Scottish Medicines Consortium

Re-Submission

temozolomide 5, 20, 100 and 250mg capsules (Temodal®)
No. (244/06)

Schering Plough UK Ltd

10 November 2006

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

ADVICE: following a resubmission

temozolomide (Temodal®) is accepted for restricted use within NHS Scotland for the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and subsequently as monotherapy treatment.

In a three-year follow up of the pivotal phase III study, a significant survival benefit was seen over placebo in patients with good performance status and favourable prognostic markers. Temozolamide is restricted to patients who have had a partial or complete macroscopic resection of their tumour and with World Health Organisation (WHO) performance status 0 or 1.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and subsequently as monotherapy treatment.

Dosing information

In combination with focal radiotherapy, the concomitant phase, at a dose of 75mg/m^2 daily for 42 days followed four weeks after completing the concomitant phase by up to six cycles of temozolomide monotherapy at a dose of 150-200mg/m^2 once daily on days 1 to 5 of a 28 day cycle.

Product availability date

10 June 2005

Comparator medications

Surgery with or without radiotherapy; surgery with radiotherapy combined with antineoplastic agents such as a nitrosourea-based regimen eg. procarbazine, lomustine and vincristine (PVC) or carmustine implants; best supportive care plus steroids with or without anticonvulsants.

Cost of relevant comparators

Drug	Dose	Cost per course of treatment*
Temozolomide concomitant plus radiotherapy	**75mg/m^2 daily for 42 days with focal radiotherapy plus 150mg/m^2 daily as monotherapy, days 1 - 5 of a 28 day cycle followed by 200mg/m^2 daily, days 1 - 5 of a 28 day cycle for five cycles or 150mg/m^2 daily, days 1-5 of a 28 day cycle for five cycles if dose escalation not achieved.**	**£9 529- £11 086**
Carmustine implant	Up to 8 implants	up to £5203
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 £2150 for 12 cycles
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 £1433 for 8 cycles

*Costs from BNF Edition 51 and eVadis accessed on 1st August 2006 and based on body surface area of 1.8m^2, where applicable. Doses are shown for general comparison and do not imply therapeutic equivalence.

Summary of evidence on comparative efficacy

The majority of brain tumours are gliomas, developing in the glial cells that support the nerve cells of the brain. Among high-grade gliomas, glioblastoma multiforme (GBM) is the most common and is highly malignant, infiltrating the brain extensively. The World Health Organisation (WHO) grades GBM as a grade IV astrocytoma. Temozolomide is a prodrug which, at physiological pH, rapidly hydrolyses to the active metabolite. It crosses the blood-brain barrier, the concentration in the cerebral spinal fluid being 20-40% of that in plasma. The cytotoxicity of temozolomide is due primarily to methylation of DNA at O^6 guanine positions, leading to cell cycle arrest and apoptosis of tumour cells.

A preliminary open-label, phase ll study in 64 newly diagnosed GBM patients determined the tolerability and efficacy of concomitant temozolomide plus radiotherapy followed by temozolomide monotherapy. Temozolomide was well tolerated and the overall survival in the intention-to-treat population was 16 months (95%CI, 11-21 months).

The pivotal, open-label, randomised, phase lll study was conducted under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC) in 15 countries. A total of 573 patients with histologically confirmed GBM were randomised equally to either radiotherapy alone (a total of 60 Gy over six weeks), or radiotherapy plus concomitant temozolomide (75 mg/m^2 per day for 42 days, from the first day of radiotherapy to the last day but no longer than 49 days), followed after a break of four weeks by temozolomide monotherapy (150 to 200 mg /m^2 on days 1 to 5 of a 28 day cycle, for up to 6 cycles). Over 85% of patients had a WHO performance status of 0 or 1 (on a scale of 0 to 5, where 0 = fully active and 5=dead), and >80% had undergone debulking surgery within 6 weeks of study entry. Salvage chemotherapy (including with temozolomide) was provided upon disease progression for both treatment arms. The primary endpoint was overall survival in the intention-to-treat population, measured from the date of randomisation until death. Secondary endpoints included progression-free survival, safety and quality of life. At database closure, median follow-up was 28 months and 480 (84%) of the 573 patients had died. The unadjusted hazard ratio (HR) for death in patients treated with radiotherapy plus temozolomide compared to radiotherapy alone was 0.63 (95%CI, 0.52–0.75; p<0.001), representing a 37% relative reduction in the risk of death. The median overall survival benefit was 2.5 months; median survival for temozolomide plus radiotherapy was 14.6 months (95%CI, 13.2 -16.8) compared with 12.1 months (95%CI, 11.2-13.0) for radiotherapy alone (p<0.001). The survival benefit for radiotherapy plus temozolomide relative to radiotherapy alone increased steadily over time. At 12 months, 51% (95%CI, 44.7-56.4) of patients in the radiotherapy group had survived compared with 61% (95%CI, 55.4-66.7) of patients in the temozolomide plus radiotherapy group and at 24 months this was 10.4%(95%CI, 6.8-14.1) and 26.5% (95%CI, 21.2-31.7), respectively.

