NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Health Technology Appraisal

Appraisal of pemetrexed disodium for the treatment of malignant pleural mesothelioma

Decision of the Panel

1. Introduction

1.1. An Appeal Panel was convened on 27th October 2006 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of pemetrexed disodium for the treatment of malignant pleural mesothelioma.

1.2. The Appeal Panel consisted of Mr Mark Taylor (chair of the panel), Professor Sir Michael Rawlins (chair of the Institute), Mrs Jenny Griffiths (non-executive director of the Institute), Dr Robert Donnelly (industry representative), and Mr Bob Osborne (patient representative).

1.3. The Panel considered appeals submitted by:

- Royal College of Nursing
- Eli Lilly & Company Ltd

1.4. 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, Professor Peter Clark, Dr Carole Longson (Director, Centre for Health Technology Evaluation), and Ms. Janet Robertson.

1.5. The Institute's legal advisor (Mr Stephen Hocking, Beachcroft LLP) was also present. In addition, Professor Robin Ferner, who acted as clinical assessor, advised the panel. He put technical questions to the Appellants and the Appraisal Committee, and assisted the panel by interpreting the responses in open session.

1.6. 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:

- The Institute has failed to act fairly and in accordance with its procedures;
- The Institute has prepared guidance that is perverse in light of the evidence submitted;
- The Institute has exceeded its legal powers.

1.7. The chair of the appeals committee (Dr Susanna Lawrence, Vice Chairman of the Institute's Board), in preliminary correspondence, had confirmed that the appellants had potentially valid grounds of appeal as follows:

- Royal College of Nursing on Ground 1 and Ground 2;
- Eli Lilly on Ground 1, Ground 2, and Ground 3.

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

2.1The Royal College of Nursing alleged that NICE had not fulfilled its duty to promote clinical excellence in the NHS.

The Royal College of Nursing did not present any further argument in support of this point, as they understood that the Chairman of the Appeal Committee had not allowed it to proceed. They accepted, however, that the Appeal Panel would consider their written submission on this point.

The Appeal Panel considered that the responses of the Appraisal Committee and the statements in the Final Appraisal Determination at paragraphs 1.1, 4.3, and 6.2 were a clear and adequate indication that the benefits to the NHS of innovation had been considered and that the committee had not acted unfairly

The Appeal Panel therefore dismissed the appeal on this point.

2.2Eli Lilly alleged that the Appraisal Committee's failed to provide clear reasons for rejecting the sub-group of patients who respond to treatment with pemetrexed disodium plus cisplatin after four cycles.

Eli Lilly stated that the proposed strategy would reduce the cost per quality-adjusted life year, and that the Appraisal Committee's reasons for rejecting the strategy were not transparent. Eli Lilly's view was that paragraph 4.3.9 of the Final Appraisal Determination failed adequately to explain the reasons. Eli Lilly accepted that there was not a statistically significant difference in the proportion of responders between patients treated with pemetrexed plus cisplatin and those treated with cisplatin alone.

The Appraisal Committee informed the Panel that the proposition had been discussed in detail, and that paragraph 4.3.9 was a précis of the discussions. In particular, they had considered all three factors described in paragraph 4.3.9 including the probability of survival benefit given the strategy, the change in cost-effectiveness, and the difficulties of judging response. The Appraisal Committee had taken into account their aggregate importance.

Eli Lilly, and Professors Hilary Calvert and Nicholas Thatcher on behalf of Eli Lilly, furthermore stated that, contrary to the assertions of the Appraisal Committee, it was possible to determine response in an accurate and reliable way. Professor Calvert did, however, explain that to do so was 'hard work.' The clear difference in survival between those labelled 'responders' and 'non-responders' after four cycles was evidence to this.

Professor Clark, for the Appraisal Committee, told the Panel that the view put forward by the Company and its experts contradicted expert advice given to the Committee, which was consistent with the views expressed by the United States Food & Drug Administration that measurement of response in patients with mesothelioma was difficult and uncertain. He explained that independent assessment of the data submitted by Eli Lilly to the Food & Drugs Administration showed a substantial discrepancy in figures for response.

