NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal:
Appraisal of pemetrexed for the treatment of malignant pleural mesothelioma

Decision of the Panel

1. Introduction

An Appeal Panel was convened on 23rd November 2007 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of pemetrexed for the treatment of malignant pleural mesothelioma (MPM).

The Appeal Panel consisted of Professor Sir Michael Rawlins (chair of the panel and chair of the Institute), Ms Jennie Griffiths and Mr Frederick George (non-executive directors of the Institute), Dr Angus Simms (industry representative) and Ms Alison Hawdale (patient representative).

The Panel considered appeals submitted by the Royal College of Physicians and the Association of Clinical Oncologists (jointly) and by Birmingham East and North Primary Care Trust.

The following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor Andrew Stevens (chair of the Appraisal Committee), Professor David Barnett and Dr Peter Clarke (members of the Appraisal Committee), Dr Carole Longson (Director, Centre for Health Technology Evaluation), Jane Robertson (technical lead).
The Institute's legal advisor (Mr Stephen Hocking, Beachcroft LLP) was also present.

The appellants were represented by:

- Dr Michael Snee for the Royal College of Physicians and the Association of Cancer Physicians(RCP/ACP);
- Dr Daphne Austin, Ms Claire Cheong-Leen, Ms Sophia Christie, Mr David Lock and Ms Jane Williams for Birmingham East and North Primary Care Trust (the PCT).

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

There are three grounds on which a panel can hear an appeal:
Ground 1: The Institute has failed to act fairly and in accordance with its published procedures;

Ground 2: The Institute has prepared guidance which is perverse in light of the evidence submitted;
Ground 3: The Institute has exceeded its legal powers.

The Appellants were invited to make introductory remarks before each of the grounds of appeal was considered separately. Having heard the opening comments from the Appellants, the Panel then considered the Appellants' case in further detail.

2. Ground 1: The Institute has failed to act fairly and in accordance with its published procedures

2.1 The PCT claimed that the Appraisal Committee had failed to act in accordance with the Institute's *Guide to the Methods of Technology Appraisal* (paragraph 5.3.1.2) in the choice of comparators. Paragraph 5.3.1.2 requires the reference case to consider as a comparator 'alternative therapies routinely used in the NHS'.

The PCT pointed out that FAD paragraph 4.3.3 stated *"Clinical specialists advised that cisplatin monotherapy would not be normally used to treat MPM in clinical practice in England and Wales because of a lack of evidence of its effectiveness and its relatively unfavourable adverse-effect profile".* In the light of this statement the PCT claimed that, in comparing pemetrexed plus cisplatin, with cisplatin alone, the Appraisal Committee had failed to apply the Institute's processes. Rather, the Appraisal Committee should have based its conclusions on a comparison of pemetrexed with active symptom control (ASC) which is routinely used in the treatment of MPM.

Professor Stevens explained that the evidence received by the committee showed that in the NHS, clinical practice in the treatment of MPM varies widely and that there is no standard comparator. Current practice includes the use of cisplatin or vinorelbine, the combination of mitomycin, cisplatin and vinblastine (MVP), as well as ASC without chemotherapy. The Appraisal Committee had explored the appropriateness of various comparators that had been used in the economic modeling but had concluded that most were subject to very considerable uncertainty. The Committee had concluded that the most robust comparison was with cisplatin; and they had therefore considered the most plausible comparison was between cisplatin and pemetrexed plus cisplatin.

Professor Stevens also pointed out that the current text of the Institute's *Guide to the Methods of Technology Appraisal* was unhelpful in advising on the choice of appropriate comparators. Paragraph 5.3.1.2 dealt with the "reference case", but other analyses were permitted. Paragraph 5.3.2 referred to the comparators being defined in the scope, and Panel noted that the original scope of the appraisal had included cisplatin as one possible comparator.

The Appeal Panel accepted the difficulties facing the Appraisal Committee in its choice of comparators and considered that, in all the circumstances, it had not breached the Institute's published procedures in electing to use cisplatin as the comparator in this instance.

The Appeal Panel therefore dismissed the appeal on this point.

2.2 The PCT alleged that the Appraisal Committee had failed to explain the full reasoning behind its decision to recommend that pemetrexed plus cisplatin should be made available to some patients with MPM. In particular, the Committee had not fulfilled the requirements of the Institute's *Guide to the Methods of Technology Appraisal* (paragraphs 6.2.6.10 and 6.2.6.11) as:

a) the final incremental cost effectiveness ratio (ICER) that would have underpinned the Committee's conclusions on cost effectiveness had not been disclosed in the FAD;

b) it was unclear as to whether the final ICER was based on 4, 5 or 6 cycles of treatment; and

c) it was unclear as to whether, or how, the Committee had considered the adverse effects of treatment.

