NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Appraisal of Paclitaxel for Ovarian Cancer

Decision of the Appeal Panel

1. Introduction

1.1 The Appeal Panel convened a hearing on 12th November 2002 to consider appeals against the Institute's Guidance to the NHS on paclitaxel in the treatment of ovarian cancer ("the Guidance") as set out in the Final Appraisal Determination produced by the Appraisal Committee ("the FAD").

1.2 The Appeal Panel comprised Professor Anthony Culyer (chair of the Appeal Panel and non-executive member of the Institute's Board), Professor Sir Michael Rawlins (chair of the Institute's Board), Ms Mercy Jeyasingham (non-executive member of the Institute's Board), Ms Gill Donovan (patient representative) and Dr Angus Sim (industry representative).

1.3 The appeal was lodged by Bristol-Myers Squibb ("BMS")

1.4 The following individuals involved in the appraisal were present to answer questions from the Appeal Panel: Ms Anne-Toni Rodgers (NICE Executive Lead), Dr David Murray (NICE Technical Lead), Professor David Barnett (NICE Appraisals Committee Chair), Dr Karl Claxton (NICE Appraisals Committee Member), Dr Carole Longson (NICE Appraisals Programme Director), Ms Nina Pinwill (NICE Technology Appraisals Project Manager on behalf of Ms Kathleen Dalby) and Mss Cathryn Fuller and Cecelia O'Halloran (Technology Appraisal Administrators).

1.5 The three grounds upon which the Appeal Panel can hear an appeal are:

(1) The Institute has failed to act fairly and in accordance with the Appraisal Procedure set out in the Interim Guidance for Manufacturers and Sponsors;

(2) The Institute has prepared guidance which is perverse in the light of the evidence submitted;

(3) The Institute has exceeded its powers.

2. **Appeal Ground One: The Institute has failed to act fairly and in accordance with the Appraisal Procedure**

2.1 The Preparation of the Assessment Report raises the suggestion of bias.

Under this ground BMS referred to the fact that two of the five external reviewers of the Assessment Report carried out data analysis and were members of the writing committee for the ICON-3 study. NICE itself, in a letter of 18 July 2002, accepted that lack of bias in the information received by the Appraisals Committee is important. In addition, the situation in relation to the reviewers contrasted with the approach of the Appraisal Committee itself. Dr Bird, a member of the Appraisals Committee who is also an employee of the Medical Research Council (MRC) under whose auspices the ICON-3 study was conducted, withdrew from the Appraisals Committee when paclitaxel was under consideration. An objective observer would conclude that the position of the reviewers gave rise to a real danger of bias, and the production of the Report infringed the EU requirement that evidence giving rise to public health decisions must be founded on the principles of independence, transparency and excellence (reference the case of Pfizer Animal Health SA v Council of the European Union (Case T-13/99).

The Panel enquired of the Appraisals Committee Chair the role played by reviewers. It was explained that these were reviewers used by the researchers who prepared the Report under contract to the NHS Research & Development Programme. They are part of a quality assurance package and the extent of their input into the final Report varies from case to case. In this case, they made only minor comments on the draft Report.

The Panel acknowledged the importance of clear, objective evidence to the Appraisal Committee in performing its task. The Panel gained no assistance from the Pfizer case in determining the standards of independence or objectivity to be met by the Report, as the case did not cover in detail the question of from whom evidence must be independent. However in any event the Panel did not consider that the role of the two reviewers in question in relation to the Report had resulted in a Report which was biased or nonobjective. Further, as regards UK law, the Panel noted that the Report was evidence considered by the Committee, but that it was the Appraisal Committee as decision-maker which was subject to the test for bias. It is in the nature of the Appraisals Committee's work that it should consider possible biases in any and all the evidence it received and that as an expert body the Committee is well-equipped to detect and respond to any suspected bias in the evidence before it, in order to reach its own unbiased decision. In this case, the Committee had been aware of the background of the two reviewers in question and had satisfied themselves that their involvement in the ICON3 report had not led to bias in the Assessment Report. The Panel found no evidence of bias arising from the role of the two reviewers in question and was satisfied by the Committee's competence to detect it, had it existed. The Panel therefore concluded that the Report itself had not been unfairly produced or relied upon, and that an objective observer would not consider

that there was a real danger that the Committee had been biased as a result of the involvement of the two Reviewers in question.

On Dr Bird's role, the Panel was told by the Chair of the Appraisals Committee that her grounds of withdrawing were related to her personal asset holdings rather than her employment with the MRC. Indeed, the Panel felt that, while her withdrawal may have been appropriate in this case, to require as a general principle that an employee of the MRC ought to withdraw when disputable evidence has been funded by an MRC grant is much too strong a requirement. It would have the effect of depriving the Appraisals Panel of one of the UK's outstanding sources of technical expertise in cases that were bound, given the immense importance of the MRC as a funder of medical research, to crop up with great frequency. The threat to the quality of the Committee's decision-making was seen as considerable. The Panel felt that a clear declaration of a "non-specific interest" was sufficient in the majority of cases, unless the employee in question had played a key role in the research under discussion.

