## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

#### **Overview**

# Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members prior to the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. In order to allow sufficient time for the overview to be circulated to Appraisal Committee members prior to the first Appraisal Committee meeting, it is prepared before the Institute receives consultees' comments on the Assessment Report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in Appendix A.

## 1 Background

#### 1.1 The condition

The majority of brain tumours are gliomas, which develop from the glial cells that support the nerve cells of the brain and spinal cord. There are four main types of glioma – astrocytoma, ependymoma, oligodendroglioma and mixed tumours. Brain tumours are graded according to their likely rate of growth, from grade 1 (slowest growing) to grade 4 (fastest growing). Grade 3 and 4 gliomas are considered high-grade gliomas. Grade 3 tumours include anaplastic astrocytoma, anaplastic ependymoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma. Grade 4 gliomas are usually glioblastoma multiforme (GBM) but can also, rarely, be giant-cell glioblastoma and gliosarcoma.

Brain tumours account for less than 2% of all primary cancers. Approximately 1860 new cases of malignant glioma are diagnosed in England and Wales each year. High-grade gliomas are more common in men than women, with a ratio of approximately 4:3. The incidence of high-grade gliomas increases with age, and is highest in people aged 70–74 years. People diagnosed with GBM are on average older than people diagnosed with grade 3 tumours

Symptoms of high-grade glioma are dependent on the size, location and degree of infiltration of the tumour. Symptoms include headaches, nausea, vomiting, seizures, visual disturbance, speech and language problems, and changes in cognitive and/or

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functional ability. Children with high-grade glioma may experience symptoms of cerebellar involvement such as ataxia (failure of muscle coordination) and nystagmus (involuntary rapid movement of the eyeball).

Approximately 30% of adults with high-grade tumours (grades 3 and 4) survive 1 year, and 13% survive 5 years. The median survival of patients with anaplastic astrocytoma is around 2–3 years, and approximately 1 year for patients with GBM. There are three factors consistently shown to be an indication of pretreatment prognosis.

- Age. Younger patients have a better prognosis than older patients.
- Performance status, for example as measured by the Karnofsky Performance Status (KPS) scale, which measures functional status on a scale from 0 ('dead') to 100 ('normal'). Patients with better performance status have a better prognosis.
- Tumour histology. Patients with grade 3 tumours have a better prognosis than patients with grade 4 tumours, and those whose tumours have an oligodendrocytic component have improved survival.

Diagnosis of high-grade glioma is provisionally made through computed tomography (CT) scan or magnetic resonance imaging (MRI). The diagnosis is then confirmed and the tumour classified histologically, either at the time of surgical resection or by a single-event biopsy if surgery is not possible. There is a growing understanding of the molecular genetics of gliomas, which allows a more accurate classification of glioma and may also give an indication of prognosis.

### 1.2 Current management

There is a lack of consensus regarding the best treatment for people with high-grade glioma. In the UK, treatment usually consists of surgical resection where possible, followed by radiotherapy.

Surgery may achieve either a complete resection or partial resection (also known as 'debulking') of the tumour. Some patients with malignant glioma require more than one operation due to recurrence of the disease. Most patients experience improved neurological status as a result of surgery, although perioperative mortality is approximately 1.5% for the first craniotomy and 2.2% for the second. If the tumour is inoperable, treatment may consist of palliative medical management.

Radiotherapy has been demonstrated to prolong survival and is usually recommended post surgery. Previous research has suggested that the optimum dose is 60 Gy. Radiotherapy is itself associated with adverse events, such as swelling, skin irritation, hair loss, fatigue and nausea. Some adverse effects may be responsive to treatment with steroids.

Adjuvant chemotherapy is not considered part of standard therapy in the UK, but is used more routinely in the USA. The most frequently used regimens are a combination of procarbazine, lomustine and vincristine (PCV therapy), or single-agent treatment with carmustine (BCNU) or lomustine (CCNU).

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A NICE technology appraisal 'Guidance on the use of temozolomide for the treatment of recurrent glioma (brain cancer)' was published in 2001 (NICE Technology Appraisal Guidance no. 23; www.nice.org.uk/TA023). The guidance recommended that temozolomide should be considered for the treatment of patients whose recurrent malignant glioma has failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of side effects). This guidance will be reviewed in 2006 alongside an appraisal of carmustine implants for the treatment of recurrent disease. NICE cancer service guidance on brain and other central nervous system tumours is in development (expected publication June 2006).

