.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 22 March 2012 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen

2. The Appeal Panel consisted of Sir Michael Rawlins and Mr Jonathan Tross (Non executive directors), Dr Lindsay Smith (NHS representative), Dr Mercia Page (Industry Representative) and Mr Peter Sanders (patient representative).

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The panel considered appeals submitted by Sanofi ("the company").

5. The Appellants were represented by Dr Jasmin Hussein, Dr Clare Proudfoot, Dr Charlie Nicholls, Dr Alison Birtle and Dr Adela Williams (solicitor, Arnold and Porter).

6. All the above declared no conflicts of interest -save that Dr Birtle confirmed that from time to time she received speaking fees from a number of pharmaceutical companies, which it was her usual practice to donate to charity. She was attending the hearing on an unpaid basis.

7. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel -Dr Amanda Adler, appraisal committee chair, Dr Ray Armstrong, appraisal committee member, Dr Mark Chakravarty, appraisal committee member, and Dr Elisabeth George, associate director, Technology Appraisals,

8. All the above declared no conflicts of interest

9. The Institute's legal adviser Mr Stephen Hocking was also present.

10. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

11. There are three grounds under which an appeal can be lodged:

- The Institute has failed to act fairly
- NICE has formulated guidance which cannot reasonably be justified in the light of the evidence submitted
- The Institute has exceeded its powers

12. The Chair of the Appeal Committee (Dr Maggie Helliwell) in preliminary correspondence had confirmed that the Appellants had potentially valid grounds of appeal as follows:

Ground 1:

"1 The committee failed to submit questions to Sanofi in relation to the evidence and prohibited Sanofi from commenting on matters of factual accuracy during the Appraisal Committee meeting; this is contrary to NICE's processes"

Ground 2:

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

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

2.3 The committee failed to understand the nature of interim data, resulting in perverse conclusions in the FAD."

13. Cabazitaxel is an antineoplastic drug belonging to a class of drugs known as taxanes. It is licensed for use in combination with prednisone or prednisolone for hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Six cycles of treatment was the median number given in the key clinical trial.

14. The appraisal that is the subject of the current appeal provided advice to the NHS on Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

15. Before the Appeal Panel inquired into the detailed complaints both Sanofi and the Appraisal Committee made preliminary statements.

16. Sanofi introduced their appeal by providing some background information on prostate cancer. They stated that it is the most common form of cancer in men in the UK and one, in the company's view, with an inadequate profile. The company explained that the aims of drug treatment are to extend life but the disease often becomes refractory to treatments designed to reduce androgen levels. Sanofi pointed out that their drug does extend life in patients whose disease has become refractory, and that it is the first product to provide significant survival benefit to patients with hormone-refractory prostate cancer previously treated with docetaxel. They re-iterated their four appeal points. In particular they stated that the committee had taken a view, unsubstantiated by evidence, whilst neglecting the company's evidence-based submission on quality of life utilities.

17. The Appraisal Committee then introduced their response to the appeal. They acknowledged that the drug extended life but that it was at too high a price for the NHS; if approved it would prevent more cost-effective care being provided for other patients with other illnesses. Further, even if the procedural point and/or the perversity points were conceded, the ICER would remain too high. They said the role of the manufacturer at the FAD meeting was limited. To support their conclusions they stated that the Scottish Medicines Group had also turned down the drug on cost grounds; that the ERG had advised the Appraisal Committee that the utility values were imprecise and implausible; and that the utility value for stable disease in a separate subsequent publication had been estimated at only 0.538. The Appraisal Committee were therefore right to be sceptical about Sanofi's utility value estimates which the Appraisal Committee had used unaltered in coming to their final ICER point estimate of 87.5K.

Appeal by Appellant

Appeal Ground 1: The Institute has failed to act fairly

Appeal Ground 1: The committee failed to submit questions to Sanofi in relation to the evidence and prohibited Sanofi from commenting on matters of factual accuracy during the Appraisal Committee meeting; this is contrary to NICE's processes.