The Appeal Panel considered that the Appraisal Committee had analysed in detail the three factors described in paragraph 4.3.9, had explained its reasons adequately and had not acted unfairly.

The Appeal Panel therefore dismissed the appeal on this point.

2.3Eli Lilly claimed that NICE had failed to disclose a written perspective, prepared by Dr Mary O'Brien, a clinical specialist who attended the meetings of the Appraisal Committee.

The Appraisal Committee informed the Appeal Panel that,in accordance with the Institute's "Guide to technology appraisal", experts are requested to provide their views, in writing, before the Committee meets, so that members should have the opportunity to frame questions to the expert. The Appraisal Committee regarded this guidance as advisory rather than mandatory. On this occasion, and in spite of requests to do so, the expert had not provided a written statement of opinion prior to the Appraisal Committee meeting but had attended the meeting and provided oral advice. There was no minute of what was said to the Appraisal Committee at the meeting, and the FAD contained no indication of what advice might have been offered.

The Appeal Panel, in considering this, noted paragraph 4.5.3.2 of the Guide to Technology Appraisal. This states : "The experts attending the Committee meeting are asked to submit, in advance, a brief written personal view of the role of the technology and its use in the NHS, as well as to provide oral evidence during the meeting. The purpose of the oral evidence provided by the experts is to enhance the evidence that is provided in the written submissions from consultees (described above), rather than to cover similar ground. During the open part of the meeting, clinical specialists and patient experts are encouraged to interact fully in the debate with the Committee, including both responding to and posing questions. The clinical specialists and patient experts are asked to withdraw from the meeting before the Committee discusses the content of the Appraisal."

Since there was neither a written summary of the expert's views, nor a minute of the oral advice the expert provided to the Appraisal Committee, the Appeal Panel

considered that this was unfair to the Appellant, who had no way of determining what advice the Appraisal Committee received and were therefore unable to engage with this aspect of the process.

The Appeal Panel therefore upheld the appeal on this point and recommends that the appraisal be remitted to the Appraisal Committee for reconsideration, either taking no account of Dr O'Brien's evidence, or ensuring that evidence is summarised in writing for circulation to interested parties.

2.4Eli Lilly considered that no explanation was given for NICE's divergence from the conclusions of the Scottish Medicines Consortium.

The Appellants argued that the Scottish Medicines Consortium was a respected and influential body, and it had concluded that pemetrexed would be available in Scotland for the treatment of malignant pleural mesothelioma. The Appraisal Committee had reached a different decision. As a result, treatment would be available to malignant pleural mesothelioma patients in Scotland that was denied to those in England. The appellant considered that this required explanation and that the Appraisal Committee's failure to offer an explanation was unfair.

Sir Michael Rawlins observed that authority for healthcare in Scotland was devolved to the Scottish parliament. Funding of healthcare in England and Scotland was entirely separate. The operation of the Scottish Medicines Consortium was entirely separate, and differed in important respects from the operation of NICE. In particular, the Scottish Medicines Consortium places different weight on the competing priorities of speed, transparency, and consultation than NICE does. It received information only from the company, while NICE also received an independent assessment on the cost-effectiveness of the treatment in this appraisal. Decisions by the Scottish Medicines Consortium to approve a drug were not binding on health providers in Scotland, but only advisory. By contrast, decisions by NICE to approve a drug have been stated by the Secretary of State for Health to create an expectation that Health Service Bodies will provide funding.

Professor Barnett, on behalf of the Appraisal Committee, advised the Appeal Panel that individual Committee members might be aware of the guidance issued by the Scottish Medicines Consortium, but the decision was not put before the Committee, and was not relevant to the Committee, for the same reasons that Professor Rawlins had outlined.

The Appeal Panel considered that the Appraisal Committee was not under any obligation to consider the views of outside bodies such as Scottish Medicines Consortium, and was under no obligation to explain why the Committee's views might differ from those of such an outside body.

