12th May 2010

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Dear ████

Re: Single Technology Appraisal – Pazopanib for the first-line treatment of advanced and/or metastatic renal cell carcinoma

The Evidence Review Group (Aberdeen Health Technology Assessment Group) and the technical team at NICE have now had an opportunity to take a look at submission received on the 16th April 2010 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 ERG and the technical team at NICE will be addressing these issues in their reports. As you may only receive the evidence review group report 5 days prior to the Appraisal Committee meeting, you may want to respond to the points raised and provide further discussion from your perspective at this stage. Although there appears to be a large number of priority requests, many of these are simply data requests specifically relating to the treatment-naïve patient population.

We request you to provide a written response to this letter to the Institute by **17:00, 26th May 2010**. 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 <u>underline</u> all confidential information, and separately highlight information that is submitted under '<u>commercial in confidence</u>' in turquoise, and all information submitted under '<u>academic in confidence</u>' 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 Christian Griffiths – Technical Lead (christian.griffiths@nice.org.uk) Any

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procedural questions should be addressed to Bijal Joshi – Project Manager (bijal.joshi@nice.org.uk) in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

General

A1. **Priority request:** P68 – Table 5.11, in answer to the question 'Was the concealment of treatment allocation adequate? It is stated 'Yes. Adequate blinding was achieved…' However blinding is not the same thing as allocation concealment. Please provide the information reported by the study that was the basis for classifying the concealment of treatment allocation as adequate.

A2. **Priority request:** pp22-23 - The statement 'Thus approximately 3.4 per 100,000 patients are estimated to be eligible to receive first-line treatment with pazopanib per year in the UK, equating to around 2120 patients in England and Wales annually.' This is based on the information given in the table on p22, which states '…approximately 40% of those treated for localised disease relapse..' However the source given for this statement (Lam 2005) does not state that this is an annual figure. Please give the rationale for this figure being taken as an annual figure.

A3. If possible, please provide available data on file for the studies VEG107769, VEG108844 and VEG113046

A4. P43 – Table 5.1 – 'Studies which are presented at conferences are usually published in full within 3 years of presentation.' Please provide support for this statement.

A5. P65 – Bulleted list of factors adjusted for in the multivariate analysis. Please explain the rationale for including 'presence of liver metastases' in this list.

A6. P127 – 'The causes of the remaining deaths are reported as 'other' or 'unknown', with the exception of an additional three deaths where the cause of death was only recorded in the parent study.' What was the cause of death for these additional three deaths?

A7. Please clarify why sorafenib, bevacizumab and temsirolimus were considered as comparators in the submission when they were not listed as comparators in the scope document.

A8. P33-35 – In the Decision problem table, please explain why, in the 'Comparators' row, interleukin-2 is listed in the 'Scope' column but is not listed in the 'Decision problem addressed in the submission column'.

A9. P141 - 'These demographic and disease characteristics...are likely to be representative of patients with advanced/metastatic RCC in the UK.' However in study VEG105192 the percentage of patients with prior nephrectomy was 83% in the pazopanib arm and 84% in the placebo arm (Table 5.7). Please explain the rationale for this statement, as independent advice suggests that the vast majority of patients presenting with advanced/metastatic renal cell carcinoma in the UK have not undergone nephrectomy.

Treatment-naïve patient population

A10. **Priority request:** It appears as though only a selection of tables from the clinical study report on pazopanib have been provided for the population of

interest (treatment naïve patients). Please provide additional tables for the treatment naïve population; a list of the required tables is appended (**Appendix 1**).

A11. **Priority request:** P7 '…these data are made available to the committee as soon as possible – expected to be in 3Q 2010'. Would it be possible to provide any additional overall survival data at this point, prior to its release in Q3 2010?

A12. **Priority request:** For the treatment-naïve group of the VEG105192 study it was stated on page 35 that the evidence available does not allow sub-groups to be considered, but no further details have been provided. Please provide the results for pazopanib and placebo for the primary and secondary outcomes for the three subgroups:
- Resected versus unresected primary tumour
- Clear cell component versus no clear cell component
- Performance status

A13. **Priority request:** P113 – Table 5.47 - Overall best response and response rate (VEG102616). Please also provide the data (n (%)) for the response categories (CR, PR etc) for the treatment-naïve group, for both independent review and investigator assessment.