## 2 The technologies

**TABLE 1: SUMMARY DESCRIPTION OF TECHNOLOGIES** 

Generic Name	Carmustine implant	Temozolomide
Proprietary Name:	Gliadel	Temodal
Manufacturer	Link Pharmaceuticals	Schering-Plough Limited
Dose:	It is recommended that a maximum of eight implants be placed if the size and shape of the resection cavity allows it.	Concomitant phase: 75 mg/m² daily for 42 days with radiotherapy (60 Gy administered in 30 fractions). Monotherapy phase: 150 mg/m² daily for 5 days followed by 23 days without treatment. The dose may be escalated to 200 mg/m² daily in the second and subsequent cycles. Maximum 6 cycles of monotherapy.
Acquisition Cost excluding VAT (BNF edition 50)	One 7.7 mg implant £650.38	5x5mg       £17.30         5x20mg       £69.20         5x100mg       £346.00         5x250mg       £865.00

Temozolomide (Temodal, Schering Plough Ltd.) is an oral prodrug that is converted into a pharmacologically active molecule in the body. It undergoes hydrolysis to produce monomethyl triazenoimidazole carboxamide (MTIC). MTIC is thought to act as an alkylating agent. Alkylating agents cause cross-linking of guanine bases in DNA thereby preventing cell division.

Temozolomide has a UK marketing authorisation for the treatment of newly diagnosed GBM concomitantly with radiotherapy and subsequently as monotherapy

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treatment. It is also licensed for the treatment of malignant glioma showing recurrence or progression after standard therapy. It is administered concomitantly with radiotherapy and then for up to 6 cycles of monotherapy.

Carmustine implants (Gliadel, Link Pharmaceuticals) are biodegradable copolymer discs about the size of a 5p coin. They are implanted into the resection cavity at the time of surgery. Each implant contains 7.7 mg of carmustine (BCNU), which interacts with DNA and RNA and may prevent the proliferation of tumour cells.

Carmustine implants are indicated for the treatment of newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation. They are also indicated as an adjunct to surgery in patients with recurrent GBM for which surgical resection is indicated.

#### 3 The evidence

#### 3.1 Clinical effectiveness

The Assessment Group (AG) identified two randomised controlled trials (RCTs) that compared the effectiveness of carmustine implants plus radiotherapy with that of placebo plus radiotherapy, and two observational studies of carmustine implants. They also identified two RCTs of temozolomide plus radiotherapy compared to radiotherapy alone, and two observational studies of temozolomide. No studies comparing carmustine implants to temozolomide, or comparing carmustine implants or temozolomide to other antineoplastic agents (for example, PCV), were identified.

#### **Carmustine implants**

The largest RCT was a multinational trial by Westphal and colleagues which had a minimum of 12 months' follow-up. Patients with grade 3 and 4 gliomas aged between 18 and 65 years and with a KPS score of 60 or greater were randomised following surgery to receive carmustine implants (n = 120) or placebo implants (n = 120). Patients also received radiotherapy at 55–60 Gy administered in 30–33 fractions. Details of longer-term follow-up of this study were presented in the manufacturer's submission.

The AG expressed some concerns regarding the analysis of the trial and noted that additional analysis of the trial data had been carried out by the US Food and Drug Administration (FDA). Some of the key issues raised are noted below and further details of the study quality are provided in pages 33–40 of the AR.

- There was an imbalance in the types of tumour between treatment arms.
   There were 101 cases of GBM in the carmustine implant arm and 106 in the placebo arm (based on the original trial pathologist's diagnoses).
- The diagnosis of a single referee pathologist was considered definitive in the trial and the FDA requested that a sensitivity analysis be conducted based on the diagnoses from an alternative pathologist. The alternative

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pathologist suggested that the number of GBM cases was 88 in the carmustine implant arm and 99 in the placebo arm.

