Public Summary Document

Product: Carmustine, implant, 7.7 mg, Gliadel®
Sponsor: Orphan Australia Pty Ltd
Date of PBAC Consideration: March 2006

1. Purpose of Application

To expand the patient population of the current Pharmaceutical Benefits Scheme (PBS) restriction for carmustine to include high grade malignant gliomas rather than limiting treatment to patients with glioblastoma multiforme.

2. Background

At the November 2005 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing carmustine implant as a restricted benefit for newly-diagnosed glioblastoma multiforme 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.

3. Registration Status

Carmustine implant was registered by the TGA on 15 May 2002 for use as adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme (GBM) for whom surgical resection is indicated.

The indication was extended on 27 October 2004 to include the use in newly-diagnosed high-grade malignant glioma patients, as an adjunct to surgery and radiation.

4. Listing Requested and PBAC's View

Restricted benefit

Newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation.

At the November 2005 meeting, the PBAC considered the wording of the restriction should include a NOTE precluding concomitant use of carmustine implant with temozolomide and vice versa. The PBAC noted that storage requirements may increase the risk of wastage and requested that the sponsor provide educational material to address this issue.

See also Recommendation and Reasons.

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. Grade III and IV gliomas are considered high grade gliomas. 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 radiotherapy.

Currently, temozolomide concomitantly with radiotherapy is used to treat newly diagnosed, histologically confirmed glioblastoma (GBM). Carmustine systemically has been used but the clinical usefulness is limited because of its short half-life, the small fraction of the systemic dose reaching the tumour at an effective concentration, and its systemic toxicity. Carmustine implants are designed to release carmustine slowly, with the polymer degrading over a 2-3 week period after they have been placed on the surface of the tumour resection cavity.

6. Comparator

Not applicable. There was no need for a comparator to be included in this minor submission.

7. Clinical Trials

The submission provided no new clinical trial data.

8. Results of Trials

The submission presented the following arguments in support of a change to the restriction which would include all high grade gliomas instead of only glioblastoma multiforme:

1. The key clinical trial with carmustine (Westphal T-301) in the November 2005 submission included patients with all forms of high grade malignant glioma (HGMG) (both grade III and IV gliomas), and the cost-effectiveness analysis was based on this entire population. Therefore, the PBS indication should reflect this.
2. The basis of the comparison was with the temozolomide key trial (Stupp et al 2005), which only recruited patients with mainly GBM, and which tumour type accounted for 86% of the carmustine population, a substantial but not complete overlap. However, the submission stated that given the 80:20 rule and the fact that in trial T-301, the comparison of carmustine with placebo demonstrated that patients with Grade III glioma did as well as, if not better than the patients with GBM, Grade III patients should not be excluded access to carmustine. The submission argued that differences in prognostic features between the T-301 and the Stupp trials did not necessarily favour carmustine. Fifteen per cent of the Stupp population had pathology missing and they were unable to accurately determine the tumour type. Given the incidence of the various HGMG tumour type, the submission claimed that therefore not all these 15% had GBM, thus decreasing the stated percentage of GBM patients in the Stupp trial. The submission also stated that the 16% of patients that did not have surgery in the Stupp trial did not mean that the patients had a more severe form of the disease and that this might reflect the site or diffuse nature of the tumour not the severity of the disease.
3. There was currently no medication that is PBS listed for grade III gliomas. Both grade III and IV gliomas had a poor prognosis and a survival measured in months.
4. In clinical practice, grade III and IV gliomas cannot be definitively separated intra-operatively, and that the neurosurgeon will proceed with treatment on the basis of a provisional diagnosis of “malignant glioma” in the operating room.
5. The populations in the Westphal T-301 (carmustine) and Stupp et al (temozolomide) studies were not the same but there was substantial overlap, allowing a comparison between the studies.
6. The use of carmustine in grade III gliomas met the requirements for the “Rule of Rescue” as follows:
   (a) No alternative was available to treat patients with grade III glioma;

(b) Grade III glioma was severe, progressive and expected to lead to premature death.
(c) Grade III glioma applied to only a very small number of patients.

9. Clinical Claim

Not applicable. There was no need to make a clinical claim in this minor submission.

10. Economic Analysis

Not applicable. There was no need to include an economic analysis in this minor submission.

11. Estimated PBS Usage and Financial Implications

Not applicable. There were no revisions to previous estimates presented in this minor submission.

12. Recommendation and Reasons

The PBAC noted that only 16% patients in the key Trial T-301 were not diagnosed with glioblastoma multiforme (GBM). In cases where a distinction between a grade III and grade IV glioma was doubtful, the PBAC was of the view that clinicians would use carmustine if they considered it an appropriate treatment in the circumstances, as stated in the submission.

The PBAC noted that the submission claimed that patients with grade III gliomas possibly responded to carmustine better that those with GBM. However, the PBAC considered that the numbers were too small to draw this conclusion. Further, patients with grade III glioma have a better prognosis than those with GBM and tend to survive longer. In such patients, a demonstration of improved quality of life would be required.

The PBAC did not agree that the rule of rescue applies in this situation because other treatment options were available to patients with grade III tumours.

The PBAC therefore 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.

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 does not agree that there is insufficient evidence of benefit, in terms of survival gain or quality of life improvements, or in the cost effectiveness of carmustine *in the broader patient population ie HGMG patients.*

The original submission considered by the PBAC at their November 2005 meeting had provided evidence of benefit in terms of survival gain, quality of life improvements and cost effectiveness of carmustine implants *in the HGMG population*, not GBM *per se*. But the PBAC had concluded that carmustine implants was no worse than temozolomide for GBM, the main indication within the HGMG population.