A14. **Priority request:** P114 – Table 5.48 – Response at week 12 (VEG102616). Please also provide the data (n (%)) for the response categories (CR, PR etc) for the treatment-naïve group, for both independent review and investigator assessment.

A15. **Priority request:** P115 – Table 5.49 – Secondary efficacy endpoints (VEG102616). Please also provide the data (n (%)) for Duration of response and Time to response for the treatment-naïve group, for both independent review and investigator assessment.

A16. **Priority request:** P116 – Table 5.51 – Summary of efficacy endpoints (VEG107769). Please also provide these data for the treatment-naïve group.

A17. **Priority request:** P125 – Table 5.61 – Treatment /emergent AEs occurring in ≥ 10% subjects (VEG102616). Please also provide these data for the treatment-naïve group.

A18. **Priority request:** P125, subsections 'Deaths', 'SAEs', 'AEs leading to permanent discontinuation of study medication', 'AEs leading to dose reductions or interruptions'. Please also provide this information for the treatment-naïve group.

A19. **Priority request:** P126 – Table 5.62 – On-therapy laboratory abnormalities reported in ≥ 10% subjects (VEG102616). Please also provide these data for the treatment-naïve group.

A20. **Priority request:** P127 – Table 5.63 – AEs reported for ≥ 5% subjects (VEG107769). Please also provide these data for the treatment-naïve group.

A21. **Priority request:** P127, subsections 'Deaths', 'SAEs', 'AEs leading to permanent discontinuation of study medication', 'AEs leading to dose

reductions or interruptions'. Please also provide this information for the treatment-naïve group.

A22. **Priority request:** P128 – Table 5.64 – Summary of worst-case toxicity grade increase from baseline for haematology and clinical chemistry parameters (VEG107769). Please also provide these data for the treatment-naïve group.

A23. **Priority request:** P53, Table 5.5 – VEG105192, 'Location' row. How many of the 28 subjects randomised by the UK centres were treatment-naïve? How many were randomised to the pazopanib and placebo groups? Which four centres in the UK were involved in the study?

A24. **Priority request:** P104 – Table 5.41 – VEG102616, 'Location' row. Were there any UK sites and if so how many patients did they enrol and how many of these patients were treatment-naïve? Which UK sites were involved?

A25. **Priority request:** P104 – Table 5.41 – VEG107769, 'Location' row. How many of the 5 UK patients were treatment-naïve?

A26. **Priority request:** P80 - Table 5.26, Quality of life. Please provide, for the treatment-naive group, a detailed breakdown of results for the pazopanib and placebo arms for each of the three instruments.

A27. P119 – 'Deaths resulting from AEs was reported in 12 (4%) subjects in the pazopanib arm and 4 (3%) of subjects in the placebo arm for the total study population.' In each of these arms how many of the subjects were treatment-naïve? 'Four patients (1%) in the pazopanib arm had fatal AEs that were assessed by the investigator as attributable to study treatment…' How many of these subjects were treatment-naïve? What were the fatal adverse events that were assessed by the investigator as being attributable to study treatment?

A28. P118 – Section 5.9.2.1.1 Extent of exposure. Could you provide the values for the median reduced dose (mg) for treatment naïve participants in the pazopanib trial, and the duration of dose reduction for those treatment naïve participants who received a reduced dose?

Statistical issues

A29. **Priority request:** P61 – Table 5.9 - The use of a pike estimator is mentioned in the statistical analysis section. What was the rationale for using a pike estimator in the Kaplan-Meier analyses and what effects did its use have on the results?

A30. **Priority request:** P77 – It is stated 'RPSFT does, however, have some limitations when applied to immature data due to the degree of re-censoring required.' Given this, what adjustments were made in the RPSFT analyses to address these limitations.

A31. **Priority request:** P95 - Table 5.32 - Is the reported confidence interval for overall survival correct, as it appears to be inconsistent with the 0.086-1.276 reported elsewhere in the submission?

A32. **Priority request:** P101 – 'It should be noted that the indirect comparison utilising the MRC RE01 trial presented in the systematic review report uses an HR for OS from VEG105192 that is not adjusted for cross-over.' What

rationale was employed in deciding when to use adjusted cross-over data and ITT data?

A33. P62-5 – Section 5.3.6.1 – How were the IPCW and RPSFT analyses carried out in practice (i.e. which statistical packages were used)?

A34. P75 & 77 – Section 5.5.1.2 - For the IPCW analyses, please explain why the univariate results were not reported in tables 5.20 and 5.22? Please could you provide the results of the unadjusted IPCW analysis?