- The measurement of 'time to decline of KPS' and 'time to progression on neurological indices' had included 'death' as an event. The FDA reanalysed these data treating 'death' as censored.
- The analyses stratified the data by country. This was not specified in the trial protocol and was found by the FDA to favour carmustine implants.
   The FDA reanalysed much of the data without stratifying by country.
- Three patients had withdrawn from the RCT but it was not clear from which arm.

The results presented below are based on the FDA's reanalysis of the data without stratification by country (as specified in the statistical analysis plan for the trial) unless stated otherwise. Results from the stratified analysis can be found in the AR and Manufacturer's submission.

The median survival was 13.8 months (95% CI: 12.1 to 15.1) in the carmustine implant group and 11.6 months (95% CI: 10.2 to 12.7) in the placebo group. The Kaplan–Meier hazard ratio was 0.77 (log rank statistic: p = 0.08). The Kaplan–Meier hazard ratio based on data from longer-term follow-up was 0.73 (log rank statistic: p = 0.02). At 12 months 59% of the carmustine implant group and 50% of the placebo group were alive, at 24 months survival was 16% and 8%, and at 36 months survival was 9% and 2% in each group respectively (all estimates calculated on the basis of survival data censored at the relevant time period).

There was no difference in progression-free survival between treatment groups: median time to progression was 5.9 months (95% CI: 4.4 to 8.3) in the carmustine implant group and 5.9 months (95% CI: 4.7 to 7.4) in the placebo group (stratified analysis). The manufacturer's analysis suggested that the time to decline of KPS and time to progression on neurological indices were statistically significantly improved in the carmustine implant group. However, the FDA reanalysis of these data, which treated deaths as censored, found that the differences were driven by the differential survival between the treatment arms and that there was no independent treatment effect on time to decline of neurological indices and KPS.

In a subgroup of patients with GBM, the median survival was 13.5 months (95% CI: 11.4 to 14.8) in the carmustine implant group and 11.4 months (95% CI: 10.2 to 12.6) in the placebo group. The Kaplan–Meier hazard ratio was 0.82 (log rank statistic: p = 0.20). A Cox proportional hazards model adjusted for baseline factors. This suggested that survival was statistically significantly better in the carmustine implant arm when based on the analysis stratified by country (p = 0.04), but the differences were no longer statistically significant when the data were not stratified (p = 0.20). The diagnosis of an alternative pathologist suggested that the number of GBM cases was 88 and 99 in the carmustine implant and placebo groups respectively and highlighted the variability in diagnoses between different

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pathologists. A sensitivity analysis of the GBM subgroup data based on these diagnoses suggested that the difference in survival between treatment arms was less than the original analysis. There was no statistically significant difference between treatment groups in progression-free survival for patients with GBM (stratified log rank test: p = 0.62).

The second RCT was based in Scandinavia (n = 32) and had a minimum follow-up of 24 months. Recruitment to the study was terminated early as the investigators were unable to source additional carmustine implants. The design and inclusion criteria for the trial were similar to those for the larger RCT reported by Westphal and colleagues. Fewer patients had a diagnosis of GBM in the carmustine implant group (69%) compared to the placebo group (100%). Median survival in the carmustine implant group was 13.4 months (95% CI: 9.7 to ? [upper bound not reported]) compared to 9.2 months (95% CI: 8.7 to 10.4) in the placebo group. This difference was statistically significant (log rank: p = 0.01). Survival at 12 months was 63% in the carmustine implant group and 19% in the placebo group; at 24 months survival was 31% and 6% respectively (estimates based on censored data). There was no statistically significant difference in progression-free survival between treatment groups. For patients with a diagnosis of GBM only, median survival in the carmustine implant group was 12.3 months (95% CI: 10.4 to 17.9) compared to 9.2 months (95% CI: 8.7 to 10.4) in the placebo group.

Intracranial hypertension was the only adverse event from either RCT to have significantly increased incidence in the carmustine implant group (9.2% compared to 1.7%; p = 0.02).

