5th March 2009

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Dear Dr Browning,

Cervical cancer - topotecan

The Evidence Review Group, Centre for Review and Dissemination/Centre for Health Economics York, and the technical team at NICE have now had an opportunity to take a look at submission by GlaxoSmithKline. In general terms they felt that it is well presented and clear. However the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both The Centre for Review and Dissemination/Centre for Health Economics York and the technical team at NICE will be addressing these points in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to address the points listed below and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **17:00, Thursday 19 March 2009 (London, UK time)**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence

information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Andres Roman – Technical Analyst (andres.roman@nice.org.uk). Procedural questions should be addressed to Bijal Chandarana – Project Manager (bijal.chandarana@nice.org.uk) in the first instance.

Yours sincerely

pp Dr Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Section A. Clarification on Clinical effectiveness.

Literature search

A1. Please provide the full search strategies for each of the individual databases searched for both cost-effectiveness and clinical effectiveness. The information currently supplied as a general search strategy (pages 171-172) has a considerable number of limitations and omissions including:

- The exact syntax, terms and keywords entered into each individual database;
- How the general search strategy was translated for each individual database;
- The number of records identified for each database and the final result set number used;
- The way in which separate results were combined;
- Accurate numbering of search sets in reported search strategy results.

An example of a search strategy is given at the back of this document.

A2. Please clarify whether Medline In-Process Citations was searched, if it was not searched please provide a reason for not doing so.

A3. Please provide the full HEED search strategy for the cost-utility search described in Appendix 5.

A4. Please provide the URL for the page from which you searched and the search terms used for the following resources:

- American Society of Clinical Oncology (ASCO) website (http://www.asco.org) annual meeting abstracts
- European Society of Medical Oncology (ESMO) website (http://www.esmo.org) annual meeting abstracts
- Canadian Medical Association Infobase website

Study Selection

A5. Please provide a clear and transparent rationale for the study selection in the systematic review. This should include a comprehensive list of trials considered at the data extraction stage (with study details e.g. design (phase II/III), population, comparators, data reported on OS and/or PFS) and where relevant the reason for exclusion. The following three points provide specific examples of where further information is required:

- Please list the specific inclusion and exclusion criteria used to select comparator studies and clarify why data from studies stopped early were not included (eg. Cadron et al, 2005: Report of an Early Stopped Randomized Trial Comparing Cisplatin vs. Cisplatin/Ifosfamide/ 5-Fluorouracil in Recurrent Cervical Cancer).
- Please explain the reasons for not including some of the single-agent cisplatin studies included in The Cancer Care Ontario systematic review (eg. Omura, 1997 and Cadron, 2005) (page 34).
- Please explain the inclusion of trial GSK-CRT-234 (page 35) and reasons for not including other phase II safety and efficacy studies of topotecan, particularly trials that may have included stage IVB patients, which were not included in GSK-CRT-234.

Direct Comparison

A6. Please provide additional QoL data. Specifically :
- The descriptive statistics for the data presented in Figure 11 e.g. mean (sd), number of patients at each time point
- Data for each of the FACT-G subscales - e.g. mean (sd), number of patients at each time point.
- Data for the UNISCALE results.

Please also clarify whether there is any QoL data available after the 9-month post randomisation period.

A7. Please clarify whether any patients were crossed over to other treatments (e.g. after treatment for haematological toxicities, were patients continued with the same treatment or were they started on a different treatment). Please provide details of any subsequent therapies received by patients in each treatment arm. This relates both to cross-over but also non-study drugs as well.

A8. Please provide tabulated data on censored patients and reasons for censoring (page 43 of MS). Please also provide details on reasons for withdrawal and data on patients followed up 2-5 years following study completion (page 44 of MS). Please present this data in the CONSORT flow chart (page 41 of MS).

A9. Please provide results from the interim analysis performed after 56 deaths were observed in the cisplatin arm. Please also clarify what the 'multiplicity issues' were that are referred to on page 44 of the MS and the reason for adjustment of significance level for the final analysis from 0.05 to 0.044.