18. Sanofi quoted paragraph 3.5.7 of the STA guide. This states that "....Manufacturer representatives...respond to questions from the Appraisal Committee and provide clarification. They contribute to the

debate with the Appraisal Committee but do not make a formal presentation to the Committee." It was a nonsense to limit the manufacturer's participation to the correction of factual inaccuracies. At the FAD meeting Sanofi had been treated unfairly because the Appraisal Committee had not followed NICE's processes and permit the company to clarify mistakes by the Appraisal Committee. Sanofi had been asked if they wanted to say anything at the end of part 1 of the meeting but when they did speak they were told that clarification was not allowed. In any case they felt that, because this was some time after the erroneous information had been discussed and which they claimed had led to the committee making erroneous conclusions, this had been unfair. After the end of part 1, Sanofi did speak to a member of the secretariat who assured them that their concerns would be passed to the chair before part 2 (the closed part of the meeting). However this did not remove the unfairness.

19. The Appraisal Committee's view was that the STA guide only requires it to ask the manufacturer to correct errors of fact. They quoted paragraph 3.4.21 of the STA guide to support this. They stated that they had asked for factual corrections and had, in fact, corrected two slides as evidence that they had complied with the process required. The secretariat had made them aware of Sanofi's concerns before part 2 of the second ACD meeting, and they had fully considered the company's views before coming to their conclusions – that the utility values were imprecise and implausible. In any event the decision not to recommend did not hang on that utility. The chair positively asserted that a manufacturer does not have the chance to tell a committee that it has "the wrong end of the stick". If a committee is completely wrong, that would amount to a factual inaccuracy and for which there was an opportunity for the company to identify and to inform the Appraisal Committee when asked.

20. Sanofi in response agreed that STA guide paragraph 3.4.21 had been followed, and that they had been engaged to the extent described by the Appraisal Committee but re-iterated their point that the STA guide paragraph 3.5.7 had not been followed. Consequently the Appraisal Committee could only have been speculating about Sanofi's concerns during part 2 of their meeting. Sanofi conceded that they had commented fully on the ACD, but the "error" had occurred later in the process. Sanofi were particularly concerned that the Appraisal Committee had made their decision whilst still misunderstanding the interim analysis. This was a new point which had not arisen from the ACD and which they should have been allowed to contest fully. Sanofi believe that STA guide paragraph 3.5.7 overrides paragraph 3.4.21 as

it makes no sense to limit a manufacturer's input when the Appraisal Committee have made an unrecognised error (ie one which the manufacturer notes but the Appraisal Committee does not). In these circumstances the manufacturer should be allowed to make a timely intervention to correct a factual error to prevent unfairness. The process guide sets out what a manufacturer can do, but not what it cannot.

21. The Appeal Panel concluded that the STA guide can and should be taken to set out definitively what the role of the manufacturer is at an FAD meeting. However, what is necessary for that role to be fulfilled fairly is a question for the Panel and ultimately for a court. The guide is at most suggestive on that question.

It is clear from the guide that the role of a manufacturer at an FAD meeting is limited. The manufacturer has already been fully engaged with at numerous points in the process prior to that meeting, beginning with the preparation of its submission, and ending with its receiving draft guidance and making comment on it. It is therefore not surprising to see a restricted role at the final meeting, and in particular not surprising that the role is limited (as the Panel finds that it is) to clarification and error checking. The principal purpose of allowing access to parts of these deliberative meetings is public transparency in a broad sense, not to allow advocacy between manufacturer and Committee.

The Panel agrees that paragraph 3.4.21 is the more relevant paragraph as it deals specifically with manufacturers. In any case the Panel does not regard paragraph 3.5.7 as being in tension with paragraph 3.4.21. Paragraph 3.5.7 was not intended to mean that the manufacturer could join in discussion at any stage because what they believed to be a misinterpretation had occurred. The first part of paragraph 3.5.7 says that the manufacturer representatives ‘respond to questions from the Appraisal Committee’ and ‘provide clarification’. That is the context for the input, consistent with paragraph 3.4.21 in seeing the role as aiding the committee rather than arguing the manufacturer case. Read as a whole the references to responding to questions and providing clarification are consistent with paragraph 3.4.21, and although the guide should not be analysed too closely, the Panel noted that the phrase used is "contribute to the debate" and not "participate in the debate". As paragraph 3.5.7 applies equally to all of clinical specialists, NHS experts, manufacturers and patient experts, it cannot have been intended to allow them all to join in discussions with the Committee.