The Appeal Panel therefore dismissed the appeal on this point

2.5 Eli Lilly claimed that the failure of the Appraisal Committee to consider the benefits of pemetrexed disodium by reference to the cost per life year gained was discriminatory.

Eli Lilly indicated that use of quality-adjusted life years was flawed when a treatment was given to patients who did not have long to live, who were elderly, or who had a rare disease. The company had submitted data to the Appraisal Committee in terms of quality-adjusted life years because the Committee had requested them. They had in addition provided the Committee with data on life years gained which they regarded as a more robust measure of benefit in patients of the sort described, including those with malignant pleural mesothelioma.

Eli Lilly also asserted that Professor Barnett had indicated that life year data would be considered in cases where the assumptions underpinning QALYs were inapplicable, which Eli Lilly claimed included this case

Professor Stevens stated that if there were difficulties with using quality-adjusted life years as a measure, these were most likely in chronic disease, not conditions that were rapidly fatal. The utility (the value assigned to a quality-adjusted life year) was not known for patients with mesothelioma but the Appraisal Committee had used quality-

adjusted life years based on patients with a type of lung cancer as a reasonable approximation. If the Appraisal Committee had used life years gained, that would have been equivalent to assuming that the utility of a year of life in malignant pleural mesothelioma was 1.0, when it was plainly not so. The value of approximately 0.6 used by the Appraisal Committee was much more likely to be correct. The Appraisal Committee had not conducted analyses to establish how sensitive the results it had obtained might be to uncertainty in this value.

Professor Barnett observed that whilst he had no specific recollection of the comment attributed to him, he felt it was likely to have been more qualified that Eli Lilly's comments suggested, and that in any event life year data had been considered, albeit that ultimately QALYs were preferred.

Professor Rawlins expressed concern that the symptomatolgy of malignant pleural mesothelioma had been equated with other forms of lung cancer. Patients with malignant pleural mesothelioma had markedly different symptoms from those with various forms of bronchial carcinomata. Professor Thatcher concurred.

The Appeal Panel recognized that there were arguments in favour of the use of either measure. The panel noted that the Appraisal Committee had adopted, as the measure of benefit, life years gained in its evaluation of some other products used in the treatment of advanced cancer (Technology Appraisal Guidance numbers 23, 25, 26, 28, 30, and 98) and noted that neither the FAD nor the supporting appraisal documents contained reasons for preferring Quality-adjusted life years in the present appraisal. The panel felt that the appellants might well have been hampered in their ability to participate in the appraisal process as a result.

The panel therefore upheld the appeal on this point and requests the Appraisal Committee to reconsider the use of life years gained in the context of this particular appraisal taking account of the nature of the indications for the product, the absence of

any recognised alternative treatments, the importance consistency with previous appraisals and the aetiology of the condition.

If the committee considers that the case for using Quality-adjusted life years remains preferable, the guidance or some other document available to consultees should explicitly state the reasons.

2.6 Eli Lilly contended that NICE's adherence to a fixed cost-effectiveness threshold was unfair and inconsistent with their process and with the approach followed in relation to other technologies.

Eli Lilly outlined the factors that should be taken into account when considering whether a higher than usual threshold should be adopted in the case of a specific health care technology. NICE had previously stated that relevant factors were:

- uncertainty in the estimates of the incremental cost effectiveness ratio
- the innovative nature of the technology
- high clinical need
- societal costs and benefits support usage of the technology.

The company claimed that pemetrexed fulfilled all these criteria.

Professor Thatcher and Professor Calvert emphasized that pemetrexed was an innovative treatment for a grave illness where even small benefits were important, and where it was proven to have a beneficial effect.

Professor Stevens stated that the Appraisal Committee was obliged to offer an explanation for recommending a drug if the cost per quality-adjusted life year was high, because it had to justify the use of NHS resources in such circumstances. It did not have to offer any explanation for failing to recommend a drug when the cost per quality-adjusted life year was above the range of £20,000 to £30,000 per Quality-adjusted life year.

The Appraisal Committee accepted that malignant pleural mesothelioma was rare; that the drug was innovative; that the condition was serious; and that society might

place a high value on its effective treatment, as it would for similar treatments and similar conditions.

