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23 December, 2005

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Dear Louise,

**RE: PENINISULA TECHNOLOGY ASSESSMENT GROUP (PENTAG) ASSESSMENT REPORT ON THE EFFECTIVENESS AND COST-EFFECTIVENESS OF CARMUSTINE IMPLANTS AND TEMOZOLOMIDE FOR THE TREATMENT OF NEWLY DIAGNOSED HIGH GRADE GLIOMA.**

Schering Plough welcomes the opportunity to comment on this report and its technical content. We have included draft comments on specific areas of the PenTAG assessment report, which constitute indications of what we will submit in our comprehensive comments on November 11th. We have outlined these in the remainder of this letter; firstly with regard to comments on the clinical sections of the report, secondly with regard to the critique of our health economic evaluation and lastly, our own comments on the PenTAG economic model.

***Clinical sections of the Assessment Report:***

1. **Confirmation of GBM status:** (section 4.8.1.1, page 60) Tumour classification is highly subjective. The large RCT conducted by EORTC and NCIC admitted only patients (n = 573) with histologically confirmed glioblastoma (WHO grade IV) [utilizing local neuro-pathologists, thus reflecting daily clinical practice]

2. **MGMT promoter methylation:** The assessment report takes this data of an unplanned retrospective analysis of a subset of patients at face value, rather than considering it as a hypothesis worthy of prospective validation. We recognise the potential importance of this gene expression in the context of optimizing treatment outcomes and are therefore supporting a large RCT to validate these findings.

3. **Clinical trial population:** The assessment team comments that the clinical trial population for temozolomide is different to the real-world patient population, and therefore questions the generalisability of the findings (section 4.8.1.2, page 62). The approval for TMZ usage in first line GBM has been granted for a population reflecting the population studied in the pivotal trial conducted by the EORTC / NCIC.

4. **Study Blinding and subsequent therapy (performance and/or detection bias):** The assessment team remarks that due to the fact that the EORTC / NCIC trial was not conducted as a double-blinded trial, the assessment of response and progression-free survival might be biased. Conversely, the pivotal study with the BCNU-W was conducted in a double-blinded fashion, and with clearly defined criteria for progression. No difference in progression-free survival could be detected.

***Critique of the Schering Plough economic evaluation:***

1. **Costs with disease progression:** The evaluation of the clinical trial data for TMZ shows that the incremental costs between the TMZ + RT and RT-only arms was reduced partly because the latter group received more chemotherapy after progression, and of these, many more received TMZ. The consideration of this treatment pathway in patients with disease progression, with regards to the costs and survival effects of this salvage TMZ treatment in the RT-only arm cannot be ignored.

2. **Lack of estimation of QALYs:** QALYs were not calculated in the original submission in part due to evidence from [redacted].

3. **Survival extrapolation:** For overall survival, the extrapolation distribution was not fitted to the 2-year survival data, but rather to the entire survival curve, thus including patients at risk after 2 years.

***Comments on the PenTAG economic evaluation:***

A number of errors were identified in the limited time given to review the PenTAG cost-utility model. In light of the structure and difficulty we have found in auditing the model, we have to question the reliability of this tool in evaluating the cost-effectiveness of temozolomide. We would appreciate further review by the NICE appraisal team to assess the internal and external validity of this model.

Our main concerns regarding the model are as follows:

1. **Health State Valuation:** We would like to challenge the utility values assigned to 'SMG+RT+TMZ' of 0.8091 and 'SMG+TMZ' of 0.8474. An analysis of HRQoL conducted by Taphoorn et al[1] has demonstrated that TMZ does not statistically significantly impair quality of life compared to RT alone.

2. **Time-dependent Risk of Death:** PenTAG assumes that transitions to death are time-dependent as opposed to state-dependent. The group has acknowledged that this assumption

is counterintuitive, as during a given cycle, patients with disease progression would be expected to have a higher probability of dying than those with stable disease.

3. **Weibull Distribution Transition Probabilities:** Time dependent transitions probabilities have been estimated using the Weibull distribution and survival data presented by Stupp et al[2]. Whilst the predicted overall survival for RT-only shows a good fit with the observed data, this is not the case for the RT+TMZ treatment arm.