A35. P81-103 – Section 5.7 (indirect and mixed treatment comparisons) – Please explain why mixed treatment analyses were not included in either the submission or the systematic review?

A36. P99 – Table 5.35 – Please comment on whether an unadjusted-for-crossover hazard ratio from the pazopanib trial should be used, perhaps as a sensitivity analysis, in the indirect treatment comparison so that it is consistent with the estimated hazard ratio from the sunitinib trial? Please clarify how this would affect the results?

A37. P99 - Table 5.36 – Please clarify why there is a major discrepancy between the methods used to estimate the 95% confidence interval around median overall survival for pazopanib? Please explain how it is possible to have negative survival as suggested by this confidence interval? Can you confirm whether this estimated interval is correct, or if it is a typo, and a misspecification in the model. If the confidence interval is correct, please could you explain what this means in terms of survival (as this wide CI reflects extreme uncertainty and does not qualify the statement on median OS in the paragraph below the table). Also, why are the median progression free survival estimates for IFN reported as being exact (e.g. the CIs for PFS is 5.4-5.4)?

Section B: Clarification on cost-effectiveness data

B1. **Priority request:** P169, Table 6.10 Summary of model inputs. Can you provide a detailed explanation of how the cost of pazopanib was generated?

B2. **Priority request:** P9 - The decision to use RPSFT for the economic base case was based on expert opinion from leading academics in this field. Please provide details of which academics, the process by which they were selected, whether they were remunerated, and whether they had any competing interests in relation to their involvement with GSK.

B3. P8 Please confirm whether the regular liver function test (every 4 weeks) has been included in the costings (blood tests are subsumed in outpatient cost but this may underestimate this element of cost)?

B4. P21 It is stated that 5 year survival with metastatic disease is 9.5%. Please comment on how consistent this estimate is compared with the model predictions.

B5. P29 It is stated that hypertension and thyroid dysfunction should be monitored; periodic urine analysis and electrocardiograms are also advised. Please confirm whether these costs are included? In addition, please clarify whether these tests (and hence costs) are required for other treatments?

B6. P145 Please provide details on the patient groups used to estimate the EQ-5D scores

B7. P146 - Table 6.2. The value for ICER progression-free does not appear to be correct. Please check whether this is the correct value.

B8. P151 Section 6.2.2, para 3. Clinically, please comment on how likely is it that patients who progress will discontinue pazopanib therapy?

B9. P151. Section 6.2.3. How was the cut off date chosen for the interim trial? What reassurance can the company give that this cut off date was not favourable to pazopanib?

B10. P152 Section 6.2.5. In the analysis it is assumed that patients cease treatment immediately if they progress. Please comment on how realistic this assumption is? Also, how long clinically would a patient be monitored before a decision that progression had occurred is made?

B11. P159. How would the results of the economic evaluation have changed had the data from VEG105192 been used as the reference treatment for the Weibull survival functions?

B12. P154 - Clinical continuation rule. Could treatment be discontinued due to adverse effects?

B13. P157 - Last paragraph on page states 'It should be noted that the HR used for OS from the sunitinib trial was not adjusted for post-study therapy in the same way as the OS data in VEG105192 and was taken from a sub-group analysis in subjects with no post-study therapy (Motzer 2009)' Was any sensitivity analysis performed around this estimate?

B14. P158 - Table 6.8, Effectiveness estimates used in the economic model, the first two lines of IFN Weibull distribution. Why were two different sources used for PFS and OS values?

B15. P168 Section 6.3.5. Who were the experts, were they paid and do they have any declared conflicts of interest?

B16. P168 Section 6.3.6. Please explain why all costs of grade 3 adverse events were not reported in appendix 16?

B17. P169 - Table 6.10 Summary of model inputs. Please clarify whether the value reported as the 'utility value' is actually the decrement rather than the actual utility value? Please clarify how the decrement of 15% was obtained?

B18. P170 Table 6.11. How was the 15% utility decrement for movement to PPS arrived at?

B19. P174 Please can the authors provide a copy of Swinburn 2010-05-07?

B20. P177 Please can you conduct sensitivity analysis around decrement for PPS utility obtained from the Oxford Outcomes study?

B21. Page 6.18. Please clarify why some rates e.g. fatigue grade 3+ are not available but rates for fatigue grade 1-2 are (when no data were available)

B22. P178 Sect 6.4.9. What is the justification for requiring that post-progression utility scores should be consistent with Remak and Parasuraman?

