NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment – (ID-518)

Dear [redacted],

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 8 November by Pfizer. 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**, **Wednesday 4 December**. 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 turquoise, 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.

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 Nwamaka Umeweni, Technical Lead (Nwamaka.umeweni@nice.org.uk). Any procedural questions should be addressed to Nicole Fisher, Project Manager (Nicole.Fisher@nice.org.uk) in the first instance.

Yours sincerely

Nicola Hay
Technical Adviser

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On behalf of Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Section 2.3.3

1. **Priority request:** Please clarify the discrepancy in median PFS for sunitinib from the A6181006/NCT00077974 trial reported in tables 4 and 12 of the addendum. In table 4, second column, median PFS of 8.3 (7.8-14.5) and 8.1 (5.5-10.4) are reported while table 12, last column, reports a median PFS of 8.8 (7.8-13.5).

Section 2.4.2

2. Please provide the baseline patient characteristics for the prior cytokine population in the VEG105192 study (the data provided in table 7 [page 10 of the addendum] is for the ITT population).

Section 2.4.3

3. **Priority request:** Please explain, based on the underlying assumptions of each method, which one of the two methods to assess the impact of crossover (IPCW and RPSFT) stated in table 8 (page 10 of the addendum) is Pfizer's preferred approach to estimating the hazard ratio.

4. Please explain whether all results in Table 8 (including adverse reactions) are only for the prior cytokine population. If not, please provide data for the prior cytokine population separately.

Section 3.1

5. Please provide further details on the methods used in the indirect comparison in section 3 of the addendum. In particular, please highlight any differences in the methods for the analysis in the addendum compared with the methods used in the original submission.

6. Based on the similarities and differences between the AXIS and VEG105192 trials, please explain whether an indirect comparison of axitinib and pazopanib is considered appropriate?

7. **Priority request:** Please explain whether the assessment of PFS was comparable in the AXIS and VEG105192 trials

Section 3.2

8. Please clarify the following sentence on page 12 of the addendum: "The results suggest that there is a 95% probability that axitinib will always be superior to placebo, pazopanib and sorafenib."
    - For example, it is not clear what is meant by a 95% probability of always being superior. Please clarify whether this is a simultaneous probability, that is, does it

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represent the probability that axitinib will simultaneously be superior to placebo and pazopanib and sorafenib?

- A similar sentence is indicated as a footnote in Table 10, referring to placebo and pazopanib. Please clarify whether this sentence also refers to sorafenib.

Section 3.3

9a. **Priority request:** Please provide further explanation to support the following assumption on page 14 of the addendum. "Given that the hazard ratio for pazopanib in each of the crossover - adjusted analyses, was 0.53, it could be inferred that the adjusted median overall survival for the BSC arm of the VEG105192 study could be lower than unadjusted median overall survival of 14.3 months from the TARGET trial". The ERG assumes that inferred in this sentence should be interpreted as statistically inferred.

9b. **Priority request:** If the reasoning for the above question was as follows: 22.7*0.53 = 12.03, then please explain why the two hazard ratios on page 10 of the addendum are being considered as equal, without taking into account the uncertainty around them.

9c. **Priority request:** Please the assumption of a "lower" median overall survival is clinically plausible.

Section 4

10. **Priority request:** Please explain what is meant by a 'naive comparison' in section 4 and 5 of the addendum submission and how this was performed.

11. **Priority request:** Please provide the confidence intervals for all the estimates presented in Table 12, or if not available, please state that this is the case

12. **Priority request:** Please clarify which median PFS and overall survival values for axitinib are considered in the conclusions from Table 12 on page 15 of the addendum.
    - The sentence "As presented in Table 12, based on a naïve comparison, axitinib demonstrates a PFS and overall survival benefit of more than 3 months compared to BSC, sunitinib and pazopanib" suggests that the median PFS and overall survival are those provided by AXIS. Please confirm or provide further clarification.
    - If the median PFS and overall survival are those from AXIS, then please explain why the simulated values are disregarded in this section.

13a. **Priority request:** The sentence on page 15 of the addendum "an additional 5.5 months survival vs sunitinib (using the mature results of the larger phase II study)" suggests that the overall survival median from AXIS and the study from Motzer et al 2006b are being compared. Please explain how it is established that the two populations of these two studies are similar / comparable.

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13b. **Priority request:** The sentence on page 15 of the addendum "an additional 6.7 months survival vs pazopanib" suggests that the overall survival median from AXIS and the VEG105192 study are being compared. Please explain how it is established that the two populations of these two studies are similar / comparable.

14. **Priority request:** All the differences in median PFS and overall survival are measured against the medians provided by the AXIS trial. This could suggest that Pfizer believes that the results from the indirect comparison should not be used. Please clarify whether this is true or not.

Section B: Clarification on cost-effectiveness data

Section 5

15. **Priority request:** In the discussion on page 16 of the addendum, it is implied that the median overall survival estimated from the indirect comparison for best supportive care is not valid, Please explain why the results from the indirect comparison are valid for the axitinib arm and not the best supportive care arm.
    - If the results of the indirect comparison are valid for axitinib, then clarify whether section 4 should be adjusted to use these results rather than the medians from the AXIS trial.
    - Otherwise, if the AXIS trial is used as reference, then the ICER of £55K per QALY gained would not be valid since the median overall survival in AXIS is lower than 33.3 months estimated in the indirect comparison.

16. **Priority request:** Please justify further, the assumption that the median overall survival for best supportive care in the prior cytokine population of 17.6 months is a valid.

17. **Priority request:** In general, when multiple treatments are compared, results should be presented as a full incremental analysis, rather than pairwise comparisons. Therefore, please present the results in a table like the one shown below, including the expected costs and expected QALYs for both pazopanib and sunitinib. Also include information on costs of treatment with pazopanib and sunitinib (including any associated patient access scheme), and the costs of treating adverse effects associated with all treatments.

	Expected QALYs	Expected costs	Incr. QALY	Incr. costs	ICER
Pazopanib					
Sunitinib					
BSC					
Axitinib					

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18. **Priority request:** In table 13, page 17 of the addendum, it is indicated that the ICERs of axitinib compared with sunitinib and axitinib compared with pazopanib are smaller than £55,000 per QALY gained. Please quantify how much smaller they are expected to be.

19. **Priority request:** All the results presented in table 13 are based on median estimates. Please provide analyses of the associated uncertainty.

20. **Priority request:** Please provide the evidence to support the following statement on page 17 of the addendum. "Advanced/mRCC patients who have received prior treatment with cytokines constitute a small patient population (less than 20 patients)".

Section C: Additional points

Section 2.2

21. **Priority request:** Please provide more details on how the non-systematic search of Medline was performed.

22. **Priority request:** Please provide details of any new publications on VEG105192 identified through updated searches.

23. Please provide more information on how the two sunitinib studies were identified. Also explain the steps taken to ensure that all relevant sunitinib studies have been identified.