

# **NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

## **Appraisal of pemetrexed disodium in the treatment of non-small-cell lung cancer**

### **Decision of the Appeal Panel**

#### **Introduction**

1. An Appeal Panel was convened on 6<sup>th</sup> June 2007 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of pemetrexed disodium in the treatment of non-small-cell lung cancer.
2. The Appeal Panel consisted of Professor Sir Michael Rawlins (chair of Panel and chair of the Institute), Ms Mercy Jeyasingham (non-executive director of the Institute), Dr Kate Lloyd (industry representative), Professor Robin Ferner (NHS representative) and Mr Bob Osborne (patient representative).
3. The Appeal Panel considered an appeal submitted by:
  - Eli Lilly and Company Limited
4. Eli Lilly were represented by Dr Adela Williams (Legal Advisor), Ms Jessamy Watkins (Head of HTA and Health Outcomes), Ms Mersha Chetty (Health Outcomes Advisor) and Dr Gary Middleton (Consultant Medical Oncologist).
5. In addition, 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), Dr Carole Longson (Director, Centre for Health Technology Evaluation), Mr Meindhert Boysen (Associate director, Centre for Health Technology Evaluation), Dr Louise Longworth (Technical Lead), Dr Peter Clark (Appraisal Committee member) and Professor Adrian Bagust (Liverpool Reviews and Implementation Group).
6. The Institute's legal advisor (Mr Julian Gizzi, Beachcroft LLP) was also present.
7. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and a number were present at this appeal.
8. 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 procedures as set out in the Institute's Guide to the Technology Appraisal Process;
  - 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.

9. The chair of the appeals committee (Mark Taylor, vice-chair of the Institute) had confirmed that the appellant had potentially valid grounds of appeal under Ground 1.

**Appeal Ground One: The Institute has failed to act fairly and in accordance with its procedures as set out in the Guide to the Technology Appraisal Process**

**Appeal Eli Lilly 2.1.1: Two of the clinical experts were unable to provide a perspective in relation to pemetrexed disodium.**

10. The appellant claimed that because two of the clinical experts had failed to provide a perspective in relation to the use of pemetrexed for non-small-cell lung cancer, there was a procedural flaw in the appraisal process. The appellant pointed out that the Guide to the Methods of Technology Appraisal (paragraph 4.4.3.2) indicates such experts are chosen *“on the basis of the extent and nature of their experience of the technology, the disease and the services provided to the NHS to patients with the condition(s) that the technology is designed to treat”*.
11. Professor Stevens stated that, under the Single Technology Appraisal (STA) process, the main evidential basis for the Appraisal Committee’s review of a technology was the manufacturer’s submission. The clinical experts were expected, primarily, to describe the context in which the product would be used. He would not expect the clinical experts to have personal experience of the use of the product because, in the case of technologies appraised under the STA programme, these would not necessarily be generally available.
12. The Appeal Panel considered, overall, that the clinical experts had provided the Committee with an appropriate context for this appraisal. The Panel accepted that, in the case of new products in the STA programme, it would be unreasonable to expect clinical experts necessarily to have personal experience with the technology. The Panel also considered that appropriate experts might fulfil some, though not all, of the criteria in the Guide to the Methods of Technology Appraisal (paragraph 4.4.3.2), which Guide is not, in any event, generally intended to be prescriptive. The Appeal Panel did not therefore consider that there had been any procedural unfairness.
13. The Appeal Panel therefore dismissed the appeal on this point.

**Appeal Eli Lilly 2.1.2.1: The Appraisal Committee has provided no explanation for its conclusion that changes to the mean body surface area (BSA) used for the economic calculation would not substantially change the incremental cost-effectiveness ratio (ICER).**

14. The appellant alleged that the Appraisal Committee had failed to explain adequately its apparent acceptance of the Expert Review Group’s approach to determining the dosage of pemetrexed likely to be used in routine clinical practice. In particular, the company claimed that a maximum of 2 vials (1000mg) would be used by oncologists, in treatment programmes, irrespective of patients’ body surface area.

15. Professor Stevens stated that the Appraisal Committee accepted the appellant's assumptions about the average body surface area of patients receiving pemetrexed. However, it had also considered that some patients, with a body surface area over  $2\text{m}^2$ , might be treated with doses of pemetrexed in excess of the contents of two vials. Dr Clark indicated that practice was likely to vary between cancer centres; and that although some might limit treatment to a maximum of two vials, others might not. In response to questioning by the Panel, the appellant agreed that the Summary of Product Characteristics did not indicate that the maximum dose was 1000mg (ie two vials).
16. The Appeal Panel concluded that the Appraisal Committee had not disagreed with the appellant's average dosage estimates; and that, in the absence of a dosage restriction to 1000mg (irrespective of a patient's body surface area) in the Summary of Product Characteristics, there had been no procedural unfairness.
17. The Appeal Panel therefore dismissed the appeal on this point.

