PUBLIC SUMMARY DOCUMENT
Product: Carmustine, implant, 7.7 mg, 8, Gliadel ®
Sponsor: Orphan Australia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought to extend the current Restricted benefit listing to include the treatment of recurrent glioblastoma multiforme (GBM) in patients for whom surgical resection is indicated and recurrence has occurred within 6 months of temozolomide or where temozolomide is contraindicated or not tolerated due to side effects.

2. Background

At the November 2005 meeting, the PBAC recommended listing carmustine implant as a restricted benefit for newly-diagnosed glioblastoma multiforme (GBM) as an adjunct to surgery and radiation on a cost-minimisation basis with one pack of eight carmustine 7.7 mg implants being equivalent to a course of temozolomide capsules. Based on the indirect comparison across the two trials provided in the submission, the PBAC concluded that, overall, carmustine was no worse than temozolomide for glioblastoma multiforme, the main indication within the requested restriction.

At its March 2006 meeting, the PBAC rejected an application to extend the listing for carmustine to include high grade malignant gliomas rather than limiting treatment to patients with glioblastoma multiforme because of insufficient evidence of benefit, in terms of survival gain or quality of life improvements, or in the cost effectiveness of carmustine in the broader population.

At its July 2006 meeting, the PBAC agreed to change the wording of the carmustine restriction to 'glioblastoma multiforme, suspected or confirmed, at the time of initial surgery'. This restriction wording change was effective from 1 December 2006.

At the March 2007 meeting the PBAC rejected an application to extend the restricted benefit listing for carmustine to include the treatment of recurrent glioblastoma multiforme in a patient for whom surgical resection is indicated because of uncertain clinical effectiveness resulting from the lack of a common reference against temozolomide, the unequal distribution of additional therapy received between the two trial populations, inadequate demographic data for the subgroup in which listing was requested and other possible unequal distributions of prognostic factors between the two key trial populations.

3. Registration Status

Carmustine implant (Gliadel®) was registered by the TGA on 27 October 2004 for use in newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation. Carmustine was registered on 15 May 2002 for use as an adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme (GBM) for whom surgical resection is indicated.

4. Listing Requested and PBAC's View

Restricted Benefit

Recurrent glioblastoma multiforme (GBM) for whom surgical resection is indicated and recurrence has occurred within 6 months of temozolomide or where temozolomide is contraindicated or not tolerated due to side effects.
NOTE
Carmustine is not PBS-subsidised for use in conjunction with PBS-subsidised temozolomide.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Malignant high grade gliomas have poor prognosis with a median survival time of 10-12 months and only 5-10% of patients surviving to 2 years. The infiltrating nature of high-grade glioma makes complete resection virtually impossible. Standard treatment at the time of initial diagnosis generally consists of cytoreductive surgery followed by concurrent radiotherapy and temozolomide for patients with newly diagnosed GBM.

Palliative chemotherapy (with temozolomide) is currently used for the treatment of recurrent high grade gliomas. There is a clinical gap with a lack of treatment for recurrent GBM in a patient whose disease has recurred within six months of temozolomide treatment (temozolomide failures) or for whom temozolomide is contraindicated or not tolerated. Carmustine is proposed to fill this clinical gap for use in recurrent tumours, which are suitable for resection.

6. Comparator

The re-submission nominated placebo implants as the main comparator in the setting of recurrent GBM. The PBAC considered this was appropriate given the proposed wording of the restriction. The PBAC considered that the use of surgery and radiotherapy alone or combined with other chemotherapeutic agents could be regarded as minor comparators.

7. Clinical Trials

In comparison with the previous submission, only one randomised controlled trial (8802) was presented, in which carmustine implants (plus standard medical management) were compared with placebo implants (plus standard medical management). A post-hoc sub-group analysis for patients with GBM was also provided as part of the evaluation.

The pivotal clinical trial (8802) had been published at the time of submission as follows:

Trial ID/First author	Protocol title / Publication title	Publication citation
Study 8802 Brem 1995	Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group.	Lancet, 345(8956):1008-12, 1995.

The Clinical Study Report of Trial 8802 provided in the submission has not been published.

For PBAC's comments on the clinical trials, see Recommendations and Reasons.

