PUBLIC SUMMARY DOCUMENT
Product: Bevacizumab, solution for I.V. infusion, 100 mg in 4 mL and 400 mg in 16 mL, Avastin®
Sponsor: Roche Products Pty Limited
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an extension to the current PBS listing for bevacizumab to include a Section 85 Authority Required listing and listing under the Section 100 Chemotherapy Pharmaceuticals Access Program (CPAP) for:
(1) initial treatment, in combination with carboplatin and paclitaxel, of a patient with advanced or metastatic non-squamous non-small cell lung cancer who meet certain criteria and;
(2) continuing treatment, as monotherapy, in a patient who does not have progressive disease.

2. Background

This drug had not been previously considered by the PBAC for this indication.

3. Registration Status

Bevacizumab was TGA registered on 27 October 2008 for the first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel.

Bevacizumab is also registered for the following indications:

- In combination with fluoropyrimidine based chemotherapy for the treatment of patients with metastatic colorectal cancer.
- In combination with paclitaxel, for the first line treatment of metastatic breast cancer in patients in whom an anthracycline based therapy is contraindicated.
- In combination with interferon-alfa-2a for the treatment of patients with advanced and/or metastatic renal cell cancer.
- Single agent for the treatment of patients with grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

4. Listing Requested and PBAC's View

Authority required
Treatment, in combination with carboplatin and paclitaxel, of a patient with advanced or metastatic non-squamous non-small cell lung cancer with a WHO performance status of 0 or 1, who has not previously received treatment for their metastatic disease.

The maximum dose that will be approved is 15 mg per kg every three weeks.

Authority required
Continuing treatment, as monotherapy, of a patient with advanced or metastatic non-squamous non-small cell lung cancer who has previously received carboplatin and paclitaxel and who does not have progressive disease.

The maximum dose that will be approved is 15 mg per kg every three weeks.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Non-small cell lung cancer is a type of lung cancer that accounts for the majority of patients (80%) with lung cancer. The aim of treatment in patients with advanced disease is to improve both the duration and the quality of the patient's remaining life.

6. Comparator

The submission nominated carboplatin and paclitaxel (Carb+P) as the main comparator for the treatment of previously untreated, advanced or metastatic non-squamous NSCLC, which was considered reasonable by the PBAC.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented four randomised controlled trials comparing the combination of bevacizumab and platinum-based doublet chemotherapy, with platinum-based doublet chemotherapy alone.

The key clinical trial presented in the submission was Study E4599, an open-label randomised controlled trial of carboplatin plus paclitaxel, with or without bevacizumab (15 mg/kg), in patients with advanced non-squamous NSCLC.

The three supportive studies were:

- Study AVF0757g: an open-label phase II, randomised controlled trial of carboplatin plus paclitaxel, with or without bevacizumab (15 mg/kg or 7.5 mg/kg) in patients with locally advanced or metastatic NSCLC;
- Study JO19907: an open-label randomised controlled trial of carboplatin plus paclitaxel, with or without bevacizumab (15 mg/kg), in Japanese patients with advanced or recurrent non-squamous NSCLC; and
- Study BO17704: a randomised double-blind controlled trial of cisplatin plus gemcitabine with placebo or bevacizumab (15 mg/kg or 7.5 mg/kg), in patients with advanced or recurrent non-squamous NSCLC.

The trials published at the time of submission are presented in the following table:

Trial ID / First author	Protocol title / Publication title	Publication citation
Study E4599		
Sandler A et al	Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.	The New England Journal of Medicine 2006; 355 (24): 2542-2550.
Sandler A et al	Treatment outcomes by tumour histology in eastern cooperative group study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer.	Journal of Thoracic Oncology 2010; 5 (9): 1-8.
Study VF0757g		
Johnson D et al	Randomized Phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non–small-cell lung cancer.	Journal of Clinical Oncology 2004; 22 (11): 2184-2191.