B23. P179 The SE for the duration of AEs has been assumed to be 0.25 by the mean duration. What is the justification for this assumption?

B24. P180 - Were EQ-5D utility values for persons with and without adverse events incorporated into the model analysis?

B25. P181 - Table 6.19 Summary of quality-of-life values used in the cost-effectiveness analysis. Please explain why it was assumed that the utility values would be the same for all interventions? Table 6.16 gives a summary of EQ-5D values for IFN and Sunitinib. Were these values used in any analysis?

B26. P183, section 6.4.14. Please clarify what the statement means " HRQL is assumed to differ for time in PFS and PPS states. Please clarify whether this means that the values used for the states differs but that the value for a state remains the same over time?

B27. P184 What is the justification for assuming that all patients with progressive disease will be discharged to management in primary care?

B28. P185 Table 6.24. Can you please provide details about how the costs presented in this table are calculated? From the text of the report it is not clear for all cost lines.

B29. P186 Table 6.26. Please clarify at which point anti hypertensive therapy will be initiated? Please confirm whether there are costs (other than the medication) involved in initiating and monitoring the use of this medication?

B30. P187 – Table 6.23, Assumed services and costs of monitoring during PFS and OS. Are these based on current practice?

B31. P187 - Table 6.24, What is the justification that the SE of cost-estimates such as cost estimates for routine follow-up and AE costs used in the model will be 25% of their mean values?

B32. P187 - Adverse events costs. Why were only 'costs of grade 3 or more and had an incidence of 5% or more' considered? Was any sensitivity analysis performed on these estimates?

B33. P188 - Table 6.26, Expected costs per grade 3+adverse events. Why were the values of some of the assumed services such as Anaemia, HFS/PPE and Neutropenia added up? Is it not the case that each item is a separate event?

B34. P192 - Table 6.28, Summary of model results compared with clinical data. Was sensitivity analysis performed assuming that the trend of outcomes remained the same?

B35. P195 and P196. The results of clinical outcomes indicate much higher life year gain in PPS state for pazopanib. Is there any biological evidence that tumours

that progress after treatment with pazopanib are different to tumours that progress after any of the other treatments?

B36. P200-203 - Why is BSC labelled as BSC2L?

B37. P203 Figure 6.10. It would be helpful if the results of the probabilistic analyses were represented as CEACs based on a net-benefit statistic rather than on the ICER.

Treatment naïve patient population

B38. **Priority request:** P 180 – Table 6.18, EQ-5D utility values for persons with and without adverse events in VEG105192. Are the data in Table 6.18 for the treatment naïve group of patients? If not, please provide these data for the treatment-naïve group.

B39. **Priority request:** P 181 – Table 6.20, Mean duration of AEs (days) in VEG105192 trial. Are the data in Table 6.20 for the group of treatment naïve patients? If not, please provide these data for the treatment-naïve group.

B40. Where additional information has been provided for treatment naive patients please revise the economic evaluation to reflect these data. If this is not possible please provide a justification as to why these data have not been used.

Section C: Textual clarifications and additional points

Clarification on presentational and additional points

C1. P78 – 'The overall response rate…' Should the first instance of 'placebo' be 'pazopanib'?

C2. P128 – Table 5.65 – Should 'N=315' be 'N=351'?

C3. P140 – 'VEG105192 was a multi-national study involving 5 sites in the UK…' However Table 5.5 (p53) states '4 centres in the UK.' Please clarify the number of UK centres.

C4. P145 - '…for which the model structure is shown in figure 6.3.' Should this state 'figure 6.1' rather than 'figure 6.3'?

Systematic review document

C5. P15 – In section 3.1.1 it is stated that a summary version of the original study protocol can be found in Appendix A1. Could the full protocol be provided please?

C6. P20 – Section 3.1.4 Data extraction strategy. Please clarify whether the data extraction "grid" for the systematic review was pre-designed? The appendix provides this data extraction grid with pre-specified adverse events. Can you confirm that no additional adverse events were reported by the included studies aside from those listed in the rows of the data extraction grid?

C7. P21 – 'Studies excluded during data each stage, along with rationale for exclusion are provided in a separate MS Excel document…' Could you provide this Excel file please?

C8. P21-22 – Section 3.1.5, Quality assessment. Please explain the rationale for using all of these three quality assessment tools in the systematic review.