4. **Patients most likely to benefit from treatment:** PenTAG have only considered the cost-effectiveness of TMZ in the overall study population. The NICE scope outlined a remit which included exploring the cost-effectiveness of treatment in those patients most likely to benefit. We would recommend further analyses are conducted (e.g. extent of surgery[3], performance status, MGMT gene silencing[4]).

5. **Comment on BMJ/Rawlins paper:** The PenTAG assessment group concludes that treatment with TMZ yields an ICER of £46,000/QALY. GBM is an end-stage cancer. Given the precedent of NICE accepting ICERs > £30,000/QALY for other treatments of end-stage cancers, £46,000/QALY may be an acceptable ICER in the consideration of TMZ (Rawlins and Culyer, 2004[5]).

Once again, we are grateful for the opportunity to comment on the PenTAG assessment report, and we look forward to continued dialogue with NICE regarding the issues raised in this letter.

Sincerely,

Alan Kane

Director, Communications & Public Affairs

**References:**


1. Taphoorn MJB et al. Health-related quality of life in a randomised controlled trial in glioblastoma patients: a joint European Organisation for research and treatment of Cancer (EORTC) Brain Tumour Group/ Radiotherapy Group and National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) study (commercial in confidence). *Lancet*, 2005; Submitted.

2. Stupp R et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*, 2005; 352(10): 987-96.

3. van den Bent and et al., Impact of extent of resection on overall survival in newly-diagnosed glioblastoma. *Poster presented at ECCO - the European Cancer Conference, Palais de Congres, Paris, France, 30 October - 3 November 2005*, 2005.

4. Hegi ME et al MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*, 2005; 352(10): 997-1003.

5. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. British Med J. 2004; 329(7459):224-7.

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Schering-Plough welcomes the opportunity to comment on this report and its technical content. We have included comprehensive comments on specific areas of the PenTAG assessment report, following our preliminary comments, sent on the 7th of November.

In summary we have a number of crucial points of concern with respect to the PenTAG assessment report:

1. In the limited time available to review the economic model a number of important errors and flaws were identified. In light of the structure and the difficulty we have experienced in auditing the economic model, we have serious concerns regarding the reliability of this tool in evaluating the cost-effectiveness of temozolomide.

2. The assessment team conveys a poor understanding of the GBM classification process both in clinical practice and in the clinical trial setting, and misinterprets this issue with respect to the evidence of clinical effect for temozolomide.

3. The PenTAG report places undue weight on a retrospective analysis of MGMT methylation status. We are concerned that the assessment team has not sufficiently emphasized the need for caution with respect to drawing inferences from unplanned analyses of this kind.

More detailed responses are presented in the remainder of this letter; firstly with regard to comments on the clinical sections of the report, secondly with regard to the critique of our health economic evaluation and lastly, our own comments on the PenTAG economic model.

***CLINICAL SECTIONS OF THE ASSESSMENT REPORT:***

***PenTAG Critique:***

*The assessment report suggests on a number of occasions that the significant advantage in progression-free and overall survival observed with temozolomide (TMZ) might be driven by a small number of grade III tumours. The report also comments that a subgroup analysis of confirmed GBM patients would have been useful. (section 4.8.1.1, page 60)*

**Schering-Plough response:**

**GBM status was confirmed.**

The large RCT conducted by EORTC and NCIC admitted only patients (n = 573) with histologically confirmed glioblastoma (WHO grade IV) on the basis of classification by local neuro-pathologists (thus reflecting clinical practice).

As one of the quality control measures of the RCT, histopathology was later centrally reviewed by one (Canada) or three (Europe) neuro-pathologists. Overall, 86% and 83% of the slides were available for pathological review for the RT and RT+TMZ treatment respectively and 229 (93%) and 221 (92%) samples were assessed by these reviewers as GBM.

There is no rationale to suggest that the number of grade III tumours present among those not reviewed centrally would differ from the small number classified by central review (7%).

**Results were not driven by the small proportion of grade III tumors**

A sensitivity analysis was conducted to determine survival in a subgroup of protocol evaluable subjects. This subgroup comprised those patients for whom GBM histology was assessed centrally and excluded those that received no treatment or had no baseline haematology counts. In this subgroup of 221 and 215 patients for the RT and RT+TMZ treatment, respectively, the median survival was 12.2 months and 14.5 months, with a HR of 1.58 (95% CI 1.28- 1.94).