A10. Please provide the survival data reported in Tables 4 and 5 to 2 decimal places. Please provide similar tables for progression free survival.

A11. Please provide hazard ratios and 95% confidence intervals for figure 12 on page 53 of the MS that details the subgroup analyses.

A12. Please clarify whether the following sentence on page 80 is taken from reference 34 or is the opinion of GSK: "The risks associated with these toxicities are considered to be lower than the risks associated with this lethal disease, and therefore justify the decision to offer this treatment option to patients".

A13. Please clarify whether the reference cited on page 19 is correct: "Topotecan has been used in a large number of patients over the last few years and pharmacovigilance assessments evaluating the post-marketing exposure to topotecan have reported that the benefit/risk profile of topotecan continues to be faviourable[14]". (Reference 14 is a report of GOG-169 comparing cisplatin with or without paclitaxel)

A14. Please confirm whether the reference in section 5.1 of the SmPC to a 180 day cisplatin free interval reflects a specific restriction in the marketing authorisation, and therefore that the use of topotecan for the treatment of women with less than 180 day cisplatin free interval would be regarded as outside of the marketing authorisation. Please provide the evidence that informed the specification of a 180 day cut point.

Indirect Comparison

A15. Please provide a tabulation of the patient characteristics for patients compared in GOG-0179 and GOG-0169 (including data on median time from diagnosis to study entry, prior radiotherapy, prior chemoradiation, and site of disease for GOG-0179, and details on cell type for patients included in GOG-0169, if available).

A16. Please provide further justification for not including study GOG-0204 in the indirect comparison. Monk et al (ASCO Annual '08 Meeting) reports response rates, adverse events, overall survival and progression free survival.

A17. Page 33 of the MS reports an HR of 1.268 for overall survival for topotecan + cisplatin versus paclitaxel + cisplatin, however 1.268 appears to be the HR for the progression free survival. Please re-run the analysis using an HR of 1.255.

Section B. Clarification on Cost Effectiveness

General Issues

B1. Please provide additional justification for employing a patient-level approach to the primary cost-effectiveness analysis as opposed to using a decision-analytic approach.

B2. Please clarify the rationale for restricting the time horizon of the indirect comparison with paclitaxel to 24-months instead of using 36-months which reflects the duration of the topotecan clinical trial. Please discuss the implications of using a shorter time horizon, with reference to the comparisons using data from both the GOG-0169 and GOG-204 studies.

B3. Please provide further justification for not quality-adjusting the overall survival estimates employed in the indirect comparison based on the aggregate data (page 93 of MS). Please discuss whether it is possible to use the aggregate data available for both PFS and OS (as well as for side-effects) to provide these quality-adjustments. Please also discuss the implications of using the data in this way.

B4. It is stated in the submission that PFS is not reported in GOG-0169 (page 96 of MS). Please clarify why the PFS data reported in Figure 1 of Moore et al (2004) is not suitable for the purposes of informing the indirect comparison.

Excel Model and Requested Re-Analyses

B5. Please provide an Excel file with the calculations used to estimate the ICERs based on the indirect comparison using results from GOG-204.

B6. Please clarify the difference between the HR (crude) and the HR (Cox) estimates reported in Cells B50 and B51 (Sheet GOG169-GOG179). Please report the source for the HR(Cox) estimate.

B7. Please supply an Excel file with equivalent OS data to that presented in range F21:J45 (Sheet GOG169-GOG179) for the full 36-months for both cisplatin and topotecan + cisplatin arms – for both the whole licensed population and the cisplatin naïve population.

B8. Please supply an Excel file with PFS data for the full 36-months for both cisplatin and topotecan + cisplatin arms – for both the whole licensed population and the cisplatin naïve population.

B9. Please undertake an additional sensitivity analysis based on applying the hazard ratio approach for paclitaxel + cisplatin to the 36-month cisplatin OS data.

B10. Please supply an Excel file with equivalent estimates for PFS derived from Figure 1 in Moore 2004 (i.e. using the same approach employed to populate OS reported in range B3:C14 - Sheet GOG169-GOG179)

B11. Please consider undertaking an additional indirect cost-effectiveness analysis utilising both the progression free and overall survival data.