8. Results of Trials

In comparison with the previous submission, no changes were made to the results of the key trial (8802). In this trial, the primary outcome measures were the 6 month survival and the cumulative mortality rate at 6 months from the time of study surgery. The secondary outcome measures were overall survival and quality of life proxied by the Karnofsky Performance State (KPS) scores and the Mini Mental State Examination (MMSE).

A summary of results of the key trial (8802) is given in the table below:

Outcome measures	**All patients (N=222)**		**GBM patients (N=145)**	
	Carmustine (N=110)	Placebo (N=112)	Carmustine (N=72)	Placebo (N=73)
6 months survival				
6 month survival rate (**before adjustment** for prognostic factors)	66 (60%) (51%, 69%) P=0.061	53(47%) (38%, 57%)	40 (56%) P=0.020	26 (36%)
6 month treatment effect (**after adjustment** for prognostic factors)	Hazard ratio: 0.58[b] 95% CI: 0.39-0.87 P= 0.009		Hazard ratio: 0.53 95% CI: 0.33-0.82 P= 0.005	
Overall survival				
Overall survival, median (weeks) (before adjustment for prognostic factors)	31 P=0.10 (Wilcoxon test)	23	28 P=0.021 (Wilcoxon test)	20
Overall survival, median (weeks) (after adjustment for prognostic factors)	40[a]	31[a]	Not available	
Overall treatment effect (**before adjustment** for prognostic factors)	Hazard ratio: 0.83 (95%CI: 0.63-1.10, P=0.19) 8 weeks		Hazard ratio: 0.81 (P=0.22) 8 weeks	
Overall treatment effect (**after adjustment** for prognostic factors)	Published study: Hazard ratio: 0.67 (95% CI: 0.51-0.90, P=0.006) 9 weeks Clinical Study Report (8802) [b] Hazard ratio: 0.75 (95%CI: 0.57-0.99, P=0.045) (p76 of the CSR).		Published study: Hazard ratio: 0.67 (95% CI: 0.48-0.95,P=0.02) Clinical Study Report (8802) [b] Hazard ratio: 0.64 (95% CI:0.45-0.90, P=0.013)	

GBM: Glioblastoma Multiforme

[a] Median survival effect measures have been estimated from the Kaplan-Meier curve by the re-submission. This graph is not available in the CSR 8802.

[b] In the Clinical Study Report, the term used to present treatment effects was risk ratio. However, given the information provided in the statistical methods used in efficacy analysis (pp17-22 of CSR), it seems that hazard ratios and risk ratios were used interchangeably.

The overall Kaplan-Meier survival curves for all patients by treatment group and tumour type (before adjustment for prognostic factors) showed that in patients with GBM, the median survival duration after study surgery was 6.51 months in the carmustine group and 4.63 months in the placebo group. The Kaplan-Meier survival curves also showed that at 15 months after the implant surgery in the GBM patients before adjustment for prognostic factors, the cumulative death rate was higher in the carmustine group compared to the placebo group (i.e. a higher survival rate for the placebo group).

The choice of KPS and MMSE as proxies for quality of life was not optimal, as these tools did not fully evaluate the effects of the tumour and adverse treatment effects on patient quality of life. There was no statistically significant difference between study arms in Trial 8802 using these proxies for quality of life.

The Clinical Study Report (CSR) of Trial 8802 provided in the submission had a longer follow-up duration than the published study of Trial 8802 and therefore the hazard ratios estimates in the CSR were different from those reported in the published study.

The CSR reported that after adjustment for prognostic factors, carmustine produced statistically significant reductions in overall mortality compared with placebo.

No new toxicity data were presented in the re-submission. Of note, 14% of patients in the carmustine arm had abnormal healing (including cerebrospinal fluid leakage, wound dehiscence and effusion) compared with 5% in the placebo arm (P=0.04). Also in the carmustine arm, 7% of patients experienced pain compared with 1% in the placebo arm.

For PBAC's comments on these results, see Recommendations and Reasons.

9. Clinical Claim

Carmustine was described as having advantages in effectiveness and comparable toxicity with respect to its comparator. The PBAC partially accepted the clinical claim described by the sponsor. The PBAC did not accept that the efficacy of carmustine in patients previously treated with temozolomide, the larger part of the population targeted by the restriction, had been demonstrated, as these patients were not included in the pivotal clinical trial. Where patients had never received temozolomide, or where exposure had been substantially truncated due to intolerance, the trial data were more applicable and clinical benefit is more robustly defined.