The Appraisal Committee considered pemetrexed to be innovative and of proven benefit in a grave condition, and had taken this into account. The Appeal Panel were satisfied that the Appraisal Committee had taken into account these relevant factors, but had found that the benefits did not justify the costs.

The Appeal Panel therefore dismissed the appeal on this point

2.7 Eli Lilly alleged that the numbers of members of the Appraisal Committee who attended the meetings on 7th March and 10th May 2006 were inadequate, and that as a result the Institute has failed to act fairly and in accordance with its procedures

For the Appraisal Committee Dr Longson accepted that only 15 of 31 members had attended the meeting on 7 March 2006, and that for many years the Standing Orders of the Committee had been interpreted as requiring a quorum of 50% of the members present and eligible to vote.

In its deliberations the Panel learned that the quorum had been set in 1999 by the Board of NICE as 12 of 24 members. This clause had not been altered or rescinded, and had been generally understood to mean that the quorum of the Appraisal Committee should be interpreted as 50% of the membership (currently 31). In the Panel's view,, this interpretation, while understandable, was erroneous and the quorum remained 12. However, the Panel also recognised that the widespread misunderstanding that the quorum was 50% was so long- standing, and widely held including outside the Institute, that for the Appeal Committee to meet under these circumstances without at least 50% of its members present, constituted unfairness.

The Appeal Panel therefore held the Appeal on this point and requested the Board of NICE to review the Standing Orders of the Appraisal Committee with respect to its quorum. Pending the Board's decision on this matter, the Appraisal Committee should transact its business with at least 16 members present.

The Appraisal Committee when meeting to reconsider the issue of "cost per life year gained" (see 2.5 above) should review also whether all other matters considered or decided at its meeting on 7 March 2006 remain its view, and should reaffirm such considerations and decisions; or, if any are repudiated, the Appraisal Committee should repeat all relevant aspects of the Appraisal process from that point.

2.8 Eli Lilly alleged that the Appraisal Committee failed to take into account the potential conflict of interest arising from the involvement of the Clinical experts in the MSO1 trial.

Eli Lilly alleged that some clinical experts who gave evidence to the Appraisal Committee had an undeclared conflict of interest, in that they were investigators in the MS01 trial. The MS01 trial was at the time of the appraisal still recruiting patients. As no arm of the MS01 trial includes treatment with pemextred disodium, it was suggested that an impartial observer might suspect that investigators in the trial might have been reluctant to see treatment with pemextred disodium become widespread, as this would make recruitment more difficult. Eli Lilly did not allege that the experts were in fact biased in this way, but that there was apparent bias.

The panel considered a paper from Eli Lilly setting out what Eli Lilly alleged was the correct legal test for bias, where the bias arises in an advisor, and not in the decision maker.

The committee members present confirmed that they were aware that the experts in question were investigators in the MS01 trial, but that the question of whether this might be a potential or apparent conflict of interest was not discussed.

The panel noted that the issue was apparent and not actual bias, and that it was not necessary for Eli Lilly to allege or to prove that the experts had in fact been biased. The panel considers it important to state that no suchallegation was in fact made. The panel agreed that Eli Lilly had essentially correctly stated the law relating to apparent

bias in its submission. Although the panel considered that the role of a clinical expert giving evidence to the Committee is not the same as an advisor, it agreed that, given the status of a clinical expert and the weight that may be given to their evidence, it was appropriate to be closely guided by the test for apparent bias that would apply to an advisor to the Committee. The panel therefore asked itself whether a reasonable person, knowing that the experts were investigators in the MS01 trial and that recruitment to that trial depended on there being patients who were not being treated with pemextred disodium, would conclude that there was a real likelihood that their evidence might be affected in some way.

The Panel concluded that no reasonable person would agree that there was a real likelihood, or indeed any likelihood, that the expert's evidence might be affected in this way. The Panel believes that a reasonable person would require significant evidence before he or she would believe that a clinician would act otherwise than in what he or she genuinely felt to be in the best interests of patients generally. No reasonable person would agree that a potential (but by no means certain) impact on the last stage of recruitment to a trial might be a sufficient reason for a clinician to adjust their evidence, either consciously or unconsciously.