For this, please apply separate utility weights to the progression-free and progressive disease periods. Also, please incorporate additional utility decrements for the major side effects and present the assumptions employed regarding the duration of these decrements. Present results separately for the comparisons with paclitaxel based on GOG-169 and GOG-204 employing both 24 and 36 month time-horizons.

B12. Please provide results using the literature-based cancer utility estimates and alternative wastage assumptions simultaneously (p136-140. Table 41-45 of the MS).

Specific Issues

B13. The All-Wales Medicines Strategy group reported that, in Wales, cisplatin was used in only 7.5% of patients, and paclitaxel / cisplatin not at all. Table 18 (p90 of MS) shows cisplatin monotherapy is the most common option, used in 39% of cases, based on IMS Oncology analysis. Please clarify whether the numbers reported are based on UK data only or include data from the 5 key European markets. If the data is not UK specific, please report the % of patients from the UK. In addition, please provide data for the period Q3 2006 to Q3 2008.

B14. Please provide the time horizons employed for all subgroups considered in the direct comparison with cisplatin (p91 of the MS).

B15. Please clarify whether the calculation of OS provides an estimate of mean OS or an estimate of the restricted mean OS (93 of MS). Please discuss the implications of using the approach employed with respect to the indirect comparisons based on both GOG-169 and GOG-204.

B16. Please clarify whether the % side-effect data used for paclitaxel + cisplatin have been taken directly from study GOG-0169 or whether these have been adjusted (p94 of MS).

B17. Please provide an estimate of the mean dose intensity index for the topotecan + cisplatin and cisplatin arms taking into account dose reduction due to AE (e.g. 83% of planned dose). Provide separate estimates for the licensed population and the cisplatin naïve population.

B18. Please clarify which clinical events resource utilisation was contingent on (p98 of MS). Please provide the resource utilisation assumptions employed.

B19. The Lin method (p98 of MS) is normally appropriate for administrative censoring ie patients entering the trial at different dates, where data are

missing completely at random (MCAR). Censoring due to loss to follow up is more problematic because data are likely to be missing at random (e.g. loss to follow up influenced by previous health) or missing not at random (e.g. loss to follow up influenced by current health). Please provide a table comparing the baseline characteristics of patients who were completely followed up or died with those who were incompletely followed up (i.e. censored during the study).

B20. Page 98 of the MS states 'the model extrapolates beyond the last observed deaths in each treat arm.' Please discuss the implications of this for the analysis, and whether this assumption is required to implement the Lin method.

B21. The submission identifies that the trial report for GOG169 only reports median, not mean survival (p99 of MS), and does not show the hazard ratio for the overall difference in rates between groups. The Parmar method for estimating the hazard ratios from a KM graph used in the submission makes assumptions about the number of patients who were censored based on minimum and maximum follow up time in each group. The spreadsheet GOG169-overall survival, column D seems to show that the submission assumed that no patients are censored (that is, column D is zero for all time periods). It is not clear how this assumption would affect the results (ie the estimated hazard ratio). Please confirm or explain further how the number at risk was calculated in this analysis.

B22. Please provide the coefficients used for this mapping of FACT-G to utility (p103 of MS), and the mean and SD values of the FACT-G variables applied to these coefficients in each treatment group.

B23. Missing (utility) data were imputed in some cases as the last observation carried forward (LOCF) (p103 of MS). As HRQL is likely to be declining in many of these patients, this assumption might over-estimate the benefit of treatment. Please provide additional rationale for using LOCF as a method of imputation.

B24. Table 20 (p104) reports higher utilities in the topotecan + cisplatin group prior to cycle 5 and 9 months after randomisation. Please provide additional discussion on these results, given the overall conclusions reported on page 52 for FACT-G and toxicity data (i.e. "no statistical evidence suggesting that reported QoL and adverse effect scores changed over time across regimens"). Please confirm whether the same imputation approach was employed for the data presented in Figure 11 and Table 20. Also please confirm whether an adjustment for baseline scores was undertaken for the utility estimates.