#### **Temozolomide**

The largest randomised trial of temozolomide was conducted by Stupp and colleagues. The inclusion criteria specified that patients aged 18–70 years with grade 4 glioma and a WHO performance status of 2 or better could be recruited to the trial and randomised following surgery to receive radiotherapy plus temozolomide (n = 287) or radiotherapy alone (n = 286). Temozolomide was administered in accordance with its UK marketing authorisation. Patients and investigators were not blinded to treatment allocation. The data were analysed on an intention-to-treat basis. Of the radiotherapy plus temozolomide group, 62% withdrew from treatment compared to 9% in the radiotherapy alone group. However the treatment phase was much longer in the radiotherapy plus temozolomide group (up to 34 weeks) compared to the radiotherapy alone group (up to 6 weeks), although the duration of radiotherapy was the same in both groups. See pages 57–62 of the Assessment Report (AR) for a discussion of the trial quality and potential biases.

The median age of patients was approximately 56 years (range 19–70 years). A diagnosis of GBM was confirmed by histology in 92–3% of patients; the proportion of grade 3 tumours was similar in both treatment groups. In the radiotherapy plus temozolomide group, tumour removal was complete in 44% of patients and partial in 39%, and only a biopsy was possible in 17% of patients. The extent of surgery was

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similar in the radiotherapy only group (45% complete, 40% partial and 16% biopsy only). Median follow-up time was 28 months.

Median survival was 14.6 months (95% CI: 13.2 to 16.8 months) in the radiotherapy plus temozolomide group and 12.1 months (95% CI: 11.2 to 13.0 months) in the radiotherapy only group. Survival rates at 12 months, based on censored data, were 61% for the radiotherapy plus temozolomide group and 51% for the radiotherapy alone group. At 24 months corresponding survival rates were 27% and 10% respectively. Median time to disease progression was 6.9 months (95% CI: 5.8 to 8.2) in the temozolomide plus radiotherapy group and 5.0 months (95% CI: 4.2 to 5.5 months) in the radiotherapy alone group.

An analysis of patients with confirmed GBM was not fully reported; however, the AG noted that an unpublished figure included in the manufacturer's submission suggested that the survival benefit for patients with confirmed GBM was slightly weaker than for the full cohort. A subgroup analysis of patients with reduced O<sup>6</sup>methylguanine-DNA methyltransferase (MGMT) activity was conducted. MGMT is an enzyme that repairs DNA damage at a site commonly targeted by cytotoxic drugs, thereby inhibiting the effect of chemotherapy on tumours. Patients with reduced MGMT activity had a median survival gain from radiotherapy plus temozolomide of 6.4 months and median progression-free survival gain was 4.4 months. In the group with normal MGMT activity, both the median survival gain and median progressionfree survival gain were less than 1 month, although the gain in progression-free survival was statistically significant. The manufacturer reported the results of an additional subgroup analysis by extent of tumour resection. For patients who underwent a complete resection, the median survival was 14.2 months (95% CI: ) in the radiotherapy only group and 18.3 months (95% CI: the radiotherapy plus temozolomide group. For patients who underwent a partial resection, the median survival was 11.7 months (95% CI: 13.5 months (95% CI: ) respectively. It is not clear how many subgroup analyses were conducted and which were prespecified.

Severe myelosuppression (a decrease in the ability of bone marrow to produce blood cells) was reported for 16% of patients in the radiotherapy plus temozolomide group. Of the reported serious (grades 3 and 4) adverse events, fatigue, unspecified constitutional symptoms and infection were statistically significantly more frequent in the radiotherapy plus temozolomide group, as were moderate (grade 2) fatigue, nausea/vomiting and rash. Of the radiotherapy plus temozolomide group, 11% discontinued treatment due to toxic effects.

A second smaller RCT was conducted in Greece by Athanassiou and colleagues. Of 130 patients recruited to the study, 57 received radiotherapy plus temozolomide and 53 received radiotherapy alone. The remaining 20 patients were either excluded from the study as ineligible due to receiving off-protocol radiotherapy or having ineligible histology, or were randomised but not treated. Patients generally had a worse prognosis than those in the larger trial. In the radiotherapy plus temozolomide group, tumour removal was complete in 18% of patients and partial in 40%, and only

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a biopsy was possible in 42% of patients. The extent of surgery in the radiotherapy only group was 15% complete, 43% partial and 42% biopsy only.