The appeal was therefore dismissed on this point.

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

3.1 Royal College of Nursing expressed the view that NICE had given insufficient weight to the opinions of those with a particular expertise in mesothelioma, and that the guidance was therefore perverse.

Royal College of Nursing stated that experts such as the London Lung Cancer New Drugs Group had advised that pemetrexed be used, and that the Committee had failed to take their views into account when formulating advice. It had also acted perversely by failing to consider the views of the Scottish Medicines Consortium.

Professor Stevens, for the Appraisal Committee, described how they had an obligation to consider both clinical and cost effectiveness. By contrast, experts and expert groups were usually concerned only with clinical effectiveness, and usually considered benefits in only one group of patients. The Committee's processes were clear, thorough, and well publicised.

The Appraisal Committee's representatives stated that they considered that pemetrexed did confer some clinical benefit, but at low cost effectiveness. If the Committee had failed to take cost effectiveness into account, then it would not have fulfiled its statutory remit.

The Appeal Panel accepted that the Committee had considered the evidence available. It was not, and could not be, bound or unduly influenced by the decisions of other bodies working to different rules and possibly provided with different information.

The Appeal Panel therefore dismissed the appeal on this point.

3.2 Royal College of Nursing stated that it was perverse to ignore patient choice, and that the Final Appraisal Determination effectively did so.

The Royal College of Nursing expressed concern that patients in England with malignant pleural mesothelioma would know from the internet and, other sources, that pemetrexed existed and had been shown to have a beneficial effect on their condition, but they would be prevented from choosing to have the treatment by reason of the Committee's conclusions. They would have then to rely on drugs that were not licensed for treatment of malignant pleural mesothelioma.

The Appraisal Committee accepted that patient choice was important, and confirmed that the Committee had considered this in the case of pemetrexed. The Appraisal Committee also accepted that NICE in its document, *Social Value Judgements*: *Principles for the development of NICE Guidance*, laid down the relevant principles.

Principle 11 of *Social Value Judgements* states that: "Although respect for autonomy, and individual choice, are important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective."

Professor Thatcher, one of the experts advising Eli Lilly, told the Panel that, in effect, the guidance would make it impossible to conduct research in malignant pleural mesothelioma, because the drug was expensive and research in oncology was funded from the budget for patient care, and not from research funds.

Professor Barnett, on behalf of the Appraisal Committee, explained the difference between licensed and unlicensed medicines. There was a difference between using a licensed medicine for an unlicensed indication ('off-label') and a medicine that was completely unlicensed for any indication. He also explained that some drugs used in oncology are licensed for specific indications, while others have much wider indications for the treatment of malignant disease. Some preparations of both methotrexate and cisplatin have marketing authorisations ['licences'] for wide indications in the treatment of malignant disease.

Dr Williams, for Eli Lilly, stated that the company said that the drugs had not been tested in malignant pleural mesothelioma, (and therefore did not have demonstrated clinical efficacy in that disease) rather than that they were not licensed for its treatment.

Professor Clark, for the Appraisal Committee, described trials involving vinorelbine, and combinations of chemotherapeutic agents, and stated that cisplatin alone was seldom used in the United Kingdom.

The Appeal Panel considers that patient choice is important, and that patients should have autonomy to choose the treatment they wish to have. However, the guidance in *Social Value Judgements* explicitly states that the primary interest for the NHS, as a whole, is to ensure that treatments are only used if they are both clinically and cost-effective. The Appeal Panel also recognized that cost-effectiveness is influenced by

the pricing policy of pharmaceutical companies. It accepted the Appraisal Committee's position.

The Appeal Panel therefore dismissed the appeal on this point.

3.3 Royal College of Nursing contended that NICE has failed to use the best available evidence, namely that pemetrexed was efficacious, and that as a result its guidance was perverse.