<u>The Appeal Panel therefore did not uphold the appeal on this point.</u>

2.2 The appraisal process lacks transparency.

At the hearing BMS did not proceed with the specific contention that Directive 89/105/EC applies to the appraisal process and had been breached in this case. The Panel did not therefore consider this point further.

BMS did proceed with the contention that the FAD was not sufficiently transparent, in that it does not make clear the reasons for the change in the guidance proposed since the previous appraisal. In particular BMS considered that the FAD gives insufficient explanation as to the weight given to the results of the ICON-3 study over those of the other studies reviewed in the evidence before the Appraisals Committee. The statement in paragraph 4.1.4 of the FAD that cross-over was unlikely to be sufficient to explain the differences between the results of GOG-132 on the one hand and of GOG111 and OV-10 on the other was insufficient to explain the weight attached by the Committee to GOG-132 as corroborating the results of ICON-3. It is not clear in the FAD whether the Appraisal Committee were aware and took account of the widespread criticisms of the ICON-3 study. The consequence of the lack of transparency is that BMS cannot make a proper response to the issues.

There were four studies having a bearing on the appraisal, each of which was described in the FAD in more detail than is often the case.

The four studies are referred to as ICON-3, GOG-132, GOG-111 and OV-10. Of these trials, the ICON-3 trial had the largest sample of women taking the relevant courses of treatment (paclitaxel in combination with a platinum-based compound compared with a platinum-based compound alone). The FAD shows that ICON-3 had results that were broadly similar to those of GOG132,

finding no statistically significant difference in progression-free survival, overall survival, or in some adverse events such as depression and anxiety. Paragraph 4.1.6 of the FAD states that, with respect to other side-effects all four studies indicated that these effects were worse with the combination treatment. The FAD acknowledges the differences between the design of the trials and the fact that matters such as patient cross-over between treatments, in all the studies, made interpretation of the trial results harder. There was a long and detailed discussion at the appeal hearing about the Committee's approach to these four studies. The Panel considered that most of this discussion was relevant to the question of perversity, i.e. whether the Guidance was perverse in light of the evidence before the Committee, rather than to the fairness issue under the first ground of appeal. That discussion is therefore dealt with in the next section of this decision. Under Ground One, the Panel considered whether the reasoning in the FAD was sufficiently unclear as to constitute a reason to uphold the appeal on the ground of NICE acting unfairly and not in accordance with its own procedures. The Panel did not consider that the FAD had to give exact indications of the levels of weight attached to different studies, as long as the Committee's analysis of evidence was clear and that the reasoning behind the decision could be followed in the FAD. The Panel considers that the detail contained in the FAD about the four studies sets out the view taken by the Committee of each of the four studies, and makes clear both the various limitations of the four studies and that the Committee was aware of these limitations. BMS had been able to engage fully with the issues in the FAD.

The Appeal Panel therefore did not uphold the appeal on this point.

2.3 NICE 's use of the superseded interim guidance rather than the revised appraisal procedures for this review is unfair.

BMS contended that it had not been made clear to them that the old procedure, i.e. the Interim Guidance, would be used in relation to this appraisal. BMS contended that the use of the old procedures was unfair (because the replacement of those procedures indicated that the Institute agreed that the old procedures were flawed). BMS also referred in particular to the fact that the use of the old procedure had allowed them only 10 days to issue an appeal rather than 15, and contended that NICE's decision to refuse an extension to the appeal period when it fell during the August holiday period was unfair.

The Panel did not consider that the introduction of new appraisal procedures indicated that the old procedures must have been unfair. NICE regards the new procedures as an improvement, but no basis was given by BMS for the suggestion that the old procedures were unfair or flawed in themselves. The Panel did not consider that, where a revised process was introduced, the Institute was required to change the procedure in the middle of an appraisal. The Panel considered that the questions under this ground of appeal were whether the procedure applied was correct in that it was in accordance with the Institute's policy on the use of the procedures, and whether the appellants were given full and correct information about the procedure which was to be followed. It became clear at the hearing that the new procedures could not

have been applied to the review of paclitaxel because they had not at the time (prior to 6 February 2001) been approved by the Board of NICE. NICE therefore had no choice but to operate under the procedures that applied at the time. The Institute's policy is that only appraisals commenced after 6 February 2001 will be subject to the new procedures. In addition, the procedures that would apply in this case had been clearly set out in a series of letters from NICE to BMS, in particular the letter dated 21 January 2001 which enclosed a copy of the Interim Guidance.

At the hearing BMS confirmed that it had not been prejudiced in its ability to present a full appeal by the fact that it was subject to an appeal period of 10 days rather than 15 days. In any event the Panel considered that the period of 10 days was the correct period under the relevant procedure and that the decision by the Institute not to extend this period at BMS's request was not unreasonable or unfair in all the circumstances.