Subgroup analysis found that overall survival in patients with poor performance status (PS≥2) and in patients who had undergone biopsy only was not significantly different between treatment groups. However, subgroup analyses were not prospectively powered to test for statistical significance. Increases in progression-free survival supported the results for overall survival with an HR of 0.54 (95%CI, 0.45-0.64; p <0.001), representing a 46% decreased risk of death or disease progression favouring the radiotherapy plus temozolomide group compared to the radiotherapy alone. Quality of life was assessed using the EORTC quality of life questionnaire core-30 (QLQ-C30) and the EORTC brain cancer module (EORTC BN-20) in 248 radiotherapy and 242 radiotherapy plus temozolomide patients. Changes from baseline in 7 pre-selected domains of fatigue, global health, social functioning, emotional functioning, future uncertainty, insomnia and communication deficit were measured. No significant difference was noted in any domain except for a difference in social functioning in favour of radiotherapy alone (p<0.005) at the first follow up during

radiotherapy at week four. The authors concluded that the addition of temozolomide to radiotherapy had no long-term negative impact on health-related quality of life (HRQOL) and that overall HRQOL did not deteriorate by a clinically significant amount in either treatment group and even improved for some assessments and scales. The European Product Assessment Report concluded that there was a small negative impact on quality of life in patients treated with combined radiotherapy and chemotherapy and a positive influence on quality of life could not be proven.

Summary of evidence on comparative safety

No clinically important new safety concerns were reported in the EORTC study but post-marketing surveillance of patients receiving temozolomide is ongoing. Haematological adverse effects are the dose limiting toxicities for temozolomide; in patients treated with temozolomide, 46 patients (16%) had a documented Grade 3 or 4 haematological event during the study, 21 patients (7%) had a Grade 3 or 4 neutropenia and 33 (12%) patients had a Grade 3 or 4 thrombocytopenia. In six subjects treated with temozolomide, death was attributed by the investigators to, or temporally associated with, serious adverse events considered at least possibly related to temozolomide, and occurring within 30 days of stopping therapy. Concomitant radiotherapy plus temozolomide therapy did not increase late toxicities associated with RT during the 18 months of follow-up; however longer follow-up is required for conclusive data.

Summary of clinical effectiveness issues

The EORTC study showed a significant improvement in median survival for patients treated with combined radiotherapy and temozolomide over radiotherapy alone. This survival benefit increased over time. It was noted in an accompanying editorial that the patient population included in the trial was relatively healthy; most patients were under 70 years of age (median age 57 years), had good performance status and were eligible for debulking surgery - all of which are favourable prognostic factors. The patient population included in the EORTC study may therefore not be typical of the total potential Scottish patient population but may identify those patients who would benefit most from therapy.

A retrospective, post hoc study of 206 patients from the EORTC study whose histology was available for analysis, investigated whether O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation was associated with a survival benefit. Significantly improved survival times were seen in all patients with this methylation, though the numbers were small and the assessment of the methylation status of the MGMT promoter is not widely available outside clinical trials. Other indicators of improved outcome included a WHO performance status of 0, age less than 50 years and patients who had undergone resection rather than biopsy.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing temozolomide and radiotherapy with use of radiotherapy alone in patients with newly diagnosed GBM. Radiotherapy represents an appropriate comparator based on current practice in Scotland.

The evaluation was trial-based using survival and resource data from the 2 year phase III EORTC trial, with data available for secondary analysis from 2.5 and 3 year follow-ups of patients in this trial. All analyses were conducted using a sample of patients in the trial for whom resource use data were collected (n=218 out of 573 in the trial, but with no strong evidence of selection bias). Patients in the radiotherapy-only arm could receive chemotherapy after disease progression, which based on the EORTC trial was predominantly temozolomide. Likely resource use by patients in Scotland after disease progression was obtained from Scottish clinical experts.

At 3 year follow-up the ICER was estimated at £25,840 for patients with a WHO performance status of 0 or 1.

Overall, assessment of the economic evidence submitted by the manufacturer suggests that temozolomide can be considered cost-effective in the sub-group of patients with WHO performance status of 0 or 1.

*Other data were also assessed but remain commercially confidential.**

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimated gross budget impact is £407K to £452K in 2007 depending on whether the actual dose administered in the EORTC clinical trial or the recommended dosing schedule for the NHS is applied. The corresponding figures for 2010 are 563K to £624K. The figures are based on an estimated 42 patients being treated in 2007 with 58 by year 5 as clinician experience of using temozolomide increases.

For the sub-group with WHO performance status of 0 or 1, the expected budget impact in Scotland is £262K-£290K (for 27 patients) in 2007 depending on dose applied rising to £359K to £398K (37 patients) in 2010. These estimates assume that 35% of eligible patients would be treated in 2007 rising to 70% of eligible patients by 2010.

Guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) has produced a Final Appraisal Determination (FAD) in March 2006 for C*armustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma*. This FAD is out for consultation with an expected date of issue for the full technology appraisal of March 2007.

Additional information

Following a full submission the SMC accepted carmustine implants (Gliadel®) for use within NHS Scotland for the treatment of newly diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation in November 2005. 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.

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 26 October 2006.

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

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

The undernoted references were supplied with the submission.

Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997-1003.

Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10):987-96.

Stupp R, Dietrich PY, Ostermann Kraljevic S, Pica A, Maillard I, Maeder P, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol 2002;20(5):1375-82.

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