Scottish Medicines Consortium

carmustine 7.7mg implant (Gliadel®) (No. 215/05)

Link Pharmaceuticals Ltd.

New indication: in newly diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation

4 November 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Scotland and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Carmustine implant (Gliadel®) is accepted for use within NHS Scotland for the treatment of newly diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation.

In the pivotal study, the use of carmustine implants was associated with a 29% relative decrease in the risk of death, which equates to an increase in median survival time of 2.3 months.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

carmustine 7.7mg implant (Gliadel ®)

Indication

Treatment of newly diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation.

Dosing information

It is recommended that up to eight implants are placed, according to the size and shape of the resection cavity.

UK launch date

December 2004

Comparator medications

The protocol for a National Institute of Health and Clinical Excellence (NICE) appraisal; *Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma*, lists surgery and radiotherapy alone or surgery and radiotherapy combined with antineoplastic agents (e.g. nitrosourea based regimens) as standard comparators. The only newly diagnosed high-grade glioma which temozolomide is licensed for is glioblastoma multiforme (GBM).

Cost of relevant comparators

Drug	Dose	Cost * (£)
Carmustine implant	**Up to 8 implants**	**up to 5203**
Temozolomide Concomitant phase	75mg/m^2 daily for 42 days concomitant with focal radiotherapy (for GBM only)	9 530-11 090
Temozolomide Monotherapy phase	*Cycle 1*: 150mg/m^2 daily for 5 days *Cycles 2-6*: 200mg/m^2 daily for 5 days (if dose escalation allowed) or *cycles 2-6:* 150mg/m^2 (if dose escalation not allowed) All cycles given every 4 weeks	
PCV	Procarbazine 100mg/m^2/day on days 1-10 Lomustine 100mg/m^2 on day 1 Vincristine 1.5mg/m^2 on day 1 (maximum 2mg) *Up to 12 cycles*	up to 2002
PCV	Procarbazine 60mg/m^2/day on days 8-21 Lomustine 110mg/m^2 on day 1 Vincristine 1.4mg/m^2 on day 8 and 29 (maximum 2mg) *Given every 6-8 weeks for up to 1 year.*	up to 1439

*Costs from BNF edition 49 and eVadis drug dictionary accessed on 23 August and 5 September 2005 and based on body surface area of 1.8m^2, where applicable.

Summary of evidence on comparative efficacy

High-grade (grades 3 and 4) gliomas include anaplastic astrocytomas (AA), anaplastic oligodendrogliomas (AO), mixed anaplastic oligoastrocytomas (AOA) and GBM. Carmustine implants are biodegradable polymer discs containing carmustine (BCNU), a nitrosourea antineoplastic agent which acts by alkylating DNA and RNA. The use of carmustine systemically is limited by its short half-life, the small fraction reaching the tumour and its toxicity.

Two phase III prospective, randomised, placebo-controlled multi-centre studies have been conducted in patients with high-grade gliomas. The larger study recruited 240 patients between the ages of 18 and 65 years with an intraoperative diagnosis of malignant glioma. Patients were required to have a Karnofsky performance status ≥ 60 (on a scale of 0 to 100, with high scores indicating better performance status) and have evidence of a single contrast-enhancing unilateral, supratentorial cerebral tumour on cranial MRI. After the diagnosis of malignant glioma was confirmed, all patients received maximal tumour resection and were randomised to receive up to eight implants of either carmustine or placebo. All patients received 55-60Gy of limited-field radiation to the tumour site and the surrounding margin postoperatively starting 14 days after surgery.

The study was stratified by country (in order to take into consideration a centre, which exists uniquely within a specific country, as a potential source of variability). The primary end-point was overall survival (defined as duration between the date of randomisation and date of death from any cause) 12 months after the final patient was enrolled, in the intention-to-treat (ITT) population by the Kaplan-Meier method (log-rank statistic stratified by country). Overall survival and 12-month survival were also determined for the GBM subgroup of patients. Secondary end-points included time to Karnofsky performance status decline and time to neurological progression.