Trial ID / First author	Protocol title / Publication title	Publication citation
Study JO19907 Nishio M et al	Randomized, open-label, multicenter phase II study of bevacizumab in combination with carboplatin and paclitaxel in chemotherapy-naive Japanese patients with advanced or recurrent nonsquamous non-small cell lung cancer (NSCLC): JO19907.	Journal of Clinical Oncology 2009; 27:15s (Abstract; Poster 8036).
Study BO17704 (AVAiL)		
Reck M et al	Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL).	Annals of Oncology 2010; 21 (9): 1804-1809.
Reck M et al	Phase III Trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL.	Journal of Clinical Oncology 2009; 27 (8): 1227-1234. Errata DOI: 10.1200/JCO.2009.23.1373.

8. Results of Trials

Key Study E4599 (Bevacizumab+Carboplatin+Paclitaxel vs Carboplatin+Paclitaxel):
Overall survival (OS):

The overall survival results for randomised patients (ITT) for Study E4599 showed that the addition of bevacizumab 15 mg/kg to carboplatin plus paclitaxel resulted in a two months absolute increase in the median duration of overall survival (12.3 months for bevacizumab plus carboplatin plus paclitaxel versus 10.3 months for carboplatin plus paclitaxel) corresponding to a statistically significant 20% relative decrease in the risk of death (unstratified analysis: HR=0.800; 95% CI: 0.689, 0.929).

Results for the stratified analysis of overall survival and from a per protocol analysis conducted by the Eastern Cooperative Oncology Group (ECOG) (HR=0.77, 95% CI: 0.66, 0.91), are consistent with those for the stratified ITT analysis.

Progression-free survival (PFS):

The results of the secondary endpoint of progression free survival (time to disease progression or death) in Study E4599 (ITT) indicated a statistically significant difference ($p < 0.0001$) in median duration of PFS favouring patients in the bevacizumab plus carboplatin plus paclitaxel treatment arm (median PFS = 6.4 months) over patients in the carboplatin plus paclitaxel treatment arm (median PFS = 4.8 months).

The supporting evidence presented in the submission was also generally consistent across the studies with overall median survival increased by about 2 months and median progression-free survival increased by around one month.

Study AVF0757 (Bevacizumab+Carboplatin+Paclitaxel vs. Carboplatin+Paclitaxel):

The PBAC noted the median survival in the non-squamous group of 14.3 vs 12.2 months, was not statistically significant; the median time to progression (non-blinded assessment) of 7.4 vs 4.3 months ($p=0.02$); and the HR for time to progression (blinded review) 0.67 ($p=0.152$), 7.0 months vs 6.0 months.

Study J019907 (background chemotherapy with Carboplatin+Paclitaxel)
The PBAC noted the median progression-free survival of 6.9 vs. 5.9 months; and HR of risk of progression or death of 0.61 (95%CI: 0.42 to 0.89).

For PBAC's view, see Recommendation and Reasons.

The safety profile of bevacizumab for the treatment of non-squamous NSCLC is similar to that previously established for other indications, eg metastatic colorectal cancer, recurrent or metastatic breast cancer.

The PBAC noted that in trial E4599, the risk of fatal adverse events in bevacizumab patients was more than 2.5 times that of patients in the carboplatin+paclitaxel alone arm (5% vs 2%, RR: 2.65 [1.24, 5.65]). Bevacizumab+carboplatin+paclitaxel was associated with higher rates of all grade ≥ 3 adverse events (77% vs 65%, relative risk (RR): 1.18 [1.09, 1.29]) and grade ≥ 3 adverse events of interest (haemorrhage, thromboembolism, hypertension, proteinuria, gastrointestinal perforation, wound healing problems and congestive heart failure) than carboplatin+paclitaxel alone (20% vs 6%, RR: 3.56 [2.33, 5.45]).

The principal significant risk associated with bevacizumab was an increase in grade ≥ 3 haemorrhage when compared with the doublet chemotherapy only arms (2% to 5% vs 0% to 2%).

