PUBLIC SUMMARY DOCUMENT
Product: Bevacizumab, solution for intravenous infusion, 100 mg in 4 mL and 400 mg in 16 mL, Avastin®
Sponsor: Roche Products Pty Limited
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought an extension to the PBS listing of bevacizumab to include use, as monotherapy, for the treatment of patients with relapsed or progressing glioblastoma multiforme.

2. Background

This drug had not previously been considered by the PBAC for subsidy for relapsed or progressing glioblastoma multiforme.

Bevacizumab was recommended for PBS subsidy for treatment of metastatic colorectal cancer in previously untreated patients with a WHO performance status of 0 or 1 in combination with chemotherapy at the July 2008 meeting of the PBAC. Listing was effective from 1 July 2009.

A Public Summary Document (PSD) is available at:
www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-bevacizumab-july08.

3. Registration Status

The TGA registration for bevacizumab was extended on 10 February 2010 to include use as a single agent, for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Bevacizumab is also TGA 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 carboplatin and paclitaxel, for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.
- In combination with interferon alfa-2a, for treatment of patients with advanced and/or metastatic renal cell cancer.

4. Listing Requested and PBAC's View

The submission proposed two listing options, as follows:

Option 1: Use in first or second relapse of glioblastoma

Authority Required
Treatment as monotherapy for relapse or progression of glioblastoma multiforme following therapy that includes temozolomide or where temozolomide is contraindicated or not tolerated.

NOTE:

Bevacizumab is not to be continued after progression of disease.

Option 2: Use in second relapse of glioblastoma only

Authority Required
Treatment as monotherapy for second relapse or progression of glioblastoma multiforme following therapy that includes rechallenge with temozolomide or where temozolomide is contraindicated or not tolerated.

NOTE:
Bevacizumab is not to be continued after progression of disease.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Glioblastoma multiforme is the most aggressive malignant primary brain tumour in adults and is nearly always fatal. Despite aggressive first-line treatment, consisting of surgery, radiation therapy and adjuvant chemotherapy, tumours invariably recur. The submission proposed that bevacizumab would substitute temozolomide, salvage chemotherapy and best supportive care (BSC) for the treatment of patients with relapsed glioblastoma multiforme following temozolomide therapy.

6. Comparator

The submission nominated temozolomide, best supportive care and salvage chemotherapy as the treatments which will be substituted by bevacizumab. Procarbazine was estimated to provide a reasonable assessment of the effectiveness of salvage chemotherapy and BSC.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

There were no studies providing direct comparisons of bevacizumab with the chosen comparators. Therefore, the submission presented single arms from different studies as evidence of the effectiveness of bevacizumab and the comparators. The first bevacizumab study was a randomised, open-label, phase II trial (AVF3708g) and the other a single-arm, open-label phase II trial (Kreisl et al, 2009). To investigate the efficacy and safety of temozolomide and procarbazine, the submission primarily uses a randomised, multi-centre, open-label, phase II trial (Yung et al, 2000).

The studies published at the time of the submission are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Bevacizumab trials		
AVF3708g Friedman et al	Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.	J Clin Oncol 2009; 27(28): 4733-4740
Kreisl et al	Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumour progression in recurrent glioblastoma.	J Clin Oncol 2009; 27(5): 740-745
Temozolomide trials		

Yung et al	A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse.	British Journal of Cancer 2003; 8(5): 301-304
Brada et al	Multicentre phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse.	Annals of Oncology 2001; 12(2): 259-266
Brandes et al	Temozolomide in patients with glioblastoma at second relapse after first line nitrosurea-procarbazine failure: A phase II study.	Oncology 2002; 63(1): 38-41
Sipos et al	Temozolomide chemotherapy of patients with recurrent anaplastic astrocytomas and glioblastomas.	Ideggyógyászati szemle (Clinical Neuroscience) 2004; 57(11-12):394-399
Terasaki et al	Salvage therapy with temozolomide for recurrent of progressive high-grade gliomas refractory to ACNU (1-(4-amino-2-methyl-5-pyrimidynyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride).	Mol Med Rep, 2009;2(3):417-421.
Yang et al	Temozolomide chemotherapy in patients with recurrent malignant gliomas.	Journal of Korean Medical Science 2006; 21(4): 739-744

The PBAC noted that further data from two clinical trials (RTOG 0825 and AVAGLIO) comparing temozolomide to temozolomide with bevacizumab in a first-line treatment setting, will become available. The trials are listed below. The first two citations are for the same trial (RTOG 0825).