Professor Stevens stated that the Committee had concluded that the most plausible ICER (for pemetrexed plus cisplatin in comparison with cisplatin alone) was significantly less than the figures discussed in the FAD (including in paragraph 4.3.8) as a result of the factors set out in the first sentence of FAD paragraph 4.3.11.

Professor Stevens indicated that, taking account of all three factors in the first sentence of FAD 4.3.11, the most plausible ICER – in the judgment of the Committee – would have been in the region of £28,000 to £29,000 per quality adjusted life year (QALY). The Committee could have requested a further economic assessment but, in view of the additional time this would have taken, it concluded that such a step was unnecessary and unreasonable; and that the Committee was confident in concluding that the ICER would have been less than £30,000. Having reached this conclusion, the Committee did not believe it was necessary to state the precise ICER figure in the FAD.

Professor Stevens also pointed out that the Appraisal Committee had given significant consideration to the substantial toxicity of the combination of pemetrexed and cisplatin. This was a component of the Committee's consideration of the quality of life in patients with MPM undergoing treatment with pemetrexed plus cisplatin. It was also reflected in the Committee's advice that this treatment should only be offered to patients with a WHO performance status of 0 or 1.

Dr Clarke explained that the therapeutic response to pemetrexed plus cisplatin was most likely to be seen after the first two or three cycles; but that the burden of toxicity would be more apparent with continuing treatment. He explained that patients who had failed to respond after two or three treatments would not typically be offered further cycles of treatment. This, he indicated, was the practice adopted by oncologists in the treatment of non-small cell lung cancer; and he was in no doubt that oncologists specializing in the management of malignant diseases of the chest would adopt the same paradigm in the management of patients with MPM undergoing chemotherapy with pemetrexed plus cisplatin. This approach had, moreover, been confirmed by the experts advising the Appraisal Committee.

The Appeal Panel accepted that it was necessary for the Appraisal Committee to exercise its judgment in assessing the cost effectiveness of pemetrexed in the treatment of MPM. It agreed that, although the Committee had not specified the ICER it had used in reaching its conclusion in respect of the treatment (and, indeed, it had not calculated a precise ICER), the reasoning the Committee had applied was clear from the FAD and its overall approach and conclusions were valid. Thus, the Committee had not departed from the Institute's published procedures; nor had it acted unfairly.

The Appeal Panel considered the approach that the Appraisal Committee had adopted in its review of the numbers of cycles that should be incorporated in the economic evaluation of pemetrexed. The Panel did not believe that the Committee's analysis of the appropriate number of cycles was unclear. The Panel considered whether the guidance should recommend a maximum of 4 treatment cycles but concluded that, in all the circumstances, the guidance was not unfair or perverse. The Panel did not believe that the Committee's alleged failure to stipulate a maximum number of treatment cycles meant that it was not possible to understand the Committee's reasoning in respect of the ICER or its overall recommendation. Thus, in considering the appropriate number of cycles, the Committee had not departed from the Institute's published procedures nor had it acted unfairly.

The Appeal Panel also accepted that the Appraisal Committee had taken a full and appropriate account of the adverse reaction profile of treatment with pemetrexed plus cisplatin in the development of its guidance; and that in doing so the Committee had not acted unfairly.

Overall, the Appeal Panel concluded that the Appraisal Committee had met its obligations as indicated in the Institute's *Guide to the Methods of Technology Appraisal* (paragraphs 6.2.6.10 and 6.2.6.11). It was also clear to the Panel that the Committee had used its best endeavours in exploring the opportunity costs associated with this appraisal and that it had not acted unfairly.

The Appeal Panel therefore dismissed the appeal on all these points.

2.3 The PCT alleged that the Appraisal Committee had failed to take account of the principles of the Institute's *Social Values Judgments: Principles for the Development of NICE Guidance".* The PCT claimed that, in reaching decisions about treatment, the Institute should assess treatments as they present and irrespective of the circumstances which led patients to contract the condition.

The Appeal Panel noted that although it is a useful and relevant reference document, *Social Value Judgments* is not part of the Institute's published procedures for technology appraisals. As a rule, therefore, failure to adhere to it or to follow its guidance will not, of itself, be a valid Ground 1 appeal point. Furthermore, the question of whether the concepts in *Social Value Judgments* have or have not been adhered to will often not be suitable for determination on appeal. However an alleged failure to consider *Social Value Judgments* at all could be raised as a Ground 1 point, and it would at least be advisable for an Appraisal Committee to explain any marked departure from the guidance it contains.