Median survival in the carmustine and placebo implant groups was 13.9 months and 11.6 months respectively, corresponding to a hazard ratio for death of 0.71 (95% confidence interval (CI): 0.52-0.96, p=0.03). When the overall survival was adjusted for prognostic factors (Karnofsky performance status, age, GBM or non-GBM, and the number of implants) the carmustine implant group still had a significantly longer survival compared to the placebo group (p=0.03). Median survival in the GBM sub-group analysis was 13.5 months and 11.4 months for the carmustine and placebo groups respectively. Comparison of the Kaplan-Meier curves in the GBM sub-group did not reach statistical significance. However, when corrections were made for prognostic factors, carmustine implants significantly prolonged survival compared with placebo (p=0.04).

Karnofsky performance status deterioration was defined as a score < 60 on two consecutive assessments during the short-term follow-up (days 7-30) or for any one assessment during the long-term follow-up (months 1-12). The percentage of patients remaining deterioration-free at 12 months was 48% and 39% in the carmustine and placebo groups respectively (p=0.05).

Neurological progression was determined by the decline in neurological evaluation of 11 pre-specified neuroperformance measures (vital signs, level of consciousness, personality, speech, visual status, fundoscopic examination, cranial nerve examination, sensory status, motor status, cerebellar examination and other signs). These were scored on a six-point scale and deterioration was defined as a decline observed over two consecutive assessments. This tool is not a validated tool referenced in the literature. The time to deterioration was significantly longer in the carmustine group compared with placebo for all

neuroperformance measures, with the exception of visual status, which did not reach statistical significance.

The second trial recruited 32 patients with similar inclusion criteria to the previously described trial. Following maximal tumour resection, patients were randomised in blocks of four to receive either carmustine implants or placebo implants. After haemostasis was achieved as many implants (up to a maximum of eight) as the space allowed were placed over the resection surface. All patients, except one in the carmustine group, received standard radiotherapy and all patients received perioperative corticosteroids to reduce brain swelling. Subsequent resections were allowed if considered necessary.

This trial was terminated prematurely due to unavailability of the drug. The primary endpoint, median time from surgery to death, was 39.9 weeks (95% CI: 37.6-45.0) and 58.1 weeks (95% CI: 42-no upper limit) for the placebo and carmustine implant groups respectively (p=0.012). The risk ratio in favour of carmustine treatment versus placebo was 0.27 (95% CI: 0.11-0.68, p=0.006).

A sub-group analysis was performed on patients with GBM (n=27), as the placebo group comprised of these patients only. The median time from surgery to death was 39.9 weeks and 53.3 weeks for the placebo and carmustine groups respectively (p=0.008).

Summary of evidence on comparative safety

In the larger study adverse events were similar for the carmustine implant and placebo arms. The only nervous system adverse event occurring in > 5% of the safety population, which was statistically more common in either of the groups, was intracranial hypertension; reported in 11 and 2 of the carmustine implant and placebo patients respectively (p=0.019). The investigators considered that the intracranial hypertension was unlikely to be linked with carmustine in 9 of the 11 patients in the carmustine group as it was a late presentation of the symptom. The summary of product characteristics (SPC) for carmustine implants recommends careful monitoring of patients for cerebral oedema/intracranial hypertension with consequent steroid use. Cerebro-spinal fluid (CSF) leakage was more common in the carmustine implant group (6 patients) compared with placebo (1 patient) although it was noted that CSF infection rates were similar in both groups. The SPC advocates attention to a water-tight dural closure and local wound care to avoid CSF leakage.

Summary of clinical effectiveness issues

In the larger study, patients started radiotherapy 14 days after surgery. This may not be possible in centres where there are long radiotherapy waiting times.

A review of a subgroup of patients (recruited from the Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh) entered in to the larger study has been published. The aim was to assess the size of the cohort of patients with malignant glioma that were eligible for the study and determine how selection criteria for the study may have determined the good outcomes reported. The review considered the parameters defined by Medical Research Council brain tumour studies as having significant independent effects; age, clinical status (Karnofsky score), resection rather than biopsy and radiotherapy treatment. The two study populations were those patients entered into the carmustine implant trial (n=14, note that half of these patients received placebo) and the non-recruited group (n=42) over a period of approximately 10 months. There were significant differences in terms of median Karnofsky score, tumour resection achieved and radiation treatment in favour of the carmustine implant trial group compared with the non-recruited group. Median

survival was 66 weeks and 19 weeks for the carmustine implant trial group and non-recruited group respectively. The authors concluded that patients with multifocal disease, poorer performance status or disease involving midline structures would be unlikely to benefit significantly from carmustine implantation. They noted that a sub-group of elderly patients who have good performance status do better than expected; in particular if they receive radiotherapy. Therefore some of these patients, with tumour features that would make them eligible for the study, may benefit from carmustine implants.

