PUBLIC SUMMARY DOCUMENT
Product: CARMUSTINE, implant, 7.7 mg, Gliadel®
Sponsor: Orphan Australia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

The submission sought a Section 85 restricted benefit listing for carmustine implant for the treatment of newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation.

2. Background

This drug has not previously been considered by the PBAC.

3. Registration Status

Carmustine implant is registered by the TGA for use as adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme (GBM) for whom surgical resection is indicated and for use in newly-diagnosed high-grade malignant glioma patients, as an adjunct to surgery and radiation.

4. Listing Requested and PBAC's View

Section 85 listing:
Restricted benefit
Newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation.

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.

5. Clinical Place for the Proposed Therapy

Carmustine implants offer an alternative treatment option to patients with newly diagnosed malignant glioma who have tumour resection.

6. Comparator

The submission nominated temozolomide given orally as the comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented two sets of randomised controlled trials to provide a basis for an indirect comparison between carmustine implants and temozolomide. Two supporting trials were also presented.

All four studies had been published at the time of submission as follows:

Trial/First author	Protocol/Publication title	Publication citation
Key trials		
T-301/Westphal M	A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary	Neuro-Oncology. 2003; 5(2):79-88.

Trial/First author	Protocol/Publication title	Publication citation
	malignant glioma.	
Stupp R,	Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.	New England Journal of Medicine. 2005; 352(10):987-996.
Supportive trials		
Valtonen S,	Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study.	Neurosurgery. 1997; 41(1):44-48.
Athanassiou H,	Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme.	Journal of Clinical Oncology. 2005; 23(10):2372-2377.

The key trial T-301 compared carmustine implants and standard care (tumour resection and radiotherapy) with placebo implants and standard care (tumour resection and radiotherapy) in patients with newly-diagnosed high-grade malignant glioma over a median follow-up of 14 months. The other key trial Stupp et al compared temozolomide and radiotherapy with radiotherapy alone in patients with glioblastoma multiforme, the most common form of high-grade malignant glioma, over a median follow-up of 28 months.

8. Results of Trials

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

Outcome	Study T-301 and long-term follow-up		Stupp R et al, 2005 [1]	
	Carmustine implants + std care	Placebo + std care	TMZ + RT	RT alone
Survival in months, median (95% CI)	13.9 (12.1 to 15.3)	11.6 (10.2 to 12.6)	14.6 (13.2 to 16.8)	12.1 (11.2 to 13.0)
Median incremental survival in months	2.3		2.5	
Unadjusted hazard ratio for death (95% CI)	0.73 (0.56 to 0.95) p=0.018		0.63 (0.52 to 0.75) p<0.001	
Relative reduction in risk of death from hazard ratio (95% CI)	27% (5% to 44%)		37% (25% to 48%)	
Adjusted hazard ratio for death [2] – Cox proportional hazards model (95% CI)	0.75 (0.57 to 0.99)		0.62 (0.51 to 0.75)	

[1] 83% of patients in TMZ + RT arm and 85% in RT alone arm respectively had tumour resection.
[2] Adjusted for prognostic factors (age, Karnofsky performance score, and tumour type) or sources of survival variability (country of treatment).
std care = standard care (tumour resection and radiotherapy); TMZ = temozolomide; RT = radiotherapy

In comparison to the respective control arm, there was a statistically significant difference in the median overall survival and the adjusted reduction in risk of death, favouring carmustine implant in the key trial T-301 and favouring temozolomide in the other key trial Stupp R et al, 2005, respectively. The increments in median survival of 2.3 months for carmustine implant over placebo and of 2.5 months for temozolomide and radiotherapy over radiotherapy alone are clinically important.

The PBAC noted that the populations in these two key trials did not have equal distributions of prognostic indicators, although they had a substantial overlap. All patients in the key trial T-301 underwent surgical tumour resection, a major intervention that can prolong survival for patients who are eligible for surgery, while only 84% of patients in the other key trial Stupp et al had tumour resection. The fact that fewer patients in the Stupp et al trial had tumour resection meant that a major intervention, other than carmustine and temozolomide, had not been comparably distributed across the two key trials. It may also have indicated that patients in the Stupp et al trial were likely to have more advanced disease. Furthermore, participants in the key T-301 trial were patients with newly-diagnosed malignant glioma, including anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma and glioblastoma multiforme (GBM). Eighty-four per cent of patients in the carmustine arm of trial T-301 had GBM, a grade IV malignant glioma that has a poorer prognosis. In contrast, 92% of patients in the Stupp et al key trial had GBM. The fact that more patients in the temozolomide trial had severe disease and fewer of them received surgical tumour resection than patients in trial T-301 was likely to introduce bias, favouring the carmustine implants. Even given the likely bias towards carmustine, the effect estimated (adjusted hazard ratio) for carmustine was weaker than that for temozolomide.

The Quality-Adjusted Time without Symptoms and Toxicity (Q-TWiST) method is a way of comparing two treatments in terms of quality-adjusted survival. An overall survival time was partitioned into three ordered and progressive health states: time-with-toxicity, time-without-symptoms-and-toxicity and relapse. The Q-TWiST analysis presented in this submission was not specified in either trial protocol and was performed post hoc. The same weight was assigned to the time-with-toxicity that was associated with both carmustine implants and temozolomide, without any consideration of the relative toxicities of these two treatments.