**Appeal Eli Lilly 2.1.2.2: The adjustments made by the ERG in respect of utilising gains during the comparison with docataxel are unexplained.**

18. The appellant complained that the adjustments made by the Expert Review Group, and apparently accepted by the Appraisal Committee, were unexplained and therefore unfair. In particular the utility gain had been re-estimated after applying a half cycle correction and then disaggregated into components attributable to the modelled survival gain and treatment-related adverse effects.
19. Professor Bagust explained that the half cycle correction was necessary because of the particular type of modelling adopted by the appellant; but that in this instance the effect on the cost effectiveness estimates was minimal. The appellant agreed that this correction was appropriate and that it had a minimal effect on the model outputs.
20. Professor Stevens stated that neither the Expert Review Group, nor the Appraisal Committee, accepted the overall survival estimates used by the appellant in their economic model. He pointed out that the company's data, in Table 16 of their submission and in the figure above this Table (page numbers not provided), do not suggest any difference in overall survival between patients treated with pemetrexed and those treated with docetaxel (mean 8.6 and 8.7 months respectively based on the Kaplan-Meier method). However, the appellant had incorporated, in the company's economic model, a survival of 0.92 life years gained representing an overall survival of 11 months for patients treated with pemetrexed (unnumbered Table on page 129 of the company submission).
21. In response to questions from the Appeal Panel, the appellant acknowledged that an error had occurred in the development of the economic model; and that the correct overall survival was, indeed, as shown in Table 16 of the company submission.
22. The Appeal Panel noted the appellant's acknowledgement of an error in the economic model; and therefore considered that there had been good reason to amend the model with the correct survival data. The Appeal Panel did not

consider that there had been any procedural unfairness.

23. The Appeal Panel therefore dismissed the appeal on this point.

**Appeal Eli Lilly 2.1.2.3: It is unclear how its Appraisal Committee took into account the quality of life effects of adverse events associated with docetaxel therapy when those were not captured by the measure used in the JME1 trial.**

24. The appellant alleged it was unclear how the Appraisal Committee took into account the quality of life of adverse events associated with docetaxel therapy when these were not captured by the measure used in the JME1 randomised controlled trial. In particular, there were substantially higher rates of febrile neutropenia with docetaxel compared to pemetrexed.

25. Professor Stevens stated that the Appraisal Committee fully accepted the company's utilities for febrile neutropenia but noted that there was no significant advantage, for pemetrexed, in the overall hospitalisation rates compared with docetaxel. Nor was there an advantage for pemetrexed in the number of hospitalisations for "all" adverse events. Dr Clark confirmed that the Appraisal Committee were fully aware of the relative toxicities of pemetrexed and docetaxel.

26. The appellant explained that the total number of hospitalisation days for patients receiving pemetrexed was greater than for those receiving docetaxel because of the excess of admissions for "social" reasons.

27. The Appeal Panel considered that the Appraisal Committee had given careful consideration to the relative toxicities of the two agents; and that its conclusions in the FAD (paragraph 4.3) had been based on the evidence provided in the company's submission. The Appeal Panel therefore concluded that there had been no lack of clarity and no procedural unfairness .

28. The Appeal Panel therefore dismissed the appeal on this point.

**Appeal Eli Lilly 2.1.2.4: No explanation is provided for the Appraisal Committee's conclusion that patients who are unable to receive docetaxel might not respond to pemetrexed.**

29. The appellant alleged that the Appraisal Committee had provided no explanation for concluding that patients unable to receive docetaxel might not respond to pemetrexed (FAD paragraph 4.9).

30. Professor Stevens pointed out that the statement in the FAD (paragraph 4.9) about the clinical effectiveness of pemetrexed in respect of patients who were unable to receive docetaxel was factually correct. Moreover, once the error in the company's economic model had been corrected (see paragraph 21 above), the Appraisal Committee concluded that pemetrexed would be cost ineffective in patients who were unable to receive docetaxel.

31. The Appeal Panel considered that the Appraisal Committee had given full consideration to this issue and that they had used the data provided by the appellant in drawing their conclusions. The Committee had not therefore acted

unfairly in relying on the Expert Review Group's re-analysis after correcting for the company's error as discussed, and acknowledged, in paragraph 21 above.

32. The Appeal Panel therefore dismissed the appeal on this point.

**Appeal Eli Lilly 2.1.3: The Institute has not explained how it had considered the relevant additional factors provided in its procedures for cases where the cost per QALY exceeds £20,000.**

33. The appellant claimed that the Appraisal Committee had failed to consider relevant additional factors, as provided in the Institute's Guide to the Methods of Technology Appraisal procedures, when the cost per QALY exceeds £20,000.

34. Professor Stevens explained that the Appraisal Committee considered the most plausible incremental cost effectiveness ratio to be over £50,000 per QALY. At such incremental cost effectiveness ratios, it was not the Committee's normal practice to take the special factors described in the Guide to the Methods of Technology Appraisals (paragraph 6.2.6.10) into account.

35. The Appeal Panel did not consider it was either necessary or appropriate for the Appraisal Committee to take such "special factors" into account when the most plausible incremental cost effectiveness ratio was at this level. The Appeal Panel did not therefore consider there had been any procedural unfairness.

36. The Appeal Panel dismissed the appeal on this point.

## **Conclusion**

37. The Appeal Panel has dismissed this appeal on all points, having found that the Institute had acted fairly and in accordance with its procedures as set out in the Guide to the Technology Appraisal Process. The Appeal Panel requests the Guidance Executive to issue appropriate Guidance to the NHS.

38. There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However the decision of the Appeal Panel and the Institute's decision 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.