Summary of comparative health economic evidence

The manufacturers submitted a cost-utility analysis of carmustine implants as an adjunct to surgery and radiotherapy compared with the use of surgery and radiotherapy alone. The base case economic model was populated with data from the larger clinical trial (which has survival data), comparing the two interventions. The mean additional survival gain for carmustine implants in the economic analysis was estimated to be 2.6 months, driven by the improvement in symptom-free survival. The cost of carmustine implants was estimated at £4,252 per patient, resulting in an incremental cost per life year gained of £19,200. Incremental cost per QALY was estimated at £28,000. The QALY estimate was based on assigning an arbitrary utility of 0.8 for the symptom-free survival period post-surgery/radiotherapy, which may be a high estimate for the quality of life of patients with high-grade glioma.

The main strength of the economic analysis was the data on survival from the clinical trial, but there were a number of important weaknesses. In particular, the economic analysis was basic, with arbitrary utility estimates and limited sensitivity analysis conducted (e.g. one way sensitivity analysis on survival or utility was not performed).

In addition to the base-case analysis, indirect comparisons were undertaken with other possible treatment options for high grade-glioma after surgery and or radiotherapy: PCV or temozolomide chemotherapy. Carmustine implants were estimated to have slightly better survival outcomes than temozolomide but lower costs due to better side effect and toxicity profile, and a 3 week survival benefit compared to PCV at an extra cost of £1,769 per patient.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The annual budget impact of carmustine implants over the next 5 years was estimated to be between £210,000 to £338,000 per annum, with 25% of high-grade glioma patients expected to be eligible for the treatment (representing 51-80 patients per annum).

Guidelines and protocols

NICE are undertaking a health technology appraisal of *carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma*, with an expected date of issue of August 2006.

Additional information

A Cochrane review, *Chemotherapy for High Grade-Glioma* produced by the Glioma Meta-analysis Trialist Group, was published in 2002. The objective was to compare radiotherapy and chemotherapy with radiotherapy alone in completed resected adults with high grade glioma. The 12 studies included in the review all used chemotherapy regimens which included a nitrosourea, given as a single agent or in combination with other drugs. A 15% relative decrease in the risk of death associated with chemotherapy was shown. This was equivalent to an absolute increase in the one year survival rate of 6% (95% CI: 3, 9%) from 40% to 46% and a two month increase in median survival time (95% CI: 1, 3 months). The authors concluded that this small but clear improvement in survival from chemotherapy encourages further study of drug treatment of these tumours. The pivotal carmustine implant study recruited patients from 1997 to 1999, which was after the recruitment period defined in the Cochrane protocol, and therefore the study was not included in the review.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 14 October 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

1. *Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro-oncology 2003; 5(2): 79-88*
2. *Valtonen S, Timonen U, Toivanen P, et al. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. Neurosurgery 1997; 41(1): 44-49*
3. *Whittle IR, Lyles S, Walker M. Gliadel therapy given for first resection of malignant glioma: a single centre study of the potential use of Gliadel. Br J Neurosurg 2003; 17(4):352-354*
4. *Medical Research Council Brain Tumour Working Party. Randomised Trial of procarbazine, lomustine and vincristine in the adjuvant treatment of high-grade astrocytoma: A medical research council trial. Journal of Clinical Oncology 2001; 19: 509-518*
5. *Levin VA et al. Superiority of post-radiotherapy adjuvant chemotherapy with PCV over BCNU for anaplastic gliomas: NCOG 6G61 final report, Int J Radiat Oncol Biol Phys. 1990; 18: 321-4*
6. *Glioma Meta-analysis Trialists (GMT) Group. Chemotherapy for high-grade glioma. The Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD003913. DOI: 10.1002/14651858.CD003913.*