B25. The submission describes two ways in which missing HRQL data were handled. In some circumstances, missing data were imputed using LOCF. In other cases, an adaptation of Lin method was used for estimating QALYs where data are censored. Please clarify in what

circumstances was LOCF used to impute missing data, and when was the Lin method used to adjust?

B26. Please present comparable utility estimates to those in table 20 (p104 of MS) using alternative imputation approaches (e.g. mean, best case, worse case).

B27. Table 25 (p111 of MS) indicates that the unit cost of 25ml paclitaxel (generic) is higher (£532.95 versus £521.73) than the unit cost of 25 ml paclitaxel (Taxol®). The BNF indicates that 25ml paclitaxel (generic) costs £500.86. Please confirm whether this is an error in the submission and if it effects the calculation of paclitaxel drug costs.

B28. The analysis assumes GCSF following neurotoxicity is included in the NHS HRG cost (p115 of MS). Please provide the usage rate of GCSF (on average, and in those with toxicity) in the trial. Please estimate the cost of GCSF. Please conduct a sensitivity analysis assuming the cost of GCSF is not included in the HRG reference cost.

B29. The submission presents few descriptive statistics for the quantity of resource use in each arm (in natural units eg days in hospital) (p120 of MS). Please provide the mean, SD, median and IQR for the key resource use items in both groups at each follow up. Please also indicate the extent of missing data (that is, item non response or loss to follow up).

B30. The submission shows the overall costs per patient (p125 table 34) but does not show the costs of components such as chemotherapy costs, follow up costs etc. Please provide a breakdown of costs in the trial similar to Table 35.

B31. Please clarify the calculation of costs in the model. For example, the costs of follow up are shown as £604 after T+C, but the spreadsheet accompanying the submission does not explain clearly how this figure has been calculated (see sheet 'cost assumptions', cell R9). Please provide additional clarification on how costs were calculated in the model.

B32. In table 46 (page 141), please clarify whether the last row should read "paclitaxel + cisplatin".

An example of the type of full search strategies required can be found below:

MEDLINE (1966 to 2006/11/wk 3) (OVID) Searched 29 November 2006. 2346 records were retrieved. 1. exp sleep apnea syndromes/ 2. (apnea or apnoea).ti,ab. 3. (hypopnea or hypopnoea).ti,ab. 4. (hypoapnea or hypoapnoea).ti,ab. 5. sleep disordered breathing.ti,ab. 6. (sleep adj2 respirat$ disorder$).ti,ab. 7. sahs.ti,ab. 8. shs.ti,ab. 9. osa.ti,ab. 10. osas.ti,ab. 11. osahs.ti,ab. 12. or/1–11 13. exp positive-pressure respiration/ 14. (positive adj3 airway adj3 pressure).ti,ab. 15. (cpap or ncpap or apap or bipap).ti,ab. 16. (c pap or bi pap or nc pap).ti,ab. 17. autocpap.ti,ab. 18. or/13–16 19. 12 and 18	**EMBASE (1980 to 2006/wk 47) (OVID)** Searched 29 November 2006. 2744 records were retrieved. 1. Sleep Apnea Syndrome/ 2. (apnea or apnoea).ti,ab. 3. (hypopnoea or hypopnea).ti,ab. 4. (hypoapnea or hypoapnoea).ti,ab. 5. Sleep Disordered Breathing/ 6. sleep disordered breathing.ti,ab. 7. (sleep adj2 respirat$ disorder$).ti,ab. 8. sahs.ti,ab. 9. shs.ti,ab. 10. osa.ti,ab. 11. osas.ti,ab. 12. osahs.ti,ab. 13. or/1–12 14. positive end expiratory pressure/ 15. (positive adj3 airway adj3 pressure).ti,ab. 16. (cpap or ncpap or apap or bipap).ti,ab. 17. (c pap or bi pap or nc pap).ti,ab. 18. autocpap.ti,ab. 19. or/14–18 20. 13 and 19

Extract from: McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, et al. Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. Appendices: Appendix 1. Health Technol Assess 2009;13(4) [cited 26.2.09].
http://www.ncchta.org/fullmono/mon1304a.pdf