With respect to the smaller RCT cited, eligibility required histologically confirmed GBM, based on WHO classification.[i] Twenty ineligible patients (5 not treated, 6 ineligible histology, 9 treated by hyperfractionated RT) were not analysed in this published analysis. Thus, the significant improvement in progression-free and overall survival for the RT+TMZ treatment was achieved in GBM patients only.

**Tumour classification within the study was reflective of normal clinical practice.**

Tumour classification is highly subjective. The fact that a central reviewer reclassifies a tumour does not necessarily mean that this is a 'true' or 'absolute' classification, simply that there is a disagreement with the local pathologist. It merely gives a measure of that pathologist's opinion. It may or may not be more valid than the local pathologist's. The study was conducted utilizing local neuro-pathologists, thus reflecting daily clinical practice. In real life, patients will be offered TMZ on the basis of the local pathologist's diagnosis; hence, analysis of this trial in these terms gives a more realistic interpretation of the outcome of such treatment and the comparison between treatments.

***PenTAG Critique:***

*The assessment report places a great deal of emphasis on the results of the unplanned, retrospective, subgroup analysis on MGMT promoter methylation. (section 4.8.2.4, page 69)*

**Schering-Plough response:**

**As with all retrospective analyses, results must be interpreted with caution and should only be used for the purpose of generating hypotheses for future clinical trials.**

The intent-to-treat population in the EORTC / NCIC trial is 573 patients. Tumour tissue was only available for 307 / 573 patients (54%) and those tissues came from 66 / 85 investigational study sites.

MGMT methylation status could only be determined for 206 tumours or 36% of the study population. Only 67% of submitted samples gave interpretable results. Certain centers and even entire countries submitted samples that were unable to be assessed due to fixation techniques.

The assay being used has not been prospectively validated for clinical use.

This subset was not randomly selected and clearly cannot reflect the patient population appropriately. In particular, patients receiving a biopsy only were underrepresented in the analysis. An assignment of p-values to this uncontrolled subset is therefore not appropriate.

We recognise the potential importance of this gene expression in the context of optimizing treatment outcomes and are therefore supporting a large RCT to validate these findings. Such a trial (RTOG 0525) is about to start accrual through an international consortium of Cooperative Groups i.e. EORTC, NCIC and the US RTOG.

**PenTAG Critique:**

*The assessment team questions the applicability of the pivotal study results to the general clinical population, noting that the Stupp RCT excluded patients over 70. (section 4.8.1.2, page 62).*

**Schering-Plough Response:**

**Results should not be extrapolated to patients whose characteristics are not in accordance with the inclusion/exclusion criteria.**

The approval for TMZ usage in first line GBM has been granted for a population which includes the population studied in the pivotal trial conducted by the EORTC / NCIC. Schering-Plough would not advocate and there is no suggestion being made that the results of RT+TMZ and/or adjuvant TMZ should be applied to patients whose characteristics lie greatly outside the recruitment characteristics of the pivotal trial.

**PenTAG Critique:**

*The assessment team remarks that due to the fact that the EORTC / NCIC trial was not conducted as a double-blinded trial, the assessment of response and progression-free survival might be biased. They also state that the absence of blinding might impact on the choice of post-recurrence therapy. (section 4.8.1.1, pages 60-61)*

**Schering-Plough Response:**

**Study Outcome was not affected by lack of double-blind design**

As further chemotherapy was given at relapse in the non-experimental arm (RT-only) of the EORTC / NCIC trial, this would be expected to lessen any observed difference in outcome between the groups and therefore lends more credibility to the study rather than less.

Conversely, the pivotal study with the BCNU-W was conducted in a double-blinded fashion, and with clearly defined criteria for progression, but no difference in progression-free survival could be detected. The assessment report therefore states:"…any claimed treatment effect must be due to differences in survival after disease progression."

Response to salvage therapy was not collected in either study. Furthermore, details of the salvage therapy utilized were not collected in the BCNU-W study. Any conclusions drawn by external reviewers are beyond the scope of the trial and cannot be confirmed.