Professor Stevens said that the Appraisal Committee accepted that pemetrexed has demonstrated efficacy, but that it had not demonstrated acceptable cost effectiveness.

The Appeal Panel accepted that the Committee recognized the expert view as to the clinical efficacy of pemetrexed, and had taken this into account when they judged whether to recommend pemetrexed.

The Appeal Panel therefore dismissed the appeal on this point.

3.4 Eli Lilly argued that the guidance given by NICE was perverse because it had not explained its reliance upon mean, rather than median, survival data in assessing the cost-effectiveness of pemetrexed disodium.

Ms Watkins explained Eli Lilly's case that mean data, used by the Committee to establish benefits, underestimated the effectiveness of pemetrexed. Because not all outcomes were known at the end of the trial, the mean survival could only be calculated by extrapolation, which inevitably introduced uncertainty. Differences in means between the two treatments used in the EMPHACIS trial minimized the true differences in survival. Median values provided more robust evidence of the true difference. In her view the Appraisal Committee should at least explain how it came to prefer using extrapolated mean values.

Professor Stevens stated that all health economists used the difference in means to calculate benefit in this data set, although he accepted that it might be necessary to use

the median if there were very few data points. In this case, the mean allowed all available data to be taken into account. Furthermore, the Appraisal Committee had chosen to base its conclusions on the extrapolation presented by the,Technology Assessment Group using the Weibull method. The company, which had used an exponential method, obtained less favourable results.

Professor Stevens also pointed out that the costs were also measured using mean data as this allowed all costs to be included. If means had been used for the denominator (cost) and medians for the denominator (benefit) the results would have been distorted. He was not able to say whether the median values were within the range the Appraisal Committee had allowed for the mean values.

Eli Lilly provided a table of incremental costs per life year gained and per quality-adjusted life year for 4 different groups, using the median and the mean in each case, so that the table contained 16 estimates of cost-effectiveness. Professor Stevens criticised the company for producing data on smaller and smaller sub-populations, and by more than one method, but Ms Watkins pointed out that NICE explicitly requested information on subsets of patients in whom a treatment might be cost-effective.

The Appeal Panel considered that the Appraisal Committee had looked carefully at both mean and median data, and had considered means obtained by more than one method of extrapolation. The Panel did not think that the conclusions reached were perverse.

The Appeal Panel therefore dismissed the appeal on this point.

3.5 Eli Lilly argued that NICE's proposed recommendations were perverse because they had the effect of limiting treatment for malignant pleural mesothelioma to products that were untested and unlicensed for this indication.

Eli Lilly put forward the view that pemetrexed disodium was the only treatment with proven efficacy against malignant pleural mesothelioma licensed in the UK. The efficacy had been established in high quality, randomised, controlled trials. Other

agents used in the UK to treat patients with this condition were unlicensed and, as recognised by the Assessment Group, the evidence base for their efficacy in this disease was limited and inconclusive.

The propositions that the treatments available for malignant pleural mesothelioma were untested and unlicensed had already been considered when the Appeal Panel discussed the Royal College of Nursing's point above.

The Appeal Panel also considered more generally the effect of the argument advanced by Eli Lilly. This amounted to the view that, where there is only one product licensed for the treatment of a particular condition, then it must be recommended (or should be looked at substantially more favourably than would otherwise be the case). The Panel understood that the granting of a marketing authorization (product licence) for a particular indication implied efficacy in that indication, because this was one of the criteria that had to be fulfilled before a licence was granted. However, if the Appellant's view were correct, then the Appraisal Committee would have to recommend a drug wholly or very substantially on grounds of clinical efficacy alone. Since NICE is bound to consider cost-effectiveness, it could not legitimately take the view the Appellant was advocating.

The Appeal Panel, having considered the matter, accepted that NICE could not simply consider clinical efficacy and that the weight given to cost effectiveness was reasonable.

The Appeal Panel therefore dismissed the appeal on this point.

3.6 Eli Lilly contended that the statement in the Final Appraisal Determination "that it is uncertain whether chemotherapy offers any benefits over Active Symptom Control/Best Standard Care in terms of survival and quality of life" was inconsistent with the trial data for pemetrexed disodium.

