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Worldwide Biopharmaceutical Businesses

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Appeal Committee Chair

National Institute for Health and Clinical Excellence

10 Spring Gardens

London

SW1A 2BU

8th May 2013

Dear [redacted]

Appeal Against the Final Appraisal Determination for Axitinib for the Treatment of Advanced Renal Cell Carcinoma After Failure of Prior Systemic Treatment

Thank you for your letter dated 23 April 2013, providing your preliminary view on the admissibility of the points raised in Pfizer's Notice of Appeal.

We provide below our response to the matters raised in your letter in relation to our points of appeal.

Ground 1

1.1 <u>The lack of transparency in relation to a submission relied upon for the purposes of the guidance is procedurally unfair</u>

Noted.

1.2 <u>The fact that Pfizer had no adequate opportunity to respond to the additional matters raised by the pharmaceutical industry commentator in response to the ACD, is unfair</u>.

In your letter, you refer to the fact that the difficulties modelling the relative benefits of axitinib, compared to best supportive care (BSC), was raised in the appraisal before and during consultation and you express the view that the additional issues raised by the pharmaceutical industry commentator did not require a further round of comment or consultation in view of the fact that these matters were also directed towards the modelling of relative benefits.

We accept that it is not always necessary to consult on the product of earlier consultation. However, in some cases, further consultation is required as a matter of fairness and we believe the circumstances of this appraisal (particularly the fact that the Committee relied upon new material submitted by an unnamed industry commentator, potentially a competitor) required that Pfizer be given an opportunity to respond. For completeness, the position of Pfizer as a consultee to the appraisal, with a substantial interest in its outcome, is clearly different from that of the industry commentator who submitted its comments as a member of the public. Pfizer would of course seek to change the conclusions of the Committee set out in the ACD, through additional data and argumentation; however we recognise that any material change to the guidance (in either direction) may, depending on the circumstances, necessitate further consultation.

It is correct that the difficulties associated with the modelling of relative benefits associated with BSC and axitinib were raised prior to consultation on the ACD and Pfizer addressed the Appraisal Committee's stated concerns, in its response to the ACD. (Pfizer could not, of course, address concerns which had not been raised at that stage.) In the FAD however, the Appraisal Committee rejected Pfizer's explanations, relying additionally on matters raised by the unidentified pharmaceutical industry commentator for its conclusion that the reliability of the results of the simulated treatment comparisons was uncertain. It is unclear whether the appraisal committee would have reached the same conclusion, following Pfizer's ACD response, if the submission by the pharmaceutical industry commentator had not been taken into account. In circumstances where the modelling of relative benefits of axitinib compared with BSC is arguably the fundamental issue in this appraisal, we believe the Appraisal Committee was required, as a matter of fairness, to allow Pfizer to respond to the submission by the unidentified pharmaceutical industry commentator, in view of the fact this was not only relied upon by the Committee for the purposes of its conclusions regarding the modelling of benefit, but was potentially based on evidence from an entity that is not impartial.

For the avoidance of doubt, Pfizer does not agree with the submission by the pharmaceutical industry commentator and it is unfair that this submission has been relied upon by the committee on the issue of modelling to such a substantial extent or at all, in circumstances where Pfizer has been given no opportunity to respond to such matters.

1.3 <u>The scope for this appraisal produces results that inevitably lack certainty.</u>

In your letter, you say that you cannot see this point of appeal as "*a standalone complaint of procedure fairness*". You suggest that the issues raised under this point could be addressed as aspects to be considered under points 1.4 and 1.7.

However, the issues raised by Pfizer under point 1.3 of its appeal, are wholly distinct from those aspects of procedural unfairness raised at 1.4 and 1.7. The issue at 1.3 relates to the fact that the choice of comparator determined by NICE's Scope for this appraisal, inevitably results in some uncertainty as to

the output of any assessment, in view of the fact that it is not possible to conduct a direct comparison with axitinib in any clinical trial. The comparator specified in the Scope is BSC, even though there is no direct clinical trial comparison of BSC with axitinib and it would not have been ethical for Pfizer to conduct one. (At the time of design of the AXIS trial, sorafenib was the only treatment licensed for the second-line treatment of advanced renal cell carcinoma and was therefore the only appropriate comparator for axitinib.) Inevitably therefore, any comparison with BSC, the comparator required by NICE, must be made indirectly or through modelling, with the uncertainties associated with those approaches.

The thrust therefore of point 1.3 of Pfizer's appeal is that, in circumstances where a substantial part of any uncertainty in this appraisal results from an approach required by the Institute, which substantially limits Pfizer's ability to produce data with the certainty preferred by NICE, rather than a matter within Pfizer's control, the Appraisal Committee should, as a matter of fairness, adopt a pragmatic approach to uncertainty which recognises these difficulties.