The PCT complained that, in reaching its recommendation, the Appraisal Committee appeared to have taken in to account the "deservedness" of patients with an occupational disease. This, in the view of the PCT, was an irrelevant consideration. The PCT also contended that the "Rule of Rescue" should play no part in the allocation of treatment in the NHS and, in this instance, pemetrexed could not be considered to alter the prognosis of MPM.

Professor Stevens confirmed that the Appraisal Committee, in reaching its conclusion in respect of the use of pemetrexed in the National Health Service (NHS), had taken into account only those matters in the first sentence of FAD paragraph 4.3.11. Those matters listed in the second sentence of paragraph 4.3.11 were noted by the Committee but were not determinative to its recommendation. He also confirmed that the Committee had not applied the Rule of Rescue. The Committee's reference to the occupational aetiology of MPM, in the second sentence of FAD paragraph 4.3.11, was contextual.

The Appeal Panel accepted Professor Stevens' reassurance.

The Appeal Panel therefore dismissed the appeal on this point but, to avoid any misunderstanding, requests the Guidance Executive to place each of the second and third sentences in FAD paragraph 4.3.11 in separate paragraphs (i.e. to create new paragraphs 4.3.12 and 4.3.13).

3. Ground 2: NICE has prepared guidance that is perverse in the light of the evidence submitted

3.1 The RCP/ACP alleged that the statement in FAD paragraph 1.1 that *"Pemetrexed is recommended as a treatment option for malignant pleural*

mesothelioma [MPM] only in people who have a World Health Organisation performance status of 0 or 1, who are considered to have advanced disease, and for whom surgical intervention is considered inappropriate" was perverse. The RCP/ACP claimed that many patients with MPM will have "surgical interventions" such as VATS pleurodesis.

Professor Stevens accepted that the phrase "surgical intervention" in FAD paragraph 1.1 was erroneous and that it should be replaced with the phrase "surgical resection". The Appellant stated that this change would fully meet the objection raised.

The Appeal Panel dismissed the appeal on this point but requests the Guidance Executive to substitute the phrase "surgical resection" for "surgical interventions" in FAD paragraph 1.1.

3.2 The RCP/ACP claimed that the guidance in FAD paragraph 1.1 was perverse as it would preclude the use of pemetrexed in patients who were candidates for clinical trials involving chemotherapy plus surgical resection (e.g. the MARS and MESO studies).

Professor Stevens stated that the guidance was for patients undergoing routine treatment under the NHS and did not preclude the use of pemetrexed in clinical trials.

The Appeal Panel was satisfied that this guidance applied only to patients undergoing routine NHS care and not to those who were participating in clinical trials.

The Appeal Panel therefore dismissed the appeal on this point.

3.3 The PCT alleged that the Appraisal Committee had acted perversely in recommending pemetrexed for the treatment of MPM as:

a) the Committee's conclusions had been based on the results of only one randomised controlled trial (RCT). There was thus considerable uncertainty especially as this trial was not against ASC;

b) there was insufficient objective evidence from that RCT that pemetrexed plus cisplatin was clinically better than ASC; and

c) it was wrong for the Committee to be influenced by the fact that MPM is a rare condition or an 'aggressive malignancy'.

Dr Clarke explained that there were only three published RCTs of chemotherapy in the treatment of MPM. One was seriously underpowered; one was a comparison of raltitrexid plus cisplatin against cisplatin alone; and the third was the EMPHACIS trial that underpinned the present appraisal. Although additional

studies would have been advantageous, the Committee had had to draw its conclusions based on the available evidence.

Professor Stevens stated that the Appraisal Committee had concluded that the QALY gain for patients with MPM would have been likely to have been greater than that incorporated in the economic model and assumed in the original appraisal. The Committee had accepted that the symptomatology of MPM was different from that of lung cancer; and that the utility gain, derived from the treatment of patients with lung cancer, was likely to be different from patients with MPM. In the absence of any direct evidence about the utility gain that patients with MPM would derive from treatment with pemetrexed plus cisplatin, the Committee had had to exercise its best judgment.

The Appeal Panel recognized the obligations of the Institute and its advisory bodies to ensure that its guidance provides for the efficient use of NHS resources. Nevertheless, it considered that the Appraisal Committee had had to undertake its appraisal of pemetrexed in the light of the available evidence. Whilst it agreed that additional studies would have reduced the uncertainty facing the Committee, the Panel did not believe that the Committee's conclusions in relation to the EMPHACIS trial were perverse in the light of the evidence available to it.

In respect of the consideration by the Committee of the fact that MPM is a rare and aggressive malignancy, the Appeal Panel reminded itself of Professor Stevens' comments in Section 2.3 above and of its own discussions. In the light of these considerations, the Panel did not consider that the fact that the Committee noted that MPM was a rare and aggressive malignancy was perverse in the light of the evidence submitted.