Professor Calvert and Professor Thatcher, on behalf of Eli Lilly, accepted that there were no relevant trials comparing pemetrexed with Active Symptom Control/Best

Standard Care in malignant pleural mesothelioma. There were, more generally, trials of chemotherapy in non-small cell lung cancer that showed a benefit over Best Standard Care but the experts accepted that the statement in the Final Appraisal Determination, paragraph 2.7 was factually correct.

The Appeal Panel accepted this statement of the facts and did not consider the Appraisal Committee to have been perverse..

The Appeal Panel therefore dismissed the appeal on this point.

3.7 Eli Lilly claimed that the restriction of treatment to the clinical trial context was perverse.

The Appraisal Committee explained that while they had decided not to recommend pemetrexed for routine use in the NHS, they considered that pemetrexed might be shown to be useful in future. The committee believed that additional trials might therefore be helpful. Far from the statement in paragraph 1.1 of the Final Appraisal Determination being a demand for more clinical trials, the effect of the statement was to permit pemetrexed to be used in trials within the NHS.

Professor Rawlins reminded the Appeal Panel that a suggestion from NICE that more research would be helpful should usually make it easier to obtain funding from within the NHS for the research. Professor Thatcher said he feared that this might not be so.

The Appeal Panel, having considered this point, accepted that the statement in paragraph 1.1 of the Final Appraisal Determination was permissive, and that such statements usually acted as an encouragement to clinical trials within the NHS.

The Appeal Panel therefore dismissed the appeal on this point.

4. Ground 3: the institute has exceeded its powers

4.1 Eli Lilly asserted that the Institute had exceeded its powers because the proposed recommendations had the effect of acting as an unlawful restriction on the prescription of pemetrexed disodium.

Eli Lilly alleged that NICE guidance engages the Transparency Directive (Directive 89/105/EEC), as it is a measure that de facto leads to a restriction on the prescription of medicinal products within the NHS in England and Wales. As NICE's assessment criteria have not been notified to the European Commission such a restriction would be unlawful. Eli Lilly felt that the audit of compliance with NICE guidance by the Healthcare Commission, and indications from at least one PCT that it would not make pemextred disodium available on the basis of the guidance in the FAD, showed that NICE guidance was taking effect in the NHS as a ban.

The panel noted that the Transparency Directive on its face applies to measures that exclude, rather than restrict, products from the scope of the NHS. The panel agreed with Eli Lilly that for the Transparency Directive to apply, an exclusion need not be total. It would be sufficient, for example, if the exclusion applied only to certain patient groups. To that extent, it could be said that the Transparency Directive applies to a case where, looked at overall, some use of a product is permitted. But the panel felt that for the Transparency Directive to apply it was still necessary for there to be an exclusion, whether limited or total. In other words there must be a ban, either of all use, or of use in some situations. A measure which merely makes it less likely that a product will be used, and/or which has the effect of reducing the use of a product overall, without banning such use in any particular case, does not engage the Directive. The panel felt that this is the position implicit in the Court of Appeal judgement in R ota Pfizer Ltd v Secretary of State for Health [2002] EWCA Civ 1566.

The panel noted that this FAD, as with all NICE guidance, will be issued with an express statement that it is to be read as guidance only, and does not override clinical

judgement. The panel considered that the wording of the recommendations and reasoning within the FAD was consistent with its status as guidance only. The panel accepted that it was reasonable to expect that the effect of the guidance would be to reduce the availability of pemextred disodium within the NHS overall, possibly very significantly. However this is not sufficient to engage the Transparency Directive. The panel did not consider that there was sufficient evidence to establish that the NHS would implement the FAD not as guidance, but as an instruction. The panel noted the involvement of the Healthcare Commission in auditing NHS trusts response to NICE guidance, but felt that there was no evidence that the Commission did not understand the status of the guidance. The panel also noted the stated position of one PCT, but felt there was no evidence that this PCT was treating the guidance as if it were a ban. The panel observes that it is quite possible that many PCTs will conclude as an exercise of their own discretion that they should not routinely fund treatment with pemextred disodium. There was no evidence that the PCT in question had not done so here.