The gains in both overall survival and progression-free survival from temozolomide were larger than those seen in the larger RCT reported by Stupp and colleagues. Median survival was lower than the larger trial: 14.6 months (95% CI: 13.2 to 16.8) in the radiotherapy plus temozolomide group and 7.7 months (5.3 to 9.2) in the radiotherapy only group. A Cox proportional hazards model suggested that after adjusting baseline characteristics, the hazard ratio was 0.66 (p < 0.001). At 12 months survival was 56% of the carmustine implant group and 16% of the placebo group, and at 18 months survival was 25% and 5% respectively (all estimates calculated on the basis of survival data censored at the relevant time period). Median time to progression was 10.8 months (95% CI: 8.1 to 14.7) in the radiotherapy plus temozolomide group and 5.2 months (95% CI: 3.9 to 7.4) in the radiotherapy only group.

#### 3.2 Cost effectiveness

The manufacturer of carmustine implants submitted an economic model that estimated the cost per life year gained of carmustine implants plus radiotherapy compared to placebo plus radiotherapy. The manufacturer of temozolomide submitted a within-trial economic analysis of temozolomide plus radiotherapy compared to radiotherapy alone. The AG reviewed both manufacturers' analyses and constructed their own economic model.

#### Manufacturers' economic evaluations

#### Carmustine implants

The economic model submitted by the manufacturer of carmustine implants assumed that following surgery patients experience a constant level of quality of life until the onset of symptoms (progression), after which time patients experience a constant deterioration of symptoms until death. The model assumes that carmustine implants delay the onset of symptoms and extend survival. Mean overall survival time was estimated from the largest RCT and time to symptoms was estimated from the median time to neurological performance score deterioration in the same study. The AG expressed concern that median, not mean, time to neurological deterioration was used in the model and that statistically significant differences were not found in other measures of disease progression in that trial. In addition, the differences in time to deterioration of neurological performance scores were statistically significant in only one of eleven indices when reanalysed by the FDA without stratification by country.

It was assumed that the only difference in costs between the two treatment groups was the cost of the implants themselves (mean: 6.54 wafers per patient). A utility value of 0.8 was assumed for patients without symptoms (it was noted that the utility value for the general population aged 45–50 years is 0.85), and constant deterioration assumed from symptoms until death.

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The analysis found that the mean incremental cost of carmustine implants was £4250 and estimated mean quality-adjusted life years (QALYs) gained were 0.16. The base-case incremental cost-effectiveness ratio (ICER) was £28,000 per QALY gained. A probabilistic sensitivity analysis was conducted by specifying the distributions of four parameters: time to symptoms; overall survival; symptom-free utility; and number of implants used. This found that the probability of carmustine implants being cost effective was 0.28 if the maximum acceptable amount to pay for an additional QALY was £20,000 and 0.57 if the maximum amount was £30,000 per additional QALY. The manufacturer of carmustine implants also included costeffectiveness estimates for temozolomide plus radiotherapy compared to radiotherapy alone (mean ICER: £53,700 per QALY gained) and for PCV plus radiotherapy compared to radiotherapy alone (mean ICER: £34,200 per QALY gained). The AG considered the model structure to be sound but concluded that the main ICER of £28,000 per QALY gained was biased in favour of carmustine implants due to questionable survival assumptions and the omission of treatment costs other than the costs of carmustine implants.

#### Temozolomide

The manufacturer of temozolomide submitted an economic evaluation based on the largest RCT. Resource-use data were collected for a subgroup of 224 patients from the original trial, including details of number of radiotherapy sessions, temozolomide cycles and dosages, concomitant medications, laboratory tests and hospitalisations due to serious adverse events. The frequency of serious toxicity-related events was also based on the subgroup. Health benefits were expressed in terms of life years gained based on data from the largest RCT. Two analyses were presented: one based on the subgroup for whom resource-use data had been collected, and the other based on extrapolating these data to the full trial cohort. In addition, two methods of estimating survival were employed: one included survival to 2 years post-randomisation only, and the other extrapolated from time of randomisation until death.

Base-case results with extrapolated survival were £11,000 per life year gained from temozolomide for the full trial cohort and per life year gained from temozolomide for the subgroup with resource-use data.