**PenTAG Critique:**

*The assessment report remarks that there is limited evidence of a small clinical benefit for TMZ (section 1.7.1, page 6)*

**Schering-Plough Response:**

**Evidence of a survival benefit at two years in this treatment population is highly clinically significant**

It should be emphasized that demonstrating a two-year survival benefit is highly difficult to achieve in the oncology setting and treatment interventions in other cancers assessed recently by NICE have been less successful with respect to this outcome (e.g. gemcitabine, pancreatic cancer)[ii]

**PenTAG Critique:**

*The assessment report refers to the lack of evidence-based treatment guidelines currently available in the literature, and the absence of a 'standard treatment' or optimal management approach in this patient population (section 3.2.1 page 15).*

**Schering-Plough Response:**

**Evidence-based guidelines for the management of glioblastoma exist for several countries and include the use of TMZ/RT as first-line management.**

Whilst we concur that this is the case in the UK, we would draw attention to more established approaches to the management of this disease elsewhere in Europe, particularly in light of the National Cancer Plan objectives to drive UK standards closer to other European countries.[iii]

The National Comprehensive Cancer Network comprised of 19 major cancer centers across the United States, established guidelines for the management of tumors, including glioblastoma multiforme, with the network and allied hospitals.[iv]

Within Europe, Italy has also published guidelines on the management of malignant glioma.[v]

**PenTAG Critique:**

The assessment report makes reference to the current delays in access to radiotherapy in the England and Wales (section 1.6.2, page 6)

**Schering-Plough Response:**

We recognise that this represents a crucial issue for the NHS and would welcome further initiatives to improve patient access to the treatments they require.

As wait time for radiotherapy has been shown to be a negative influence on overall survival, further improvement in this area will have substantial impact.[vi]

***CRITIQUE OF THE SCHERING PLOUGH ECONOMIC EVALUATION:***

**PenTAG Critique:**

The assessment report comments that the observed incremental costs of RT with TMZ patients are almost certainly under-estimated, and that the analysis lacked control or adjustment for post-progression differences in treatment. (section 5.3.5.4, page 85-86)

**Schering-Plough Response:**

The evaluation of the clinical trial data for TMZ shows that the incremental costs between the TMZ+RT and RT-only arms was reduced partly because the latter group received more chemotherapy after progression, and of these, many more received TMZ. In the economic analysis, it was intended that the Lin and Carides methods for censored cost analysis be used in order to calculate the differences in the cumulative costs per trial arm. However, the follow-up for those alive at two years since randomization differed significantly between the two treatment arms. Therefore, the intended methods were not applied.

However, it should be noted that salvage TMZ therapy also confers an additional overall survival and progression-free survival benefit in the RT-only group due to this administration. Since TMZ was already recommended by NICE in 2001 for patients with recurrent GBM, the consideration of this treatment pathway in patients with disease progression, with regards to the costs and survival effects of this salvage TMZ treatment in the RT only arm cannot be ignored.

**PenTAG Critique:**

The assessment report is critical of the fact that the evaluation submitted by Schering-Plough does not include a cost-utility analysis. (section 5.3.5.3, page 84)

**Schering-Plough Response:**

QALYs were not calculated in our original submission in part due to evidence from [redacted]

In addition, quality of life was assessed in the trial using the EORTC QLQ C30, for which no preferences weights or utilities were available. This data could not be used to calculate QALYs.

**PenTAG Critique:**

The assessment report makes a number of criticisms with respect to the extrapolation of survival by means of fitted distributions in the evaluation submitted by Schering-Plough. (section 5.3.5.3, page 84)

**Schering-Plough Response:**

For overall survival, the extrapolation distribution was not fitted to the 2-year survival data, but rather to the entire survival curve, including patients at risk beyond 2 years. An extrapolation of the survival per treatment arm was made by estimation of a Weibull distribution from the observed survival.

The mean restricted two year observed survival (Irwin's restricted mean) [vii] and the extrapolated mean survival were reported in Table 12 of the original Schering-Plough submission.

***COMMENTS ON THE PENTAG ECONOMIC EVALUATION:***

A number of errors were identified in the limited time given to review the PenTAG cost-utility model. In light of the structure and difficulty we have found in auditing the model, we have to question the reliability of this tool in evaluating the cost-effectiveness of temozolomide. We would appreciate further review by the NICE appraisal team to assess the internal and external validity of this model.