The most common bevacizumab-related bleeding events were of pulmonary origin, with a higher incidence of all grades of haemoptysis in the bevacizumab arm than in the carboplatin+paclitaxel arm (6.3% vs 3.9%) in trial E4599.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described bevacizumab, when used in combination with carboplatin plus paclitaxel, as superior in terms of comparative effectiveness and inferior in terms of comparative safety over carboplatin plus paclitaxel alone.

This claim was considered by the PBAC reasonable and was consistent with the evidence in the clinical trials.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented with a model developed from the results of study E4599.

The incremental cost/additional year of quality adjusted overall survival was estimated to be greater than $200,000.

The PBAC noted that the net incremental cost is largely due to bevacizumab drug cost, and incremental outcomes are due to the progression delay (and overall survival gains) seen in bevacizumab patients in study E4599.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost/year to the PBS was estimated by the submission to be in the range of $10 – $30 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The addition of bevacizumab 15 mg/kg to carboplatin plus paclitaxel resulted in a two months absolute increase in the median duration of overall survival (12.3 months for bevacizumab plus carboplatin plus paclitaxel versus 10.3 months for carboplatin plus paclitaxel) corresponding to a statistically significant 20% relative decrease in the risk of death (unstratified analysis: HR = 0.800; 95% CI: 0.689, 0.929). The PBAC noted that the data also indicate a statistically significant difference ($p < 0.0001$) in median duration of PFS favouring patients in the bevacizumab plus carboplatin plus paclitaxel treatment arm (median PFS = 6.4 months) over patients in the carboplatin plus paclitaxel treatment arm (median PFS = 4.8 months). The supporting evidence presented in the submission was also generally consistent across the studies with overall median survival increased by about 2 months and median progression-free survival increased by around one month.

The PBAC considered that carboplatin in combination with paclitaxel was a reasonable comparator and the use of this regimen aided the interpretation of the incremental benefit of bevacizumab. However, the PBAC considered that the incremental benefit of the monotherapy component of the regimen had not been quantified.

The PBAC considered that the clinical claim of the submission that bevacizumab, when used in combination with carboplatin plus paclitaxel is superior in terms of comparative effectiveness and inferior in terms of comparative safety over carboplatin plus paclitaxel alone was reasonable and consistent with the evidence in the clinical trials. However, the PBAC was concerned that the combination of carboplatin plus paclitaxel was more toxic than the doublet chemotherapy regimen carboplatin in combination with gemcitabine. The PBAC considered that the addition of bevacizumab to carboplatin and paclitaxel resulted in only a marginal gain in overall survival of 2 months, and was at a cost of treatment-related deaths. The PBAC noted that in Trial E4599, there was greater than a 2.5 fold increase in fatal adverse events for the bevacizumab plus carboplatin plus paclitaxel arm versus the carboplatin plus paclitaxel arm.

A stepped economic evaluation was presented with a model developed from the results of study E4599. The PBAC noted that the net incremental cost is largely due to bevacizumab drug cost, and incremental outcomes are due to the progression delay (and overall survival gains) seen in bevacizumab patients in study E4599. The results of the sensitivity analyses indicate that the model is most sensitive to the treatment effect of bevacizumab, adenocarcinoma histology and the choice and application of utility weights. The PBAC noted that the inclusion of the higher administration cost in the economic model did not have a material impact on the ICER.

The PBAC noted that the utility values in the base case are applied generally to the progression-free and progressed health states and did not capture treatment-related differences in quality of life (eg due to adverse events and/or additional infusions due to bevacizumab treatment). A sensitivity analysis including disutilities for bevacizumab-related adverse events increases the ICER. The utilities for progression and progression-free health states are based on a patient population on second-line treatment for metastatic lung cancer, therefore, were considered conservative for patients on first-line treatment.

The PBAC considered the total financial cost to be high and uncertain as the estimated respective market shares for each drug are highly uncertain and may impact the total cost considerably.

The PBAC therefore rejected the submission on the basis of an unacceptably high and uncertain cost-effectiveness ratio.

The PBAC also acknowledged and noted the consumer comments on this item.

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 had no further comment.