The Appeal Panel therefore did not uphold the appeal on this point.

3. **Appeal Ground Two: The Institute has prepared guidance which is perverse in the light of the evidence submitted.**

3.1 It was perverse to have given ICON-3 and GOG-123 equal weight to the GOG-111 and OV-10 studies.

BMS contended that the FAD provided no information as to any differential weight it had attached to data but it was perverse to attach equal weights to studies having such different characteristics and quality. As regards the weight given to ICON-3, BMS contended that this was perverse given the many criticisms of and concerns about that trial, including the fact that its source data had not been verified, the lack of certainty about the dosage used, the fact that it included patients with disease stages outside Paclitaxel's licensed indications and the fact that limited evidence of adverse events had been collected from some centres.

The Panel asked the members of the Appraisal Committee present at the hearing whether they had been aware of the criticisms of ICON-3. It was plain from the detailed discussion which ensued that the Appraisal Committee had been very aware of the methodological issues raised by these four studies and had considered them in detail and at length before reaching its decision on the appropriate Guidance.

The Panel was clear that the scopes and methodological differences between the four studies, including the limitations of ICON-3, were well understood by the Appraisals Committee. Although the Committee did not state any explicit weight to be attached any of the studies (equal or otherwise), the Panel did not consider this to be perverse. The exercise of the Committee's judgment in complex matters such as these, involving both scientific judgments and social value judgments, may not be helped by the explicit assigning of weights to individual items of evidence.

The Panel noted that, when asked whether reliance on ICON-3 was the sole reason for the change in the Guidance on paclitaxel, Professor Barnett responded that the Committee had given ICON-3 weight as a significant piece of new evidence, which could not be ignored, even though there were concerns about its conduct which also had to be considered. However, the results of ICON-3 were not the sole reason in themselves for the change in the Guidance. Rather, ICON-3 had added to the process of analysis and consideration. The Panel considered that this approach was not perverse, given that (as indicated above) the Committee clearly indicated how they had taken account of the flaws in ICON-3, and given that the effect of the Guidance proposed by the Committee was not to preclude the use of paclitaxel in combination, but only to provide a choice between the combination therapy and the alternative. The Panel noted that the conclusion of the Committee from ICON3 and the other studies was not that the combination therapy should not be used, but only that it should not be assumed to be the main therapy. On that basis it considered that the weight given to ICON-3 by the Committee was not perverse.

The Panel considered that the reasons adduced by the Committee in paragraphs 4.3.2, 4.3.3 and 4.3.4 of the FAD are reasons that appear to the Panel to be plausible and rational and not perverse in the light of the evidence.

<u>The Appeal Panel therefore did not uphold the appeal on this point</u>.

3.2 The summary of the GOG-11 study (FAD paragraph 4.1.2) is inaccurate, misleading and therefore perverse.

On investigation, it became plain that the discrepancy in the data used by the Committee and that considered by BMS to be the appropriate data arose from the use by the Committee of pre-publication material which had been slightly altered in the later published form. It was agreed by both the NICE Appraisals Committee members present and BMS that the Institute's Guidance would quote the published data and the published version of the authors' conclusions. The parties agreed that the differences in the data did not materially affect the reasoning being set out in the FAD, and BMS indicated that this action would satisfy it on this point.

3.3 The wording of the FAD does not explain why the Appraisals Committee discounted the patient cross-over between treatments in the GOG-132 study as explaining the difference in its findings as compared to GOG-111 and OV-10.

The Panel questioned the members of the Appraisal Committee to ascertain why the statement had been made in the last sentence of paragraph 4.1.4 of the FAD and whether the cross-over features of this study had been fully considered. Dr Claxton referred to the GOG-132 paper itself, in which the authors had stated that they could not draw the conclusion that the difference was due to cross-over, and went on to consider other possible reasons such as toxicity. Although it is true that the FAD does not give a detailed

explanation for the statement about the cross-over effect, given the explanation given by the Committee at the hearing and the clear indication in the FAD and at the hearing that the features of the four studies had been considered in detail by the Committee, the Panel did not think that the conclusion the Committee reached was perverse nor that its failure to discuss in detail in the FAD the weight attached to this particular element of this particular trial was perverse.

The Panel recognises that the Committee has a difficult task in determining the degree of detail to be included in a FAD and that there will always be an element of judgment involved in the decision. To be perverse, however, the degree of detail omitted would have to have been of an extent, and of a significance for the recommendations made, as to be thought perverse by a reasonable member of the Appraisals Committee.

The Appeal Panel therefore did not uphold the appeal on this point.

4. Appeal Ground Three: The Institute has exceeded its powers

4.1 The appellant did not appeal under this ground.

The Appeal

5. The appeal is not upheld on any point. The Panel therefore anticipates that the FAD will be issued as the Institute's Guidance to the NHS, subject to the amendment of the data references referred to under paragraph 3.2 above.

6. There is no possibility of a further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal panel and a decision by the Institute to issue the Guidance may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this Decision or the issue of the Guidance.