Our main concerns regarding the model are as follows:

6. **Health State Valuation:** We would like to challenge the utility values assigned to 'SMG+RT+TMZ' of 0.8091 and 'SMG+TMZ' of 0.8474. These utilities are the result of a

questionable weighting calculation, based on a proportion of patients experiencing Grade 3/4 AEs during concomitant and adjuvant TMZ.

The methodology employed by the researchers is far from transparent, but represents a bias in the model against TMZ. An analysis of health related quality of life conducted by Taphoorn et al. has demonstrated that TMZ does not significantly impair HRQoL compared to RT alone.[Error! Bookmark not defined.] We argue that utility values of 0.8239 and 0.8872 should be assigned to these health states, respectively.

7. **Time-dependent Risk of Death:** PenTAG assumes that transitions to death are time-dependent as opposed to state-dependent. The group has acknowledged that this assumption is counterintuitive, since during a given cycle patients with disease progression would be expected to have a higher probability of dying than those with stable disease. The justification for adopting this approach is weak and we are not convinced by their conclusion that the only respect in which this assumption might affect the results is in relation to any costs that are attached the particular transitions to death. We would ask that NICE seek validation of this approach from clinicians with experience in treating GBM.
8. **Weibull Distribution Transition Probabilities:** Time dependent transition probabilities have been estimated using the Weibull distribution and survival data presented by Stupp et al.[viii] Whilst the predicted overall survival for RT-only shows a good fit with the observed data, this is not the case for the RT+TMZ treatment arm. For overall survival, the fitted curve departs from the observed data at 18 months, whilst for progression free survival, this occurs at 12 months. This sub-optimal fitting is likely to result in an underestimate of the survival benefit associated with TMZ, and hence increase the ICER. Time limitations and the design of the model have prevented a thorough testing of the effect of this discrepancy.
9. **Patients most likely to benefit from treatment:** One-way sensitivity analysis has shown that the results generated by the model are most sensitive to differences in survival between the two treatment arms. PenTAG have only considered the cost-effectiveness of TMZ in the overall study population. The NICE scope outlined a remit which included exploring the cost-effectiveness of treatment in those patients most likely to benefit. We would ask that further analyses are conducted (e.g. extent of surgery,[ix] performance status, MGMT gene silencing[x]) but do not imagine that this would require significant additional work.
10. **Costs of taking temozolomide with radiotherapy:** The Summary of Product Characteristics recommends that TMZ should be administered at a dose of 75 mg/m$^2$/day for 42 days, during the concomitant phase of treatment.[xi] The model, however, determines the cost of this phase of treatment based on 49 days treatment. This is incorrect and needs to be addressed.
11. **Costs with disease progression:** In the base case analysis, 70% of patients whose disease progresses are assumed to receive chemotherapy consisting of PCV[1] (procarbazine, lomustine and vincristine). While this assumption is reasonable for those that have been treated with concomitant and adjuvant TMZ, this is not the case for those treated with radiotherapy alone. In clinical practice, a significant proportion of these patients would be treated with TMZ on disease recurrence. As stated in section 4.1, page 44 of the Schering-Plough submission to NICE projections made from IMS sample data suggest that TMZ is used in 80% of all second-line treatments and ≥50% of first-line treatments. The model should be adapted accordingly.

[1] The cost per week of PCV (£68.31) used in the model is incorrect. Each cycle is given on a 6 weekly basis. The cost per cycle (£136.61) should therefore have been divided by 6 rather than 2.

Once again, we are grateful for the opportunity to comment on the PenTAG assessment report, and we look forward to continued dialogue with NICE regarding the issues raised in this letter.

Sincerely,

Alan Kane
Director, Communications & Public Affairs

References

[i] Athanassiou H, Synodinou M, Maragoudakis E, Paraskevaidis M, Verigos C, Missailidou D, et al. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol* 2005; 23(10):2372-2377.
[ii] Technology appraisal No. 25. Guidance on the use of gemcitabine for the treatment of pancreatic cancer. National Institute for Clinical Excellence. May 2001.
[iii] http://www.dh.gov.uk/
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[vii] Karrison TG. Use of Irwin's restricted Mean as an Index for Comparing Survival in Different Treatment Groups -Interpretation and Power Considerations. *Controlled Clinical Trials* 1997; 18: 151-167.
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[x] Hegi ME et al MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*, 2005; 352(10): 997-1003.
[xi] Schering-Plough, Temodal Capsules Summary of Product Characteristics.