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6th September 2012

Dear [redacted]

Re: Single Technology Appraisal – Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment

The Evidence Review Group Kleijnen Systematic Reviews and the technical team at NICE have now had an opportunity to take a look at submission received on the 13 August 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 **12:30pm, Thursday 20 September.** 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 [redacted] – Technical Lead ([redacted]) Any

procedural questions should be addressed to [redacted] – Project Manager ([redacted]) in the first instance.

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Please note that all page and section references are based on the revised manufacturer submission without the patient access scheme.

Section A: Clarification on effectiveness data

1a. **Priority request:** Please provide the complete clinical study report (CSR) for the AXIS study.

1b. **Priority request:** Please also provide the supplemental report with the final OS analyses (see ref 63, page 192 of the manufacturer submission): Pfizer Ltd. Final supplemental clinical study report. Axitinib (AG-013736) as second-line therapy for metastatic renal cell cancer: AXIS trial. 2011; Data on file.

2. **Priority request:** Please provide the actual trial data to go with the WinBUGS code from section 10.14 (appendix 14 of the manufacturer submission).

3. Please provide full references for the 25 RCTs found through the RCT search (see flow chart on page 39 of the manufacturer submission) and, if possible, full papers.

4. Please provide full references for the 4 publications found through the search in Appendix 15 (see flow chart on page 353 of the manufacturer submission) and, if possible, full publications.

5 On page 82 of the manufacturer submission, it is stated that: *"Similar methodologies have been accepted in recent HTA appraisals to overcome gaps in the evidence network which rule out a standard indirect comparison approach, including NICE TA171 (Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy."* The ERG have looked at the submission and the ERG report for lenalidomide (TA171) and this does not seem to contain a simulated treatment comparison (STC). The actual meta-analysis in the systematic review is based on a pooled analysis of 2 trials comparing the same treatments (using all the IPD, and using summary measures) and there is a mixed treatment comparison.

- Please clarify which aspect of the analyses used in TA171 is being used as an example of an STC in an appraisal?

- Please clarify whether the manufacturer is aware of STCs being used in any other NICE appraisals?

6. **Priority request:** From the AXIS trial, please provide full QoL data (FKSI-15, FKSI-DRS and EQ-5D) in a table for each treatment arm and differences between treatment arms with corresponding confidence intervals separately for the cytokine refractory and sunitinib refractory subgroups.

7. **Priority request:** Section 6.9 of the manufacturer submission reports on the adverse events from the AXIS trial. Please provide data by treatment arm as reported in tables 30-32 separately for the cytokine refractory and sunitinib refractory subgroups.

Section B: Clarification on cost-effectiveness data

Section 7.2

1. Please clarify why a time horizon of 15 years was chosen in a scenario analyses, and why this time horizon was not used in the base case.

Section 7.3

2. **Priority request:** It appears from the model that each cycle, patients may discontinue treatment with axitinib. However, it also appears that the only difference between the patients who withdraw and the patients who stay on treatment is the cost; no treatment costs are applied to patients who withdraw from treatment. Please clarify the rationale for assuming that patients who withdraw from treatment continue to follow the PFS and OS curves for axitinib, rather than following the PFS and OS curves of the BSC group after withdrawal. The implication of the approach currently in the model is that more favourable ICERs will be found if more patients withdraw from treatment.

Section 7.3.2

3. Please clarify the rationale for not including the gamma distribution as part of the set of distributions used for analysis.

4. Please provide log-cumulative hazard plots for all distributions considered (both for PFS and OS, for both subgroups).

5. Please provide more details about the procedure to select the base case model. For example:

   - When AIC and BIC rank ordering are not the same, how are the 3 best fits selected?

   - The three distributions with the best fit were included, with the base case representing the most plausible survival estimate: how is the plausibility of the survival estimate determined?

   - The best fit is determined based on 3 criteria: how are these three combined to come to a selection. From the descriptions later in that section it appears that expert opinion was always dominant in the model selection.

Cytokine Refractory Overall Survival curves

6. In the description of the model selection it is stated that the exponential and lognormal distribution showed poor fit (pg 140). However, in Appendix 19 according to AIC the Gompertz is ranked 4th and according to BIC ranked 5th. Therefore, the lognormal distribution appears to be a better candidate than the Gompertz. Please clarify the reasoning behind the choice of distributions.

7. The manufacturer submission states that the loglogistic distribution provided the best fit in statistical term (page 141). However, this does not seem to be consistent with table 34, where the Weibull appears to have the best fit. Please clarify this apparent inconsistency.

8. Please clarify why, if in the base case the application of proportional hazard was required, accelerated time failure models were considered?

Cytokine Refractory Progression Free Survival curves

9. The manufacturer submission states that the *lognormal* distribution provided the best fit in statistical term (pg 142). However, this does not seem to be consistent with table 35, where the Weibull distribution appears to have the best fit. Also, it is noted that the exponential distribution gives the best BIC (appendix 19) but is not considered one of the 3 candidates. Please clarify the reasoning behind the choice of these distributions.

10. The manufacturer submission states that *similarly to the OS data*, the lognormal distribution provided the best fit (pg 142). Please explain this statement, as the lognormal distribution is not considered for the OS data.

