6 August 2010

Dear ██████

Single Technology Appraisal

Pazopanib for the first line treatment of advanced and/or metastatic renal cell carcinoma

The Evidence Review Group Aberdeen HTA Group and the technical team at NICE have now had an opportunity to take a look at submission received on 20 July 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.

We request you to provide a written response to this letter to the Institute by **5pm, Friday 20 August 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.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Christian Griffiths – Technical Lead. Any procedural questions should be addressed to Lori Farrar – Project Manager in the first instance.

Yours sincerely

Frances Sutcliffe

Associate Director – Appraisals

Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority request:** With regard to the ongoing head-to-head study of pazopanib versus sunitinib (COMPARZ and sub study VEG113078), please provide an explanation and/or justification on clinical or other grounds the value of the non-inferiority margin (1.22) in treatment effect between pazopanib and sunitinib that would mean that a difference greater than this would be clinically important.

A2. **Priority request:** Please provide the median (and interquartile range) follow-up time for treatment-naïve patients randomised to (a) the pazopanib and(b) placebo arms of VEG1015192 for the new clinical cut off date of 15 March 2010.

A3. **Priority request:** Please provide the interquartile range for the median time to crossover for placebo patients, as this is not available in Table 1.5 of section 1.3.1 (page 10 of the addendum submission).

A4. **Priority request:** From Table 1.1 on page 8 of the addendum submission, the section on "Primary reason for early termination from study" which was included in Table 5.10 of the original submission (page 67) is missing. Please confirm that since the interim analysis there has been no change in the data that would be provided for this section.

A5. **Priority request:** Please provide an explanation for the apparent anomaly between Table 1.2, on page 8 of the addendum, where the mean daily dose of pazopanib is 800mg/day when dose interruptions are included and Table 5.52, on page 118 in the original submission, where the mean daily dose of <800mg/day.

A6. **Priority request:** With regard to the baseline factors adjusted for in the analysis and listed in the second last paragraph of section 1.4 (iv) on page 15 of the addendum, please provide the following::

    a) the interquartile range for the median time since diagnosis for
        i) treatment naïve pazopanib patients in VEG105192
        ii) treatment naïve placebo patients in VEG105192
        iii) patients in VEG107769

    b) the proportion of patients with a time since diagnosis of <1 year/≥1 year for
        i) treatment naïve pazopanib patients in VEG105192
        ii) treatment naïve placebo patients in VEG105192
        iii) patients in VEG107769

    c) the number of metastatic sites for
        i) treatment naïve pazopanib patients in VEG105192
        ii) treatment naïve placebo patients in VEG105192
        iii) patients in VEG107769

    d) the proportion of patients with liver metastases/without liver metastases for
        i) treatment naïve pazopanib patients in VEG105192
        ii) treatment naïve placebo patients in VEG105192
        iii) patients in VEG107769

A7. **Priority request:** Baseline data has not been reported for patients in VEG107769 who were treatment naïve at entry to the parent VEG105192 study, although median overall survival is reported for this group in Table 1.8 (page 17 of the addendum). Please provide baseline data for this group of 41 patients, particularly for the following relevant baseline factors:

  a) age (mean, SD and median, IQR and range)
  b) gender (number/% male, number/% female)
  c) MSKCC risk score (intermediate-poor/favourable)
  d) time since diagnosis (median, IQR and range/proportion with time since diagnosis of <1 year/≥1 year)
  e) stage of disease at initial diagnosis (stage I or II/stage III or IV)
  f) number of metastatic sites
  g) presence of liver metastatses (yes/no)
  h) ECOG status (0, 1, 2, unknown)

A8. **Priority request:** With regard to Table 1.8 on page 17 of the addendum, please provide interquartile ranges for both median overall survival results in this table.

A9. **Priority request:** Please provide updated versions of Tables 5.17 and 5.19 from the original submission (pages 73 and 74).

A10. **Priority request:** Please confirm that the updated Table 1.10 in the addendum (page 18) accounted for receipt of other cancer therapy whereas Table 5.18 in the original submission (page 74) did not. There appears to be a discrepancy in the titles of these tables.

A11. **Priority request:** Please provide 'numbers at risk' tables be provided for Figures 1.3 B and C (page 23 of addendum), as shown for Figure 5.5 in the interim analysis from the original submission (page 76).

A12. **Priority request:** Please provide baseline data for patients with no post-study therapy as discussed in section (iv) of 1.5.2 (page 24 of addendum), for those factors mentioned, i.e.:
    a. ECOG PS
    b. number of metastatic sites
    c. MSKCC risk scores

A13. **Priority request:** Please confirm that the hazard ratios for Pazopanib vs placebo/BSC in Tables 1.19, 1.20, 1.21, 1.22 and 1.23 in the addendum (pages 18 and 19) are also based on scan dates as reported in corresponding Tables 5.37, 5.38, 5.39a, 5.39b and 5.39c of the interim analysis provided in the original manufacturer's submission (pages 101-102).

A14. **Priority request:** With regard to page 8 of the Appendix 1 document provided alongside the addendum – In the IPCW baseline model, study week is reported as an additional term as being the number of weeks from randomisation. Please provide the following:

a) the endpoint for this measure (and whether this was included for all patients)
b) the means and standard deviations for the pazopanib and placebo groups.

A15.   **Priority request:** With regard to page 9 of the Appendix 1 document provided alongside the addendum – when the hazard ratio and confidence interval were calculated for the IPCW analysis, please explain why the preferred method of calculating a p-value (described in footnote 1) was not used.

A16.   **Priority request:** With regard to pages 26, 29 and 34 of the Appendix 1 document provided alongside the addendum - In the IPCW analysis, time since progression was used as an interaction term with disease progression. Please clarify whether time since progression was also included as a term on its own in the time-dependent covariate model. If so, what are the descriptive statistics for this variable (equivalent to those shown for other covariates in Tables 3, 6 and 11)?

Section B: Clarification on cost effectiveness data

B1. **Priority request:** In Table 2.3 "Summary of economic model base case for sunitinib" the values for PFS and PPS are 11.0 and 15.4 where as the corresponding values in Table 6.28 of the original submission (page 192) were 11.4 and 15.0. Please indicate which of these values are used in the cost-effective analysis.

B2. **Priority request:**
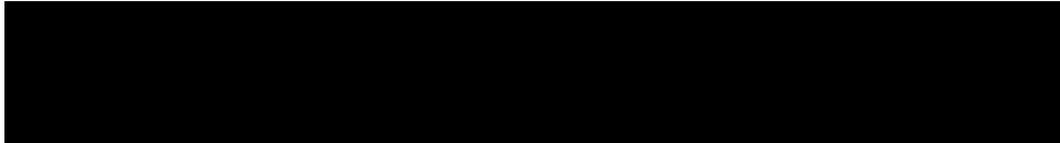
Section C: Textual clarifications and additional points

C1. In the PAS submission template document on pages 18 and 19 the heading and results on table 4.4 and 4.5 are exactly the same. Cost effectiveness results without the 12.5% discount are not reported. Please provide these results.