#### **Assessment Group's economic evaluation**

The AG constructed a Markov model with a time horizon of 5 years. The model estimates the costs and QALYs for a cohort of 1000 people with operable grade 3 and 4 gliomas and a mean age of 55 years. Each cycle of the model represents one week. The model was designed to compare each of the treatments individually with no treatment. The model structure remained the same for both of these analyses, but the parameter values were specific to each of the active treatments.

Six health states are represented in the model: surgery; postoperative recovery; radiotherapy; stable disease; progression; and dead. All patients enter the model in the 'surgery' state and are assumed to remain in that state for one week. The model

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allows the possibility of death after any of the health states. Patients surviving surgery are assumed to remain in the post-operative recovery state for a median of 2 weeks in the carmustine implant analysis, and 5 weeks in the temozolomide analysis (based on data from the trials for each treatment). Patients surviving the postoperative recovery period are assumed to undergo a course of radiotherapy at 60-Gy fractions (5 fractions per week) for a maximum of 6 weeks. Rates of discontinuation of radiotherapy for both temozolomide and carmustine implants are taken from the largest trial of temozolomide as the trials of carmustine implants did not report this information.

Following radiotherapy, the model assumes that patients enter the stable disease or progression health states (or die). Disease progression is considered as symptomatic progression rather than pathologically defined progression. Aside from perioperative mortality, the risk of death in the model is time dependent rather than state dependent (that is, a patient's probability of dying at a given point in time depends only on the length of time since surgery and not on whether their disease is stable or progressive). Risk of death was estimated from the largest temozolomide trial for the temozolomide analysis and the largest carmustine implant trial for the carmustine implant analysis (descriptions of how survival estimates were obtained are provided in pages 92–3 of the AR). The survival estimates from the trials include the survival gain from subsequent surgery or chemotherapy and are therefore also included in the model.

In the absence of appropriate published utility data, the AG conducted their own study to elicit utility values. Scenarios describing states of health were developed based on a published study and valued by 93 members of the general population using the standard gamble method (further details provided in pages 95–8 of the AR). In the analysis of carmustine implants, the patients with stable disease who had received treatment and patients with stable disease who had received placebo were assumed to have the same health-related utility (mean: 0.89). In the analysis of temozolomide, patients with stable disease receiving temozolomide were assumed to have a lower utility (mean: 0.85) compared to patients with stable disease not receiving temozolomide (mean: 0.89) to reflect the side effects associated with treatment. Patients in the progressive disease state were assumed to experience constantly deteriorating quality of life (modelled as a reduction of 0.5% per week). The impact of subsequent surgery or chemotherapy on health-related quality of life is not incorporated in the model (the possible impact of these may be positive from the effects of debulking or negative from the effects of surgery and treatment).

Resource use and cost data were taken from the published literature, manufacturer submissions and the AG's expert review group. Drug acquisition costs were based on the standard licensed doses for temozolomide and the number of carmustine implants from the largest trial of carmustine implants (mean: 6.54). Of patients in the progressive disease state, 60% were assumed to receive further chemotherapy with PCV, and a further 10% were assumed to undergo reoperation followed by PCV. Full details of resource use and costs are provided in pages 98 to105 of the AR. Costs were discounted at 6% and benefits at 1.5%. A host of one-way sensitivity analyses were conducted as well as a probabilistic simulation.

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The base-case analysis for the comparison of carmustine implants compared to placebo found that the mean incremental costs of carmustine implants were £6100 and mean QALYs gained were 0.107. The additional cost per QALY gained was £57,000. Of the one-way sensitivity analyses, the analyses that reduced the ICER the most were: varying the difference in time spent in the progression-free state to 12 weeks, doubling the median survival difference, and assuming that only 4 implants are used per patient (thereby reducing the cost of treatment). The probabilistic analysis found that carmustine implants were likely to be a cost-effective treatment option if the maximum acceptable amount to pay for an additional QALY gained is £50,000 or more. A range of threshold analyses that estimate how much a parameter value must change to be cost effective at different thresholds is presented in pages 116–9 of the AR. In addition, a speculative analysis of patients with a better prognosis found that the mean incremental cost per QALY was just under £37,000 (see AR page 121).