1.4 <u>The Appraisal Committee's refusal to find that use of axitinib in post-cytokine patients satisfied the "end of life" criteria on the basis that no comparison with sunitinib or pazopanib had been provided, was inconsistent with the Scope for this appraisal.</u>

Noted.

1.5 <u>The Committee's approach to the assessment of QALY gains occurring in the post-sunitinib group following disease progression and its conclusion that the post-progression model outputs lacked "clinical plausibility" was not transparent.</u>

In your letter, you suggest that the Appraisal Committee may have no obligation to provide an explanation for its rejection of the submissions made by Pfizer and by the clinical specialist in relation to the clinical plausibility of QALY gains occurring following disease progression in the post-sunitinib group.

We do not believe this is correct. It is well established that procedural fairness requires a public body adequately to explain why it has acted or reached the decision that was in fact reached. The duty to provide reasons enables consultees to take part in the consultation process, demonstrates that the decision maker has focused on the correct questions and that the issues have been conscientiously addressed and informs consultees why they have won or lost.

In this case, the Appraisal Committee was reluctant to accept Pfizer's modelling of QALY benefits arising in the post-sunitinib population following disease progression, on the basis that such results were not seen in the clinical trial, were not modelled in another patient population and that the Appraisal Committee therefore concluded that Pfizer's modelling was not clinically plausible. Both the clinical specialist and Pfizer provided full responses to the matters raised by the Appraisal Committee, explaining why their concerns

were misplaced. However, the Appraisal Committee simply repeated its view that the QALY benefits modelled by Pfizer lacked clinical plausibility and provided no reasoning to justify rejecting the explanations provided by Pfizer and the clinical specialist.

Pfizer does not believe that this is a case which simply involves a disagreement between experts. The lack of any response to the matters raised by the clinical specialist and Pfizer indicates a lack of rigour; it leaves Pfizer in a position where it is unable to understand why its position has seemingly been rejected and where the basis for the Committee's decision is unclear.

Finally, we note your comment that whether any explanation provided by Pfizer is persuasive, is "*a question of justification (ground 2) rather than fairness*". While Pfizer has chosen to advance this point of appeal as a matter of transparency (procedural fairness), we recognise that it could be formulated under ground 2: to the extent that there is no basis for the Committee's decision (or where any reasons are flawed or inconsistent with the evidence) there is a strong inference of arbitrariness, which does not reflect a reasonable approach. Therefore, if you are not willing to allow us to bring our point of appeal under ground 1, we are willing to advance it under ground 2, as suggested in your letter.

1.6 <u>While the Committee found explanations for post-progression QALY gains "clinically implausible" they failed to request attendance by the clinical specialist at the second Appraisal Committee meeting so that any concerns could be discussed.</u>

In your letter, you express the preliminary view that this point of appeal should not be referred to the Appeal Panel, in view of the fact that a previous Panel rejected a similar point in another case.

While we agree that earlier decisions of Appeal Panels, may provide some guidance as to the likely approach in future cases, we do not believe that is the appropriate approach in relation to any requirement to invite the attendance of the clinical specialist at second or subsequent meetings of the Appraisal Committee. This issue is strongly dependent upon the particular factual situation in the individual case. Therefore, the decision of an Appeal Panel in an earlier case, provides little assistance in determining whether the attendance of the clinical specialist should have been requested in another case, involving different clinical issues, different questions and different internal expertise on the Committee.

In the context of the appraisal of axitinib, the issue of clinical plausibility of a survival benefit accruing to patients following discontinuance of treatment in the prior sunitinib population, is one that was not discussed during the first meeting of the Appraisal Committee. The consideration of this issue during the public part of the meeting was limited to asking the clinical specialist whether he thought the Pfizer results were clinically plausible, which he said he thought they were in the prior sunitinib population. No alternative views were expressed and there was no more general debate about post-progression survival benefits. In circumstances where the Appraisal Committee had no

internal renal oncology expertise and where the issue had not previously been discussed, it is surprising that the Committee believed it was able to reach a conclusion of clinical implausibility, contrary to the evidence submitted by Pfizer and the written submission of the clinical specialist, without any discussion with an appropriate expert. We believe that fairness required that the Appraisal Committee put itself in a position to obtain independent clinical specialist opinion on a controversial issue, that is central to the appraisal and that the failure to do so in the particular context of this appraisal was unfair.

1.7 The Appraisal Committee's final conclusions in relation to the cost-effectiveness of axitinib are not stated and its reasons for failing to recommend second line treatment in patients with advanced or metastatic RCC are therefore unclear, in circumstances where the ICER values appear to fall within the range generally regarded as acceptable in other appraisals.

Noted.

We hope that these additional submissions have responded to the matters raised in your initial scrutiny letter. However, to the extent that you have any further questions or require additional clarification, we will be pleased to assist.

Yours Sincerely,

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Head of Oncology Business Unit UK