The appeal was therefore dismissed on this point.

4.2 Eli Lilly argued that NICE's reliance on the fact that the results of the MS01 study would be published in 2007 was outside the scope of this appraisal, and that in relying on this, the Institute had exceeded its powers.

Eli Lilly put forward the view that, in formulating its conclusions in the Final Appraisal Determination, NICE places substantial weight on the fact that the MS01 Study is being conducted. That trial is investigating the effects of alternative treatments and best supportive care for patients with malignant pleural mesothelioma, in the context of inadequate evidence supporting such therapies.

The Appraisal Committee accepted that the Final Appraisal Determination contained references to the MS01 study, but the Appraisal Committee had not intended to imply that their guidance on pemetrexed was contingent on the existence of or outcome from that trial. Their guidance was based on the evidence the Committee had before them. They would agree to remove any mention of MS01 from the FAD , so that any possible implication regarding the Appraisal Committee's reliance on its results would be avoided.

The Appeal Panel accepted that the Appraisal Committee did not rely on the existence of or potential outcome from the MS01 trial and therefore had not in this regard exceeded the Institute's powers.
The Appeal Panel therefore dismissed the appeal on this point.

The Panel did, however, note that there was potential for misunderstanding the references to MS01 in the appraisal document as it now stands, and requested that references to it be removed.

4.3 Eli Lilly contended that NICE's proposed determination was inconsistent with the stated policy of the European Union to encourage innovation of medicinal products to treat rare conditions.

Eli Lilly alleged that the guidance was inconsistent with EU policy on orphan drugs. Eli Lilly observed that "orphan" drugs are given privileged treatment in certain regards, as a measure to incentivise manufacturers to develop such drugs. Eli Lilly alleged that in failing to make explicit its approach to evaluating the cost effectiveness of such drugs, (which it is claimed by their nature will be expensive) NICE had acted unlawfully.

The panel accepted that although pemextred disodium was not an orphan drug it was "orphan like". The panel also observed that none of the special treatments afforded to orphan drugs in law in themselves impact on the role and remit of NICE. However the panel noted that NICE has been directed by the Secretary of State to have regard

to the importance of innovation, and whilst the issues of orphan drug status and innovation are not the same, there is some overlap.

Clearly, however, the cost effectiveness of a treatment is not affected by its status as an orphan or orphan like treatment. Affordability may be so affected (because it is reasonable to assume that the overall volume of an orphan drug which will need to be funded will be small) but this is not a matter within NICE's remit. The most that can be said is that the orphan or orphan like status of a treatment might be taken into account in determining whether a given level of cost effectiveness should or should not be recommended to the NHS, (provided that this does not amount to considering affordability by another name). As there are no specific duties laid upon NICE in respect of orphan or orphan like drugs, the panel felt that it was sufficient that the committee was aware of the prevalence of the disease in question, any relevant special features of the disease, the availability of other treatments, and the degree of innovation shown by the product. As there was clear evidence that the committee was aware of all of these issues, the committee could not be said to have exceeded its powers, or otherwise to have fallen into error.

The appeal was therefore dismissed on this point

5. Conclusion and effect of the Appeal Panel's decision

The Appeal Panel has upheld the appeal on three points raised by Eli Lilly & Company (paragraphs 2.3, 2.5 and 2.7)

Additionally the Panel has requested:

1. The Board of NICE to review the Institute's Standing Orders with respect to the quorum at meetings of its sub-committees (2.7); and
2. The Appraisal Committee to remove the references to the MSO1 trial in the FAD (4.2); and
3. The Appraisal Committee, when reviewing the issue of cost per life year gained (2.5), to confirm the matters considered at its meeting on 7 March 2006 and, if it decides to repudiate any of the decisions made then (save only the

matter of cost per life year gained), to repeat all relevant aspects of the Appraisal Process from that point.

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 issuing of the Guidance.