PUBLIC SUMMARY DOCUMENT

Product: Carmustine, implant, 7.7 mg, Gliadel®

Sponsor: Orphan Australia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

To extend the current restricted benefit listing to include the treatment of recurrent glioblastoma multiforme in patients for whom surgical resection is indicated.

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 the PBAC considered an application to expand the patient population of the current restriction for carmustine to include high grade malignant gliomas rather than limiting treatment to patients with glioblastoma multiforme. The PBAC noted that only 16% patients in the key Trial T-301 were not diagnosed with glioblastoma multiforme.

The PBAC rejected the submission 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.

3. Registration Status

Carmustine implant is registered by the TGA for use in newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation. Gliadel is also indicated 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 in patients for whom surgical resection is indicated.

See Recommendation and Reasons for the PBAC's view

5. Clinical Place for the Proposed Therapy

Carmustine implants will provide an alternative treatment option to temozolomide for patients for whom surgery is appropriate for recurrent glioblastoma multiforme (GBM).

6. Comparator

The submission nominated temozolomide given orally as the comparator in the setting of recurrent GBM.

The PBAC considered that standard medical management of recurrent GBM eg surgical resection or focal radiotherapy or other chemotherapy (eg carboplatin and etoposide) as minor comparators would also have been appropriate.

7. Clinical Trials

Two sets of randomised controlled trials were provided as a basis for indirect comparison between carmustine implants and temozolomide (TMZ). The key trial Study 8802, compared carmustine implants and standard care (tumour resection and radiotherapy) with placebo implants and standard care (tumour resection and radiotherapy) in patients with recurrent malignant glioma over a median follow-up of 71 months. The other key trial, Yung et al, compared TMZ after radiotherapy with procarbazine (PCB) after radiotherapy in patients with glioblastoma multiforme at first relapse, over a median follow-up of 24 months.

These trials have been published at the time of submission as follows:

Trial/First author	Protocol title/Publication title	Publication citation
STUDY 8802/Brem H et al (1995)	Placebo-controlled trial of safety and efficacy of intra-operative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas	Lancet 1995; 345(8956):1008-12
Yung WK et al (2000)	A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse.	British Journal of Cancer 2000; 83(5):588-93.

The submission assumed that procarbazine has not been shown to have any significant effect on survival in glioblastoma multiforme patients and can be considered to act as placebo.

8. Results of Trials

The results of the key trials are summarised in the table below.

Key results of the comparative randomised trials*

Outcome	**Study 8802 100% GBM[a] (N=145)**		**Yung W et al, 2000 91% GBM, 9% non-GBM (N=220)**	
	Placebo plus standard care (N=73)	**Carmustine plus standard care (N=72)**	**TMZ plus previous radiotherapy (N=110)**	**PCB plus previous radiotherapy (N=110)**
6 months survival (95% CI)	26 (36%) (NR) p=0.020	40 (56%) (NR)	67 (60%) (51%, 70%) p=0.019	50 (44%) (35%, 53%)
Adjusted[b] risk ratio (95%CI)	0.53 (0.33, 0.83)		0.73 (0.58, 0.96)	
Overall survival Adjusted[b] hazard ratio for death - Cox multiple regression (95%CI)	0.67 (0.48, 0.95)		NR	
	65% GBM, 35% non-GBM (N=222)		**91% GBM, 9% non-GBM (N=220)**	
	Placebo + standard care N=112	**Carmustine + standard care** N=110	**TMZ + prior radiotherapy** N=110	**PCB + prior radiotherapy** N=110
6 months survival (95% CI)	53 (47%) *(38%, 57%)* p<0.061	66 (60%) *(51%, 69%)*	67 (60%) (51%, 70%) p<0.019	50 (44%) (35%, 53%)
Adjusted risk ratio for death (95% CI)	0.58 (0.39, 0.86)		0.73 (0.58, 0.96)	
Overall survival, median (months) (95%CI)	5.42 (4.73, 6.44)	7.24 (6.05, 8.54)	7.2[c] NR	5.7[c] NR
Incremental survival (months)	1.82 (p=0.297)		1.50 (p=0.33)	
Unadjusted hazard ratio for death (95%CI)	0.83 (0.63, 1.10) p=0.19		*0.69*[d] (NR) p=0.019	

Italics = calculated during the evaluation;
* the primary efficacy outcome for the trial by Yung et al was progression free survival at 6 months whereas the primary efficacy outcome in Study 8802 was survival at 6 months: only the outcomes common to the key trials are considered during the evaluation; [a] whole trial population in Study 8802 constituted 65% GBM patients and 35% non GBM patients. Subgroup analysis was pre-planned; [b] adjusted for drug treatment, KPS, local radiation versus whole brain, active versus quiescent, previous nitrosourea versus none, >75% resection versus < 75% resection, age, interval from previous resection, tumour type (GBM, AA); [c] estimated from the Kaplan Meier curve in Yung et al (2000); [d] calculated from the inverse of the hazard ratio for survival (1/1.44); PCB = procarbazine; GBM = glioblastoma multiforme; AA = anaplastic astrocytoma; KPS = Karnofsky Performance Score; PFS = progression free survival.

