the observed survival gain of 3 – 4 months was clinically meaningful. It did note however that in Australian practice the commonly used chemotherapy regimens are infusional rather than bolus, and that there is a possibility that this could alter the incremental effectiveness of bevacizumab in clinical practice.

The PBAC agreed that there is uncertainty concerning the magnitude of the clinical benefit of bevacizumab in the second line setting following progression after use of bevacizumab in the first-line setting. The data on the use of bevacizumab in this setting come from an observational study (BRiTE) and although the study reported significant benefits associated with first-line followed by second-line treatment with bevacizumab (in terms of overall survival and survival beyond disease progression), the interpretation of these results was problematic given the potential for serious confounding and bias in the study.

The Committee considered that the toxicity of bevacizumab in day to day practice is generally not an issue, but that occasional patients experience life-threatening adverse events, including arterial thromboemboli, bleeds from metastases, poor wound healing and gastrointestinal perforations.

The PBAC did not agree that a longer time horizon was appropriate for the economic model but confirmed the submission's choice of a 5 year time horizon. In this context, the Committee noted that the registry data overestimated survival in the patient group likely to be treated under a PBS listing, as it included patients whose metastatic disease is fully resected and who therefore survive for a longer period.

The PBAC also could not see any reason not to quality adjust the survival gains included in the incremental cost-effectiveness ratios for bevacizumab.

The PBAC noted that the submission provided a stepped economic evaluation. Step 7 in the model related to first-line followed by second-line therapy use. Step 7, as it initially appeared in the submission, included the costs of second-line chemotherapy regimens as well as the costs and outcomes of continuing bevacizumab use as part of second-line therapy, using the results from the BRiTE study to estimate the outcomes of second line therapy (bevacizumab assumed to be continued in 50% of patients in the second-line setting following first-line use).

The Pre-Sub-Committee response provided a more complete analysis of Step 7, in that even when the bevacizumab is not continued as part of second line therapy (0% bevacizumab use beyond progression), it remains relevant to include the costs associated with second-line chemotherapy therapy in the model. The base case was also recalculated. This resulted in reduced incremental cost-effectiveness ratios, though still more than of $75,000 per extra LYG and per extra QALY gained for the scenario which assumed no usage of bevacizumab in second line therapy. However, the PBAC did not accept these calculations because it considered that the original submission's time horizon of 5 years was more appropriate.

Overall, the Committee considered that even the most favourable incremental cost effectiveness ratios per extra QALY gained in both the first line setting and in the combined first and second line setting were too high to be acceptable. In addition, the ICER allowing for post-progression (second-line) use of bevacizumab remained subject to considerable uncertainty arising from the uncertainty in the magnitude of clinical benefit in second-line use.

The PBAC also considered that there was uncertainty surrounding the uptake of the drug and hence total expenditure due to potential for use outside the restriction.

Finally, the PBAC noted advice from the Highly Specialised Drugs Working Party which did not support the inclusion of bevacizumab under the HSD program.

Thus the PBAC rejected the submission on the grounds of an unacceptably high cost effectiveness ratio in the first line setting only and an unacceptably high and uncertain cost-effectiveness ratio in combined first- and second-line use, and noting the high overall cost to Government should listing proceed.

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 acknowledges the PBAC comments and concerns. The sponsor wishes to address these issues and will continue to work with the PBAC towards a mutually acceptable solution.