The Panel therefore concludes that the Appraisal Committee had correctly understood the manufacturer's limited role at this meeting.

The question then arises whether the manufacturer was allowed to fulfil that limited role fairly. The Panel is aware of the need for such meetings to be chaired effectively and efficiently. Whilst it may be surprising to hear that a manufacturer is not allowed to remark, even if a Committee "has the wrong end of the stick", the Panel understood this to be shorthand for a Committee taking a view with which the manufacturer disagrees. While clearly it is important that all those inputting at a meeting are treated with courtesy and respect, the Panel agrees that dialogue of that sort is properly conducted for example through consultation on the ACD and not at the Committee meeting. If a Committee has truly fallen into material error in its proposed guidance during its meeting then it may be corrected by a manufacturer as a factual error at the time, or by an appeal panel under appeal ground 2. In this case the Panel was satisfied that the issues which the manufacturer wanted to raise during the meeting did not amount to material factual errors, and, (as an entirely secondary point,) had not affected the guidance.

22. Nevertheless, the Institute's Board will be asked to make the roles and responsibilities clearer to manufacturers (i.e. that a manufacturer is not allowed to debate factual or clarification points until invited to do so by the Chair – as was followed in this case).

23. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 2: NICE has formulated guidance which cannot be reasonably justified in the light of the evidence submitted

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

24. Sanofi highlighted the perverse conclusions in the FAD described in their appeal submission. The EAP trial patients (from which the stable disease utility values were derived) had essentially the same characteristics as the TROPIC trial patients (from which the stable disease clinical outcomes were derived). Both sets of patients were healthier than the "average" patient with mHRPC because they have to have a high (ECOG 0-1) functional status to be considered for the chemotherapy. Indeed they may have been healthier than the average age-matched man because those with various co-morbidities were excluded from both TROPIC and EAP.

25. EAP was an open label study with a relatively small number of UK

patients. However patients whose disease has progressed, but who are fit enough to have treatment, in any case form a small group. Patients in the EAP study were typical of those that would be eligible for this drug if funded. Many were taking opiates, all had metastatic disease, and some had other symptoms such as lymphoedema. Selection was the same as would apply in routine clinical practice, and they were no healthier than the "standard" patient. They all had to be fit enough to travel to receive treatment, but this would be no different from any other patient receiving the drug during routine care (or any other form of specialist care).

26. The Appraisal Committee Chair stated that there were 15 exclusions to the EAP study (in the manufacturer's submission) and so it could not be claimed that it was an unselected group of men with mHRPC. It was the open label aspect of the EAP trial that was at issue, not the self assessment inherent to the EQ-5D. Thus the Appraisal Committee were firm in their view that the utility value for stable disease, in this study, was too high. However she agreed that the statement concerning ability to travel in the FAD was a non-sequitur, and that the FAD was not well expressed at this point.

27. The Appraisal Committee did fully understand that the falling numbers of patients contributing utility values to the later cycles of the EAP trial were to be expected; they considered this in their discussions. However, they were concerned about the drop in numbers between cycles in the stable disease group, which was not accounted for by Sanofi. When the data from EAP study was subsequently presented in a conference Abstract, it appeared that most of these "drop outs" were in fact patients whose disease had progressed.

28. Sanofi were asked about the pooling of cycle 2 and cycle 4 patient utility values; and about their choice of cycle 2 for stable disease utility values (rather than baseline). Both Sanofi and the Appraisal Committee agreed that this was acceptable as a result of the pain reduction typically experienced by patients on treatment, and that this was not a point of disagreement. Sanofi pointed out that they had responded to ERG queries, re-run analyses and used the same utility values in the model for both arms.