Whilst the primary efficacy outcome in the trial Yung et al is progression-free survival (PFS), in the carmustine trial, Study 8820, it is six month survival. The PBAC agreed this was justifiable given the unsuitability of PFS as an outcome in a carmustine treated group where post operative oedema, enhancement of the implants and the subsequent effects of radiotherapy might bias such measurement. The suitability of the population for whom listing of carmustine wafers was sought was further complicated by the fact that in current

clinical practice, temozolomide may not be utilised for patients unresponsive to the drug (likely the majority of patients with recurrent glioblastoma multiforme).

The PBAC noted advice that unequal distributions of prognostic indicators between the populations in the two key trials, the lack of a common reference and differences in the measurement of the primary outcome of survival made the indirect comparison between carmustine implants and TMZ in recurrent glioblastoma multiforme difficult and ultimately inappropriate. The adjusted benefits observed take into account the different prognostic factors between groups within the trials rather than between the relevant trial arm in both studies. A comparison of the absolute risks between carmustine and standard care with temozolomide after radiotherapy further appeared to be inappropriate.

The two key trials used different tools to investigate patients 'quality of life' at various time points (Karnofsky Performance Score (KPS) and Mini-Mental State Examination in Study 8802 versus the EORTC (European Organisation for Research and Treatment of Cancer) Quality of Life Questionnaire (QLQ-C30 (+3) in Yung et al 2000). An assessment of the comparability of these two measurement tools was not provided. In both trials, a sustained deterioration in quality of life scores occurred during disease progression. Quality of life reduction at time of surgery for both carmustine and placebo arms was most likely related to brain surgery.

9. Clinical Claim

The submission claimed that carmustine implants were at least as effective as temozolomide with the same or less toxicity. This claim was based on an indirect comparison.

The PBAC considered that the groups were not strictly comparable and there remains significant uncertainty around the indirect comparison and the claim that carmustine is no worse than temozolomide in the treatment of recurrent GBM.

For further details, see Recommendation and Reasons.

10. Economic Analysis

A preliminary economic evaluation was presented. The PBAC advised the choice of the cost-minimisation approach was not considered valid, as the trials did not contain adequate information, such that many assumptions were required and variables sourced externally. The Pre-Sub-Committee Response disagreed with the re-calculation undertaken during the evaluation which was based on 3 cycles of temozolomide. A trial-based incremental cost per extra survival was undefined because there was no survival benefit.

A modelled economic evaluation was not presented. However, the PBAC advised modelling was required to generate an adequate economic analysis.

11. Estimated PBS Usage and Financial Implications

The submission predicted that less than 10,000 patients would be treated in Year 1 at a cost of less than 10 million per year.

12. Recommendation and Reasons

The PBAC noted that the sponsor clarified that the requested restriction appropriately should exclude combined treatment of PBS-subsidised carmustine and temozolomide, in line with the current wording for newly diagnosed patients.

The submission had nominated temozolomide given orally as the comparator. The PBAC considered that standard medical management of recurrent glioblastoma multiforme (GBM) eg surgical resection or focal radiotherapy or other chemotherapy (eg carboplatin and etoposide) as minor comparators would also have been appropriate.

The PBAC noted that the submission had based its comparison on the Yung et al trial which compared temozolomide after radiotherapy with procarbazine after radiotherapy in patients with glioblastoma multiforme at first relapse, over a median follow-up of 24 months. The PBAC considered that the submission's assumption, that procarbazine has not been shown to have any significant effect on survival in GBM patients and can be considered to act as a placebo, was not supported by the evidence provided.

The PBAC was of the opinion that the unequal distributions of prognostic indicators between the populations in the two key trials, the lack of a common reference and differences in the measurement of the primary outcome of survival hamper the comparison between carmustine implants and temozolomide in recurrent glioblastoma multiforme. The Pre-Sub-Committee Response stated that, despite the lack of a common reference, all the generally accepted prognostic factors such as age, KPS and previous nitrosourea chemotherapy in the two trials are similar. The Pre-PBAC Response also discussed its view that patients enrolled in the Yung et al did not have a poorer prognosis in comparison with patients enrolled in the carmustine trial, but noted that the proportions of patients with GBM, a more severe grade of astrocytoma and also a generally accepted prognostic factor, did differ across the trials. The PBAC concurred with ESC advice that the groups are not strictly comparable and there remains significant uncertainty around the indirect comparison and the claim that carmustine is no worse than temozolomide in the treatment of recurrent GBM.

A further problem about the trial population in the key carmustine study arose because it was carried out 18 years ago. Since 1989, pathological diagnosis of brain tumours has changed, in particular 1p/19q codeletion to identify the oligodendroglial phenotype, which has a better prognosis than GBM and greater chemosensitivity. Thus, some patients in the key trial may have been misclassified as GBMs. Further, new imaging techniques are now available to assist in the diagnosis of recurrent disease, and this causes further uncertainty when in making cross-trial comparisons. Furthermore, surgical techniques have changed and patients now will be exposed to multimodality treatments which are different from those available in 1989.

The PBAC also indicated that any comparison would need to base the cost of carmustine on a full pack of 8 wafers, as with use in the primary setting, because it is not practical to expect unused wafers from an open packet to be stored adequately for future use.

Although there was disagreement about the appropriate number of temozolomide cycles in the comparator arm, this was not considered by the PBAC to be a pivotal issue in its decision to reject the submission.

The PBAC therefore rejected the submission because of uncertain clinical effectiveness resulting from the lack of a common reference, 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.

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, for whom surgical resection is indicated.