The Appeal Panel therefore dismissed the appeal on all these points.

3.4 The PCT alleged that the Appraisal Committee had acted perversely by taking into account the fact that MPM is typically contracted via occupational exposure. The PCT argued that, in reaching decisions about treatment, the Institute should assess treatments as they present and irrespective of the circumstances which led to them contracting the condition. By taking into account occupational exposure, the Institute risks discriminating against patient groups and/or on gender grounds.

The Appeal Panel reminded itself of Professor Stevens' comments in Section 2.3 above and of its own discussions. In the light of these considerations, the Panel did not consider the Appraisal Committee's recommendation of pemetrexed was perverse.

The Appeal Panel therefore dismissed the appeal on this point.

3.5 The PCT alleged that the Appraisal Committee's choice of comparator was perverse. Rather than cisplatin, the appropriate comparator was best supportive care.

The Appeal Panel reminded itself of Professor Stevens' comments in Section 2.1 above and of its own discussions. In the light of these considerations the Panel did not consider that the Committee's conclusions as to the appropriate comparator were perverse.

The Appeal Panel therefore dismissed the appeal on this point.

3.6 The PCT alleged that the Appraisal Committee had acted perversely in basing its conclusions on the "potential availability of a 100mg pemetrexed vial" due to uncertainties about the availability and price of the 100mg vial.

Professor Stevens explained that the manufacturer (Eli Lilly) had given an undertaking to make a 100mg vial of pemetrexed available. It was reasonable to assume this would reduce the acquisition cost of the product because of less wastage of the drug substance when treating those patients for whom a 500mg dose was excessive. Although the manufacturer had originally agreed to make the 100mg product available by the end of 2008, it was now expected to appear on the market during the first quarter of 2008. Professor Stevens explained that to have declined to adopt an economic assessment based on a 100mg vial would have meant that the Appraisal Committee would have been required to re-consider the product in about 3 months time. This, he claimed, would have represented an inappropriate use of both the Committee's time and the Institute's resources. In response to questioning by the Appeal Panel he stated that the guidance was not predicated on the availability of the 100mg vial strength and that the Committee would have recommended the treatment even had the 100mg vial not been promised to be available.

Professor Stevens explained that the manufacturer had stated that the cost of the 100mg vial would, on a mg basis, be the same as that of the 500mg vial.

Having considered the PCT's argument and the comments of Professor Stevens, the Appeal Panel accepted that the account taken of the potential availability of the 100mg vial and the acquisition costs thereof when considering the cost effectiveness of pemetrexed plus cisplatin was not perverse in the light of the evidence submitted.

The Panel considered whether the implementation of the guidance should await the availability of the 100mg vial but concluded that as the Committee's recommendation was not based on the availability of the 100mg vial this should not be done.

The Appeal Panel therefore dismissed the appeal on this point.

4. Ground 3: The Institute has exceeded its legal powers.

4.1 The PCT alleged that the Institute had exceeded its powers as a result of the recommendation by the Appraisal Committee of a treatment in a form that was presently unavailable (the 100mg vial).

The Appeal Panel reminded itself of Professor Stevens' comments in Section 3.6 above and of its own discussions. It particularly noted the fact that the 100mg vial is due to be available in early 2008. It was of the view that the Appraisal Committee had not mandated use of the 100mg vial (with the result that the 500mg vial could be used until the 100mg vial is available).

The Appeal Panel dismissed the appeal on this point.

4.2 The PCT alleged that the Institute had exceeded its powers as, by recommending treatment for a disease that is contracted by occupational exposure, the Committee had, in effect, sought to use the NHS as a form of 'quasi-statutory compensation' for occupationally-contracted diseases'.

Following questioning from the Appeal Panel, the Appellant explained that its argument, in essence, was not that the effect of the Appraisal Committee's recommendation was to create a quasi-statutory compensation scheme for occupationally-contracted diseases but that, in taking into account the fact that MPM is occupationally-contracted, the Appraisal Committee had taken into account an irrelevant consideration.

The Appeal Panel therefore regarded this point to fall more appropriately within Ground 1 than Ground 3. It noted its own conclusions in relation to Section 2.3 above.

The Appeal Panel therefore dismissed the appeal on this point.

5. Conclusion

The Appeal Panel rejects this Appeal on all of the points put forward by the Appellants. It does, however, request the Guidance Executive to:

- replace the words 'surgical intervention' in paragraph 1.1 of the FAD with 'surgical resection'; and
- place each of the second and third sentences in FAD paragraph 4.3.11 in separate paragraphs (to create new paragraphs 4.3.12 and 4.3.13).

There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel 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 issuing of the Guidance.