- 'Temozolomide and Radiation Therapy With or Without Bevacizumab in Treating Patients With Newly Diagnosed Glioblastoma', estimated primary completion date, April 2010. http://www.clinicaltrials.gov/ct2/show/NCT00884741?term=Bevacizumab+glioblastoma&rank=21
- 'Trial of conventional, concurrent chemoradiation and temozolomide plus bevacizumab versus conventional, concurrent chemoradiation and temozolomide in patients with newly diagnosed glioblastoma'. (RTOG 0825). Planned closing date is not stated. http://www.uwhealth.org/ourservices/braintumors/brain-tumor-clinical-trials/26120.
- 'A randomized, double blind, placebo controlled, multicenter Phase III trial of bevacizumab, temozolomide and radiotherapy, followed by bevacizumab and temozolomide versus placebo, temozolomide and radiotherapy followed by placebo and temozolomide in patients with newly diagnosed glioblastoma', expected completion date October 2014, http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-090833

The PBAC further noted the following planned study for lower grade glioma:

- Randomized Trial Assessing the Significance of Bevacizumab in Recurrent Grade II and Grade III Gliomas - The TAVAREC Trial. http://www.clinicaltrials.gov/ct2/show/NCT01164189?term=Bevacizumab+glioblastoma&rank=56.

8. Results of Trials

The six-month progression-free and overall survival, and the median progression-free and overall survival, plus the response rates were presented, using data from the randomised and non-randomised studies.

These data suggested that bevacizumab appeared to be more effective than temozolomide and procarbazine. This conclusion relied on accepting that the trial populations were comparable, and the use of phase II data was adequate. The PBAC agreed with the Economics Sub-Committee (ESC) that the trial populations were not comparable. Any deviation from this assumption will make the results highly uncertain. Patients using bevacizumab had a longer median life expectancy and progress later than when using temozolomide or procarbazine. The weakness of the analysis lies in the reliance on different trials to populate the two arms of the comparison. The key data for the comparator (Yung et al, 2000) was relatively old, and may not best represent current outcomes for these therapies. Importantly, the patients in the trials differ in terms of prior treatment (in that a greater proportion of patients had undergone surgery in the bevacizumab population and were thus likely to have better outcomes), disease severity and number of relapses.

The toxicity profile of bevacizumab was different from that for either temozolomide or procarbazine: however identifying whether it was better or worse was not possible due to the data originating from different sources, and being collected over a different time period.

9. Clinical Claim

The submission described bevacizumab as providing a clinically relevant efficacy gain relative to temozolomide, salvage chemotherapy or best supportive care. It described the safety profile as acceptable for patients in this population group.

The PBAC considered that the clinical benefit was uncertain.

10. Economic Analysis

The submission presented a stepped economic evaluation with a Markov model estimating progression-free, overall and quality adjusted survival over 3 years, for an entire patient cohort having access to bevacizumab as per the proposed listing, or not.

The PBAC noted that the base case ICER was estimated to be in the range of $75,000 – $105,000 per QALY and after additional multivariate sensitivity analyses were conducted during the evaluation, the ICER was estimated to be more than $200,000 per QALY, which was considered unacceptably high.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year estimated in the submission was less than 2,000 in Year 1 for each proposed listing option. The submission's estimate was uncertain as the take-up rate of bevacizumab was based on expert opinion.