The base-case analysis for the comparison of temozolomide plus radiotherapy compared to radiotherapy alone shows that the mean incremental cost of temozolomide plus radiotherapy was £8560 and mean QALYs gained were 0.187. The additional cost per QALY gained was £45,800. Of the one-way sensitivity analyses, those that reduced the ICER the most were: doubling the median survival difference, assigning a utility value of 1 (equivalent to 'full health') to patients in the stable disease state, decreasing the cost of temozolomide by 30%, and using a 2-year time horizon The probabilistic analysis found that temozolomide was likely to be a cost-effective treatment option if the maximum acceptable amount to pay for an additional QALY gained is £50,000 or more. Details of threshold analyses are presented in pages 128–33 of the AR. A speculative analysis of patients with a better prognosis found that the mean incremental cost per QALY was just under £43,000 (see AR page 121).

#### 4 Issues for consideration

The submissions from patient groups highlight the effects, both physical and psychological, of the disease and associated treatment upon patients' quality of life. The submissions also highlight attitudes towards the different methods of administration of the treatments and towards patients' informed involvement in decision-making regarding their treatment.

The AG expressed some concerns regarding the analysis of the largest trial of carmustine implants and noted that some of the trial data had been reanalysed by the FDA. The AG also noted that the largest trial of temozolomide included some patients with grade 3 tumours, although the UK marketing authorisation for temozolomide is for the treatment of newly diagnosed GBM (grade 4). The quality of all the trials has been assessed by the AG (see AR pages 33–40 for carmustine implants and pages 57–62 for temozolomide).

Consideration should be given to the generalisability of trial data (and consequently economic analyses) to the wider patient population. In particular, patients included in the trials were on average younger than patients seen in normal clinical practice.

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The trials and economic analyses did not compare carmustine implants or temozolomide with other active treatment regimens (for example, PCV).

The AG's economic analyses suggest that the cost effectiveness of the treatments is less favourable than that suggested by the manufacturers' economic analyses. The limitations of all the economic analyses should be considered.

- In particular, the AG considered that the incremental costs of temozolomide had been underestimated in the analysis submitted by the manufacturer of temozolomide. The strengths and limitations of this analysis are discussed in pages 83–8 of the AR. The results of the analysis were also expressed in terms of incremental cost per life year gained. Consideration could be given as to how this would translate into an incremental cost per QALY gained.
- The main concerns of the AG relating to the economic analysis submitted by the manufacturer of carmustine implants were that the incremental costs may have been underestimated, that time to neurological decline was used as an indication of time to disease progression, and about the assumptions surrounding the survival estimates. A detailed discussion of the model is provided in pages 81–3 of the AR.
- The AG notes the limitations of their own model (see AR pages 135–6). In particular, they note that there is a large amount of uncertainty around the model and key inputs, and that they have had to rely on evidence from single RCTs. The AG experienced some problems in the elicitation of health-related utility estimates, which will add to the uncertainty surrounding the estimates. The effects of varying many of these assumptions have been explored in extensive sensitivity analyses.

Consideration could be given to whether there are any subgroups of patients for whom the technologies may be particularly cost effective. This must include a consideration of the strength of evidence for, and biological plausibility of, and differential effects. For example, the subgroup analysis of patients with reduced MGMT activity in the largest trial of temozolomide suggested that the survival gain is greater for these patients (see AR page 69). The median survival in this group was 21.7 months and the median survival gain was 6.4 months. However, it is not clear that this was a pre-specified subgroup, nor is it clear how many other subgroups were examined. The threshold analyses and speculative analysis of patients with better prognosis may give a general indication of the possible level of cost effectiveness in this group. However, the current availability, complexity and costs of testing for MGMT should also be considered.

The scope of the appraisal applies to adults and children; however, RCT and economic evidence are only available for adult populations.

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### 5 Author

Louise Longworth

Health Technology Analyst, NICE Appraisal Team

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## 6 Appendix A. Sources of evidence considered in the preparation of the overview

- A Garside R, Pitt M, Anderson R et al. (PenTAG), The effectiveness and costeffectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation, September 2005
- B Submissions from the following organisations:
  - I Manufacturers/sponsors:
    - Link Pharmaceuticals
    - Schering-Plough
  - II Professional/specialist and patient/carer groups:
    - Brain and Spine Foundation
    - CancerBACUP
    - Royal College of Nursing
    - Tenovus

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