C9. P25 – In section 3.2.1 it is stated that a summary version of the original study protocol can be found in Appendix A2. Could the full protocol be provided please?

C10. P63 – '…from personal communication with Motzer RJ…' Would it be possible to provide a copy of this correspondence?

C11. P78-79 – Table 36, Specific AEs experienced by randomised patients (across all grades). Can you confirm that all of the adverse events reported by the included studies are included within the groupings in the table. If not, which adverse events are not listed here?

C12. P98-99 – Table 45, Result of meta-analysis – AEs (all grades) versus IFN. Can you confirm that all of the adverse events reported by the included studies are included within the groupings in the table. If not, which adverse events are not listed here?

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_____

Appendix 1

A2. **Priority request:** Please provide the following additional tables, listed in the clinical study report, for the treatment-naïve group of patients:

Table 6.1 Summary of Populations (Intent-to-Treat Population)
Table 6.4 Summary of Inclusion/Exclusion Criteria Deviations (Intent-to-Treat Population)
Table 6.8 Summary of Race and Racial Combination Details (Intent-to-Treat Population)
Table 6.26 Summary of Duration of Follow-up (Intent-to-Treat Population)
Figure 7.1 Graph of Independent Radiologist-Assessed Kaplan Meier Progression-Free Survival (Primary Analysis)
Figure 7.6 Forest Plot of Primary and Sensitivity Analyses of PFS
Figure 7.11 Forest Plot of Primary and Subgroup Analyses of PFS
Figure 7.14 Hazard Ratios and 95% Confidence Intervals from Cox Proportional Hazards Regression Model for Overall Survival
Figure 7.29 Hazard Ratios and 95% Confidence Intervals for Progression-Free Survival (PFS Sensitivity Analysis 9)
Table 7.8 Summary of Kaplan-Meier Estimates of Progression-Free Survival (Sensitivity Analysis 6) (Intent-to-Treat Population)
Table 7.9 Summary of Kaplan-Meier Estimates of Progression-Free Survival (Sensitivity Analysis 7) (Intent-to-Treat Population)
Table 7.15 Summary of Kaplan-Meier Estimates of Progression-Free Survival by Baseline ECOG Score (ECOG 0) (Intent-to-Treat Population)
Table 7.16 Summary of Kaplan-Meier Estimates of Progression-Free Survival by Baseline ECOG Score (ECOG 1) (Intent-to-Treat Population)
Table 7.25 Summary of Kaplan-Meier Estimates of Overall Survival (Intent-to-Treat Population)
Table 7.26 Summary of Cox Proportional Hazards Regression Model (Unadjusted) for Overall Survival (Intent-to-Treat Population)
Table 7.27 Summary of Cox Proportional Hazards Regression Model for Overall Survival (Intent-to-Treat Population)
Table 7.49 Summary of Kaplan-Meier Estimates of Overall Survival (Unadjusted) (Intent-to-Treat Population)
Table 7.102 Summary of Stratification Factors (Second-Line Stratum) (Second Line Intent-to-Treat Population)
Table 8.10. Summary of adverse events related to investigational product (Safety population)
Figure 8.101 Cumulative Pazopanib Exposure
Table 8.11. Summary of adverse events related to investigational product displayed in descending order by total incidence (Safety population)
Table 8.12 Summary of Serious Adverse Events (Safety Population)
Table 8.13 Summary of Fatal Serious Adverse Events (Safety Population)
Table 8.16. Summary of serious adverse events related to investigational product (Safety population)

Table 8.17 Summary of Post Therapy Adverse Events (Safety Population)
Table 8.2 Summary of Deaths (Intent-to-Treat Population)
Table 8.26 Summary of Dose Reductions (Safety Population)
Table 8.27 Summary of Dose Escalations (Safety Population).
Table 8.28. Summary of dose interruptions (Safety population)
Table 8.63. Summary of common on-therapy adverse events (>=10% in Pazopanib arm) (Safety population)
Table 8.69. Summary of adverse events related to investigational product by maximum grade (Safety population)
Table 8.54 Summary of ECOG Performance Status Changes from Baseline by Baseline ECOG Performance Status (Safety Population)
Table 13.4 summary of EQ-5D
Table 13.5 Summary of EQ-5D thermometer and utility scores
Table 13.6 summary of change
Table 13.8 Summary of mixed model repeated measures analysis for change from baseline in EQ-5D utility score

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