The submission estimated the net financial cost per year to the PBS to be in the range of $10 – 30 million in Year 1. The submission's estimate was uncertain as take-up of bevacizumab was based on expert opinion. The figure assumed that patients discontinue on progression, which may not occur in practice and therefore costs may be underestimated.

12. Recommendation and Reasons

The PBAC noted that there were no studies providing direct comparisons of bevacizumab with the chosen comparators, temozolomide, best supportive care and salvage chemotherapy. The submission presented single arms from different studies as evidence of the effectiveness of bevacizumab and the comparators. The PBAC considered that there was no common comparator to allow a reliable indirect comparison.

The PBAC agreed with the ESC that there were significant comparability issues including differing patient characteristics (most importantly number of previous relapses, Karnofsky scores, previous resection rates, and previous use of temozolomide). The PBAC also agreed that the data were not comparable between the more recent bevacizumab trials and the older Yung et al. (2000) trial because the standard of care has changed since the Yung trial, particularly a more aggressive approach to surgery and better supportive care.

The PBAC noted that there were limitations to the use of progression free survival (PFS) and response rates (RR) in brain cancer, particularly in relation to the vascular endothelial growth factor (VEGF) inhibitors, which includes bevacizumab. The PBAC noted that the McDonald criteria were used to assess PFS and RR. The limitations of the McDonald criteria were now widely recognised but one of the biggest limitations was the use of contrast-enhancement as a surrogate for tumour size i.e. greater than a 25% change infers tumour progression. However, contrast enhancement was non-specific, and depended on passage of contrast into a disrupted blood brain barrier. This was influenced by radiological techniques, amount of contrast injected, seizure activity, radiation effects, corticosteroid dose and also the use of bevacizumab. The PBAC noted that International Advisory Committee of Oncology Drugs now considered that RR and PFS are inappropriate endpoints for anti-VEGF therapies. The PBAC also noted that in some cases it was possible that the effects of bevacizumab were analogous to the impact of steroids i.e. a “pseudo-response.”

The PBAC considered that comparisons with historical controls (1995-97) in brain cancer were therefore unreliable. The PBAC noted that there have been dramatic changes in imaging modalities, that aggressive surgery which was minimally destructive and radiotherapy were now used which impacts on survival, and histological assessments had improved because of better surgery. Due to the limitations described above, no imaging modality had adequate sensitivity and specificity to differentiate recurrence from treatment effects and that surgery was the only reliable way to do this, but was not an ethical means of ascertaining true outcomes. The limitations associated with imaging made it particularly challenging to compare outcomes across trials.

Therefore, the PBAC concluded that overall survival was the most robust indicator of benefit in brain cancer. The median survival reported in studies of bevacizumab was 9.3 months (AVF3708g) and 7.2 months (Kreis et al 2009) compared with temozolomide studies which was approximately 7.4 months and similar to radiotherapy alone. The PBAC considered that bevacizumab possibly has efficacy but the extent of benefit had not been quantified.

Further RCTs were needed which were underway in the first-line treatment setting. Whilst these were first-line studies, the PBAC agreed with the ESC that they will determine whether bevacizumab offers any benefit and if so the extent of benefit.

The PBAC noted that the original dosing of bevacizumab was 5 mg/kg second weekly. However, subsequent trials have doubled the dose without justification and that this strategy may deliver higher side effects and cost without benefit.

The submission presented a stepped economic evaluation with a Markov model estimating progression-free, overall and quality adjusted survival over 3 years, for an entire patient cohort having access to bevacizumab as per the proposed listing, or not.

The PBAC noted that the base case ICER was estimated to be between $75,000 and $105,000/QALY and after additional multivariate sensitivity analyses were conducted during the evaluation, the ICER was estimated to be more than $200,000/QALY, which was considered unacceptably high. The PBAC also noted that there was potential for leakage outside the requested PBS listing, such as use in patients with Grade III tumour and especially in the relapse of a Grade III tumour, and that this was not addressed in the economic evaluation.

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

The PBAC noted the consumer comments received for 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.