17 February 2012

Dr Maggie Helliwell
Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA

Dear Dr Helliwell

Re: Final Appraisal Determination - Cabazitaxel for the treatment of metastatic hormone-refractory prostate cancer

Thank you for your letter of 3rd February setting out your initial views in relation to our appeal request. Sanofi welcomes the opportunity to provide further clarification in relation to a number of our appeal points, before you make your final decision on admissibility.

1. Ground one: The Institute has failed to act fairly

1.1: The failure to invite clinical or patient experts to the second Appraisal Committee meeting is contrary to NICE's processes and was unfair.

This point of appeal essentially relates to whether the decision by the Chairman of the Appraisal Committee, not to invite the clinical and patient experts to attend the second meeting of the Appraisal Committee, may have unfairly prejudiced a fair understanding and assessment of the issues considered.

In the ACD, the Appraisal Committee expressed serious concerns and uncertainty in relation to important clinical issues relevant to this appraisal including :

- whether the patients recruited from European centres more closely reflected UK patients than the full trial population from TROPIC);
- The quality of life of this patient population and the reliability of the utility data presented (paragraph 4.11).

These preliminary conclusions of the Appraisal Committee appeared to us to misunderstand both the available data and the clinical situation of patients with metastatic prostate cancer. Accordingly, in our response to the ACD, we provided substantial additional clinical data and information relating to these issues. In the FAD, the Committee has developed its conclusions, particularly in relation to the quality of life associated with cabazitaxel therapy, and has expressed a number of controversial views in relation to the condition and quality of life of patients with metastatic prostate cancer (paragraphs 4.14 -

4.17 of the FAD), which are unsupported by evidence and were reached in the absence of the clinical and patient experts. By way of example, the Committee has disputed the relevance of the Pickard et al review to patients considered in this appraisal (paragraph 4.16 of the FAD).

Sanofi does not believe these conclusions appropriately reflect the situation of patients with metastatic prostate cancer. The quality of life experienced by patients considered in this appraisal was clearly an important issue from the first Appraisal Committee meeting, on which there was significant disagreement between the Committee and other stakeholders. Given that the health status of these patients was a key issue, we believe it was essential for the Committee to have appropriate input from expert clinicians and patient groups in order to consider the issues fairly. For the avoidance of doubt, the issue raised by Sanofi in this appeal is not the understanding of the EQ-5D instrument by the Committee, but our view that the utility data from the EAP are reliable.

The Committee has no specific experience in relation to the medical management of patients with metastatic prostate cancer and has seemingly based its comments on general medical knowledge or understanding rather than the informed advice of the experts. This is unfair.

1.2: The Committee has failed to properly take account of various sources of evidence provided by the manufacturer through the consultation process; or has failed to explain why these have been disregarded.

We are particularly concerned that the conclusions drawn in relation to the EAP utility data are flawed in light of the evidence presented. We have presented evidence that points to different conclusions to those expressed by the Appraisal Committee on the EAP utility data, including literature (Pickard 2007a, Pickard 2007b) and evidence from the PORTREAT registry:

This evidence has not been addressed in the FAD or otherwise refuted by the Committee (save for the inclusion of “Comment noted” in the table of comments on consultation) and accordingly the Committee’s response to these matters is unclear, suggesting that they have not been appropriately considered.

By way of example:

- In Sanofi’s response to the ACD, we addressed the relationship between utility and performance status to support the evidence we had submitted indicating that patients who participated in the EAP, would, contrary to the Committee’s view, have utility similar to that seen in the age-matched general population. There is however no indication in any of the materials provided to us to explain the Committee’s consideration of this issue and why our view was seemingly rejected.

- The evidence from PORTREAT has been misrepresented. The FAD (paragraph 4.16) states that “The Committee further noted that the PROTREAT study indicated lower utility values than the baseline utility

values from the second interim analysis of the early access programme". Given that the actual difference was in fact only [redacted] we consider that this statement misrepresents the evidence.

We assert that, as a matter of fairness, the Appraisal Committee is required to explain why it has rejected the evidence presented by Sanofi in relation to these important issues and on what basis an alternative view is preferred. This is currently absent in the FAD and we would again request that the Committee representatives explain their reasoning.

1.4: The basis for the Committee's conclusion that utility values for second-line metastatic prostate cancer process must be lower than demonstrated by EAP is unexplained

We did not receive a reply to this point in your letter of the 3 February 2012 and therefore assume that we may present it to the Appeal Panel.

Ground two: The conclusions expressed in the FAD are not reasonable in light of the evidence submitted

2.1: The description of the EAP trial was misinterpreted, resulting in perverse conclusions in the FAD.

While we agree that the Appeal Panel would have to consider whether the conclusion of the Appraisal Committee is capable of justification, as we have explained we do not believe the Committee's conclusions are reasonable.

This is not merely a difference of scientific opinion. The evidence referenced by the Committee is incorrectly described and the interpretation is not supported by the evidence presented.

We consider that the EAP trial has been incorrectly interpreted. Trial evidence forms the backbone of all NICE submissions, therefore to criticise the EAP on the basis that it is a "selected population of patients" (paragraph 4.14) and to suggest that the results may not be generalisable to the general population (paragraph 4.15), appears perverse. The EAP was a trial based solely in the UK, which was intended (as well as providing utility data) to provide early access ahead of launch to cabazitaxel, in a setting where although other active drugs are used (primarily mitoxantrone) no other drug had demonstrated a survival benefit. Therefore, there are actually likely to be fewer issues of generalisability with the EAP relative to most trials - the patients included in the EAP are likely to be highly representative of those who have gone on to receive cabazitaxel following launch. This view goes to the heart of the Committee interpretation of the EAP data and we consider it essential that this is revisited.

2.2: Data from the EAP trial, and additional contextual data from the literature, were incorrectly interpreted resulting in perverse conclusions in the FAD.

The key issue here is related to how the Committee approached data from a clinical trial. We consider it unreasonable that data from a clinical trial, which is the only clinical trial extant to have captured EQ-5D data in second-line mHRPC, should be disregarded on the basis of a belief unsupported by evidence. Given that there was no available alternative evidence in this setting at the time of the Committee meeting we consider that it is the responsibility of the Committee to provide a reason to support their assertion that the only available evidence is “implausible”. In addition to the trial data, we provided literature supportive of our data, and indeed also note that the recent abiraterone submission found similar utility values via a different methodology (mapping FACT-P to EQ-5D - academic in confidence). We therefore consider that without evidence to justify them to the stakeholders and public, the conclusions drawn by the Committee with the regard to the EAP data are unreasonable and should be changed.

Please do not hesitate to contact me if you have any further queries. I look forwards to hearing from you shortly.

Yours Sincerely

Charlie Nicholls
Head of Health Outcomes