11. The manufacturer submission states that the lognormal model predicted a higher proportion of non-progressed patients at 10 years, which was felt to be clinically implausible by the experts and a reference is made to table 35 (pg 142). Please clarify why this was considered to be clinically implausible and how table 35 is seen to support this.

Sunitinib Refractory Overall Survival curves

12. In the description of the model selection it is stated that the exponential and loglogistic distributions showed poor fit (pg 143). However, in Appendix 19 the ERG notes that according to AIC and BIC the Gompertz is ranked 4th whilst the loglogistic is ranked 2nd. Thus, the loglogistic distribution appears to be a better candidate than the Gompertz. Please clarify the reasoning behind the choice of distributions

13. In the manufacturer submission it is stated that the sunitinib refractory subgroup and the cytokine refractory subgroup are considered by many clinicians to comprise different subgroups. In light of this, please explain why it is plausible that the results of the fitted lognormal model for OS in the *sunitinib refractory* subgroup are similar to the results of the *cytokine refractory* 5-year follow-up from the axitinib phase II trial as stated on pg 143.

Section 7.4

14. Please explain why for the post progression utility estimate only the mean utility at the end of treatment was used instead of also including the utility measurement at the 28 days follow-up.

15. **Priority request:** Please provide the utility estimates for progression free and post progression survival for the prior sunitinib and the prior cytokine subgroups separately. Please also test the hypotheses that these utilities are the same in each subgroup.

16. Please clarify which patients were used for the estimation of utility post progression, is this based on only patients receiving axitinib or also patients receiving sorafenib?

17. In the manufacturer submission it is stated that while patients receiving axitinib may expect to experience some reduction in health-related quality of life related to the treatment, they will also receive HRQoL benefit in terms of symptomatic control and disease stabilisation. However, from the study by Swinburn (2010) it is clear that grade III diarrhoea, grade III fatigue and grade III hypertension influence the utility score for stable disease from 0.795 to 0.534, 0.591 and 0.642 respectively [TTO with UK members of the general public]. Also the study by Zbrozek (2010) shows the influence of serious toxicity on the utility score. In the light of these findings, please provide further justification of the assumption that patients receiving best supportive care would experience the same utility as patients receiving active treatment with axitinib.

Section 7.5

18. In the NICE specification section 7.5.3, NICE requests a systematic search of relevant source data for resource identification. In the submission it is stated that a systematic review was not completed and that evidence for this section comes from clinical opinion, published sources, the manufacturer's submission for the everolimus STA and the PenTAG model developed for the NICE bevacizumab, sorafenib, sunitinib and temsirolimus MTA. An initial examination of these sources shows publication dates of 2009 & 2008 respectively.

    a) Please provide further justification as to why no systematic review of resource use in the treatment of renal cell carcinoma was conducted.

    b) Please clarify the steps made to ensure that the information used in the submission is up to date.

    c) Please provide a list of all the published sources used and how these were identified. Please include the details of any search strategies used.

19. **Priority request:** Please provide the dose intensity for the patients who were sunitinib refractory and cytokine refractory in the AXIS trial separately and clarify why in the base case analysis the overall dose intensity was used instead of sub-group specific. Please provide ICERs with the sub-group specific dose intensities.

20. Please provide further justification for the assumption that no hospitalisations take place in the progressed disease state.

21. **Priority request:** Please clarify what the costs of death represent and how the estimate for these costs (before inflating to 2011 costs) was derived from the Coyle paper.

22. Please explain why the Mickisch study was not used for the AE costs of hypertension and diarrhoea. Please also explain the current assumptions underpinning the AE costs related to hypertension and diarrhoea.

23. Please clarify the difference between the costs of AE in table 40 and in table 45.

24. **Priority request:** Please clarify the adverse event rates associated with best supportive care. In the manufacturer submission (table 45) adverse events associated with best supportive care includes a percentage of anaemia of 5.1% while in the model 2% hypertension is used and no anaemia.

Section 7.6

25. **Priority request:** Figures 36 and 37 present the results of the univariate sensitivity analysis in tornado diagrams. For these analyses ranges of +/- 20% were used. However, such a range could be much larger or much smaller than the confidence interval of a specific parameter. In order to get a sense of the realistically possible variation in the outcome, please provide univariate sensitivity analyses (both with and without PAS) with ranges based on 95% confidence intervals (as also used in PSA) instead of a general +/- 20%.

Section 7.8

26. **Priority request:** Please provide the spreadsheet used for the validation process that is mentioned in the text of the manufacturer submission.

Appendix 19

27. Please provide further justification for the derivation of the survival curves for best supportive care (using the hazard ratio), either by providing a mathematical proof that this is a reasonable approach or by providing references.

Section C: Textual clarifications and additional points

1. Please could you confirm the following details for the Clinical effectiveness searches for the Web of Science (10.2) searches:

   - The ERG does not recognise the search syntax as being ISI Web of Knowledge, in some lines it appears to be Ovid, but there appear to be mixed use of adjacency operators i.e. “adj” and “near”. Please can you confirm which host was used?

   - Within the Web of Science, please can you confirm which indices were searched? i.e. Science Citation Index etc

   - Please can you provide the date range searched?

- The strategy presented is up to 2010. Was an update search undertaken as with the other searches in this section? Please confirm the search dates.