For PBAC's view see Recommendations and Reasons.

10. Economic Analysis

Whereas the previous submission presented a cost-minimisation analysis, the re-submission presented a trial-based cost-effectiveness analysis based on data from Trial 8802. The ICER was expressed as incremental cost per life year saved. A modelled economic evaluation was not presented, because the key trial duration was considered sufficient on which to base an analysis of the effectiveness of treatment.

The base case incremental cost-effectiveness ratio was estimated to be in the range of $45,000 – $ 75,000 per life year gained (LYG).

For PBAC's views, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of patients/year to be less than 10,000 in Year 2010.
The re-submission estimated the financial cost per year to the PBS/RPBS (based on the weighted price of carmustine proposed in the submission) to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that the trial population in the pivotal trial Study 8802 (Brem et al 1995) was markedly different to the requested PBS population: The participants did not have prior

exposure to temozolomide and the median time from first resection was 11 to 13 months, whereas the requested PBS listing seeks use in patients who have failed temozolomide within the previous 6 months, and patients with intolerance or a contraindication to temozolomide would only represent a small proportion of the patients eligible for treatment under the proposed restriction. At the time the pivotal trial 8802 was conducted the ability to recognise the oligodendroglial component of gliomas was less well developed than is currently the case. The diagnostic accuracy of neuropathology has improved because; more tissue is provided to the pathologist, radiology has improved, the pathologist is better able to recognise oligodendroglial components using morphology aided by FISH. It is likely therefore that a proportion of the trial participants would have had an unrecognised oligodendroglial component of their tumour.

Although a survival advantage for carmustine was noted in the total trial population and in patients with GBM after adjustment for prognostic factors, the PBAC considered that the use of this sub-group analysis introduced some uncertainty about the extent of the effectiveness advantage claimed by carmustine with respect to its comparator. Overall, the methods used for adjustment appear to be appropriate and the factors adjusted for were plausible predictors of the outcome measures. However, there remains a potential for bias inherent in the post hoc selection of the prognostic factors. Additionally, with regard to toxicity, carmustine treatment appears to be associated with an increased risk of abnormal healing events and pain compared to placebo, thus the claim of comparable toxicity was not adequately supported by the data.

The PBAC also considered that there was considerable uncertainty around whether prior use of temozolamide would diminish the likelihood of benefit with carmustine, and this uncertainty is not able to be addressed by the data from the key trial. It is now known that many patients who fail to respond to temozolamide do so because their tumour expresses/over-expresses methylglutamine methyl transferase (MGMT). Over-expression of MGMT is also a major mechanism of resistance to carmustine. Therefore the benefits obtained in the group targeted by the restriction are likely to be less than observed in the Brem, 1995 study.

Taking into account these uncertainties around the extent of clinical benefit associated with carmustine, the PBAC concluded that the incremental cost effectiveness ratio (ICER) for temozolomide-treated patients could not be estimated with any degree of confidence and would most likely be significantly higher than the base-case ICER which was in the range of $45,000 - $75,000 per life year gained (LYG) which was based on the most favourable hazard ratios (0.64 - 0.75) i.e., those calculated after adjustment for prognostic factors. The ICER based on unadjusted rates (8 week survival advantage, rather than 9 weeks) was estimated to be in the range of $45,000 - $105,000/LYG.

The PBAC considered that where patients had never received temozolomide, or where exposure had been substantially truncated due to intolerance, the trial data were more applicable and clinical benefit is more robustly defined. However the trial based ICER per LYG in the range of $45,000 - $75,000 remains unacceptably high.

Whilst the PBAC was sympathetic to the need for effective therapy for patients with GBM that recurs rapidly after current standard first line care with surgery, radiation and temozolomide, there is major uncertainty about the clinical efficacy of carmustine implants

after subsequent resection in such patients. The PBAC considered that the pivotal trial results from temozolomide naïve patients overestimated any benefits.

Therefore, the PBAC rejected the submission because of uncertain clinical benefit and high and uncertain cost-effectiveness.

Recommendations
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 is disappointed by the PBAC rejection and intends to work with the PBAC to make PBS-subsidised carmustine implant available to the small group of patients, with recurrent glioblastoma multiforme, that recurs rapidly after standard first line care with surgery, radiation and temozolomide, and for whom surgical resection is indicated.