The Committee said that it had been given, prior to the second meeting, two values for utility in stable disease (0.763 for cycle 2 and 0.762 (for cycles 2 and 4 pooled)) which closely matched the age matched figure for otherwise healthy males. There appeared, therefore, to be no decrement for those with the disease. The

Committee considered that this lacked face validity. Sanofi replied that as those with co-morbidities, which would make them unsuitable for chemotherapy were excluded, you could not simply read across from the age matched figure to the patients' figure.

29. The Appeal Panel concluded that the Appraisal Committee did understand the EAP trial. The Panel felt it was understandable that the utility values presented seemed high when compared with the age matched population, and that this could be seen to lack face validity. The Panel considered that this was a reasonable position. Equally, the Panel understood Sanofi's explanation which was also reasonable. Although some of the Committee's reasons in the FAD did not add to its overall conclusion, and could with advantage be removed, overall the Panel was not satisfied that the conclusion reached could not be justified. It was clear that the Committee had considered the issue of utility values carefully. The Panel also noted (see below) that, even with the manufacturer's utility values, the ICER would be higher than any that the Institute had ever considered to be a cost effective use of NHS resources. The Panel, moreover, reminded itself that it considered appeals against guidance rather than against any given statement in a FAD.

30. The Appeal Panel therefore dismissed this appeal point.

31. It was conceded by the Appraisal Committee that the references to: travel to hospital and self-assessment (in FAD 4.14); and to the numbers of patients in cycles 2 and 4 and the lack of peer-review (in FAD 4.15) were not relevant to their decision on which utility values to use. The Panel therefore recommends to the Guidance Executive that they should be removed from the FAD.

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

32. Sanofi stated that the EAP trial was the only study to collect utility values for patient with mHRPC and thus its utility value had to be used in the modelling. The trial patients represented men who would be eligible for NHS treatment with the drug. Their literature review had found a small number of papers which had also found utility values (0.7-0.8) similar to those observed in the EAP study. This was similar to the male general population because to be eligible for EAP/TROPIC men had to have good functional status (ECOG 0-1). Sanofi objected to the description of the EAP utility data as implausible or too high.

33. The Appraisal Committee commented that they had understood the literature and in particular the strengths and weaknesses of the papers quoted – none of which were strictly applicable. The Appraisal Committee felt that Sanofi had adopted an optimistic view of the supporting literature; they pointed out that when the PORTREAT data was subsequently published the adjusted utility value was lower than the one which was quoted by Sanofi in their original Manufacturer's Submission. The uncertainty around the stable disease utility value resulted in uncertainty about the progressive disease utility value – which was derived from the stable disease one; and then both of these issues led onto more uncertainty in the modelling. However, the ICER offered by the ERG, £87,500, was based on the manufacturer's own figures.

34. The Appeal Panel concluded that the Appraisal Committee had not incorrectly interpreted data from the EAP trial, nor the additional contextual data from the literature. The Panel understood both sides' positions and regarded them both as reasonable. The Panel reminded itself that under this ground it should only intervene if the Committee has reached a conclusion which cannot be justified. The committee has not done so. The Panel also noted that the Committee had not in fact modelled any figures other than those offered by the manufacturer, and that the guidance could not have been affected by this difference of opinion between Committee and manufacturer.

35. The Appeal Panel therefore dismissed this appeal point

Appeal Point Ground 2.3: The committee failed to understand the nature of interim data, resulting in perverse conclusions in the FAD.

36. This matter had already been covered in detail in earlier discussions. Sanofi believed that the Appraisal Committee had not understood the interim data analysis and that had led the Appraisal Committee to make a judgement based on incorrect interpretation (see above, paragraphs 27 and 28).

37. The Appraisal Committee stated that they fully understood the interim data even though Sanofi felt that this could not be possible as Sanofi had not been permitted to correct factual “errors” which they had noted in part 1 of the second Appraisal Committee meeting.

38. The Appeal Panel concluded that the Appraisal Committee had not failed to understand the nature of interim data.

39. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 3: The Institute has exceeded its powers

40. There was no appeal under this ground.

Conclusion and effect of the Appeal Panel's decision

41. The Appeal Panel dismissed all the grounds for appeal in this appraisal.

42. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.