Summary of the results of the Q-TWiST analysis

	Trial T-301		Stupp R, et al 2005	
	Carmustine implants + std care	Placebo + std care	TMZ + RT	RT alone
Q-TWiST (days)*	430.0	378.8	354.4	292.5
Q-TWiST increment (days)	51.2		61.9	

* Q-TWiST is estimated under the assumptions that the utility for TWiST is 1.0, and that the utility for both toxicity and for relapse is 0.5.
std care = standard care (tumour resection and radiotherapy); TMZ = temozolomide; RT = radiotherapy

The submission conducted a parallel review of the toxicity for carmustine implants and temozolomide from each trial. The most common adverse events for carmustine implants were intracranial hypertension (9.2%) and cerebrospinal fluid leakage (5%). The most common adverse events for temozolomide were grade 3 or 4 haematologic toxic effects. During concomitant temozolomide therapy, grade 3 or 4 neutropaenia was documented in 12 patients (4%), and grade 3 or 4 thrombocytopenia occurred in 9 patients (3%). During adjuvant temozolomide therapy, 14% of patients had either grade 3 or 4 haematologic toxic effects, 4% had grade 3 or 4 neutropaenia, and 11% had grade 3 or 4 thrombocytopaenia.

9. Clinical Claim

The submission claimed that carmustine implants were at least as effective as temozolomide with the same or less toxicity. The PBAC noted that this claim was based on an indirect comparison involving Q-TWiST analysis. The proposition that local carmustine implants were associated with the same or fewer systemic toxicities than temozolomide was

considered plausible, but the Q-TWiST analysis presented relied on different durations of treatment effect rather than different severities in toxicity.

However, based on the indirect comparison across the two trials provided in the submission, the PBAC concluded that, overall, carmustine implants were no worse than temozolomide for glioblastoma multiforme, the main indication within the requested restriction.

10. Economic Analysis

A preliminary trial-based economic evaluation was presented. The choice of the cost-utility approach for each trial was considered valid. The resources included were the cost of carmustine implants, the cost of temozolomide and the costs of drugs co-administered with temozolomide.

The trial-based incremental cost/extra life-year gained for carmustine implant was between $75,000 to $105,000 (based on 6.5 implants) over standard management, which increased to over $105,000 if the revised number of implants (eight) were used to calculate costs. The trial-based incremental cost/extra life-year gained was $75,000 to $105,000 for temozolomide over radiotherapy alone.

The trial-based incremental cost/extra quality adjusted life year (QALY) gained was $105,000 to $200,000 for carmustine implant over standard management (based on 6.5 implants), which increased to over $200,000 if the revised number of implants (eight) was used to calculate costs. The trial-based incremental cost/extra QALY gained was $75,000-$105,000 for temozolomide over radiotherapy alone.

The incremental economic evaluation in terms of carmustine implants versus temozolomide was not provided. The PBAC noted that assuming that a true difference in survival had been detected, then temozolomide was dominant (associated with higher survival and lower costs). At the requested price, it remained dominant even if the PBAC concluded that carmustine was no worse than temozolomide.

A modelled economic evaluation was not presented. This was considered reasonable because the key trials have long periods of follow-up to capture most expected overall survival.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients/year was less than 10,000 patients Year 2 of listing. The PBAC considered that this was a likely under-estimate in the submission.

The PBAC noted that as there was no explicit wording to exclude the possible <u>combined</u> use of carmustine implants and temozolomide in the requested restriction, and combined use of these drugs was considered likely, the cost-savings to the PBS are unlikely to be realised.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis with one pack of eight carmustine 7.7 mg implants being equivalent to a course of temozolomide capsules, with costs calculated from the Strupp et al trial, accepting the intention-to-treat approach, but adjusted for resources provided according to the *Manual of Resources and their Associated Costs* rather than on a per mg basis. Based on the indirect comparison across the two trials

provided in the submission, the PBAC concluded that, overall, carmustine implants are no worse than temozolomide for glioblastoma multiforme, the main indication within the requested restriction. The PBAC did not accept the submission's approach to estimating the costs of adjuvant phase temozolomide.

The PBAC considered that a NOTE should follow the restriction to preclude the PBS-subsidised use of temozolomide in conjunction with carmustine implant. This was because there was no evidence that such use would produce additional health gains without additional harms sufficient to justify the additional costs. A similar NOTE should be appended to the temozolomide listing. The PBAC noted that the cold storage requirements may increase the risk of wastage and requested that the sponsor provide educational material to address this issue.

CARMUSTINE, implant, 7.7 mg, 8

Restriction:	Restricted benefit Newly-diagnosed glioblastoma multiforme as an adjunct to surgery and radiation. NOTE: Carmustine is not PBS-subsidised for use in conjunction with PBS-subsidised temozolomide.
Maximum quantity:	1
Repeats:	Nil

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 agrees that carmustine implants have similar efficacy to temozolomide. The sponsor does not agree that patients in the Stupp trial for temozolomide had more severe disease than those in the key trial for carmustine implants. The fact that some 16% did not have surgery may be due to the site or diffuse nature of the tumour and unrelated to disease severity.

Regarding therapeutic relativity, comparative efficacy was based on a number of hard outcomes including overall survival, not just the Q-TWiST. The sponsor believes that the statement that one treatment is dominant is inappropriate since there are no head-to-head data on which this claim can be proven. The difference in incremental survival between the two products is approximately 1 week.