**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**Health Technology Appraisal**

**Appeal Hearing**

**Advice on cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck**

**Decision of the Panel**

**Introduction**

1. An Appeal Panel was convened on 22nd August 2007 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the use of cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck.

2. The Appeal Panel consisted of Professor Sir Michael Rawlins (chair of the Panel and chair of the Institute), Dr Margaret Helliwell (non-executive director of the Institute), Dr David Webster (industry representative), Mrs Jean Gaffin (patient representative) and Professor Robin Ferner (NHS representative). Members of the Panel confirmed, at the commencement of the appeal, that they had no specific or non-specific interests to declare.

3. The Panel considered appeals submitted by:
    i. Merck Serono (the "Company")
    ii. The Mouth Cancer Foundation ("MCF")
    iii. Royal College of Radiologists ("RCR")

4. 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), Dr Peter Clark, and Ms Janet Robertson.

5. The Institute's legal advisor (Mr Dario Giovannelli, Beachcroft LLP) was also present.

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.

7. There are three grounds on which an appeal can be lodged:
    i. The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process;
    ii. The Institute has prepared guidance that is perverse in light of the evidence submitted;
    iii. The Institute has exceeded its legal powers.

8. The chair of the Appeals Committee (Mr Mark Taylor), in preliminary correspondence, had confirmed that the appellants had potentially valid grounds of appeal as follows:
    i. Merck Serono: Grounds 1 and 2
    ii. The Mouth Cancer Foundation: Grounds 1 and 2
    iii. Royal College of Radiologists : Ground 2

9. The Final Appraisal Determination considered at this Appeal was for the drug cetuximab, which inhibits the action of epidermal growth factor, and which is given by injection to treat squamous cell cancers of the head and neck in combination with radiotherapy.

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

**Merck Appeal Point 1: The lack of a scoping stage to this appraisal was unfair**

10. Dr Andrea Rappagliosi, for Merck Serono, stated that the Company had been informed in a letter of 26th May 2006 that the Appraisal would be conducted under the Interim STA process, and there would be no scoping exercise. The Company had defined the decision problem. There had also been an informal meeting between the Institute's staff and the Company in July 2006, and correspondence with the Evidence Review Group. However, without a scoping exercise, the Company had been unfairly disadvantaged because there had been insufficient discussion of how those who might be suitable for treatment could be defined.

11. Professor Stevens indicated that the Appraisal Committee accepted the Company's formulation of the decision problem.

12. Dr Rappagliosi agreed with the Chairman that the Company had been asked in a letter of 31st August 2006 how they proposed to define the target group, but argued that the study available (the Bonner study) was not designed to have the statistical power to answer the question. The Company asked the Appeal Panel to consider further analyses of the data from the Bonner trial provided at Appendix 1 to their appeal submissions and in a further document provided to the Institute on 17 August 2007. After hearing submissions from the Company and the Appraisal Committee, the Panel decided to allow the Company permission to rely on this data.

13. Mr Stephen Ralston, for Merck Serono, stated that, in response to the letter of 31st August 2006, the Company had provided a list of criteria, but many of the patients defined by those criteria would have been excluded from the Bonner trial.

14. Professor Stevens explained that these details would not have been discussed during a scoping exercise. The Appraisal Committee had reviewed the European Medicines Evaluation Agency report on cetuximab, which included a pre-specified analysis by performance status. That analysis was not present either in the Bonner paper, or in the Company's submission, and therefore would not have formed any part of the discussion during a scoping exercise. This report concluded that those with a Karnofsky Performance Score of 80 or less would not benefit from cetuximab. Nor would patients over the age of 65 years. From the data submitted, the Appraisal Committee was unable to identify subgroups of patients who would benefit.

15. The Appeal Panel considered it was clear that the Company had itself framed the decision problem, and that the Appraisal Committee agreed this was reasonable and relevant and had undertaken their appraisal accordingly. The Panel also noted that the Company had been invited, on several occasions, to provide data that would assist the Appraisal Committee in considering whether cetuximab was clinically and cost effective in the particular group defined by the appellant Company itself. The Panel was very concerned that the appraisal process had been hampered by the Company's failure, despite repeated requests, to provide relevant information. In the view of the Panel, the Company was in a position to provide, and should have provided, a full breakdown of median survival by Karnofsky Performance Score, together with some estimate of the variation around the median (e.g. 95% confident intervals). The

Appeal Panel concluded that, notwithstanding the absence of a scope, the Institute had acted fairly and that there had been more than ample opportunity for the Company fully to engage with the process.

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

**Merck Appeal Point 2: NICE had failed adequately to explain why it has rejected use of cetuximab treatment in the subgroups considered**

17. Dr Rappagliosi stated that the Company were unable to discuss the sub-groups with the Appraisal Committee, and this had resulted in unfairness. However, he accepted that the Company had defined the subgroups that might benefit in its response to an enquiry from the Evidence Review Group. Furthermore, he accepted that the Company had commented on the matter in response to the Appraisal Consultation Document.

18. The Company did not have any evidence to provide to the Appraisal Committee that supported the use of cetuximab in the suggested subgroups.

19. Mr Don Cowling, for Merck Serono, said that the Company disagreed with the view of the Appraisal Committee that patients with active vascular disease or any form of myelosuppression would have a Karnofsky Performance Score below 90.

20. Professor Stevens accepted on behalf of the Appraisal Committee that there were patients who could not receive cisplatin therapy but who nonetheless had high performance status.

21. Dr Clark believed that the risks of nerve damage were less with carboplatin, especially when it was used in relatively low doses, as it was in treatment of head and neck cancer.

22. The Appeal Panel concluded that the Company had themselves defined the subgroups but had failed to offer adequate evidence that cetuximab would be effective in them. The Panel considered that the appellant had had the opportunity to comment, and had done so. There had been no inability to engage with the process or unfairness as alleged. The Appeal Panel also noted that Appraisal Committee had considered the evidence on patients with possible contra-indications to cisplatin, and concluded that

carboplatin was a reasonable alternative with fewer adverse effects. While the Company and the Appraisal Committee disagreed on certain conclusions, the Institute had not acted unfairly.

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

**Merck Appeal Point 3: The Appraisal Committee's failure to consider specific sub groups proposed By Merck Serono was unfair**

24. Professor Stevens agreed that the Company had suggested other groups, for example, those with PEG feeding tubes and those under the age of 40 years, for whom cisplatin therapy was unsatisfactory who would be eligible for treatment with cetuximab. The Appraisal Committee had discussed these groups, but the numbers involved had been very small and they were not listed in the Appraisal Consultation Document.

25. The Company had seen the Appraisal Consultation Document, but not commented on this omission, and the groups were not mentioned in the Final Appraisal Determination.

26. The Company did not raise objections to the omission at the Appraisal Consultation Document stage. Dr Rappagliosi stated that the Company would never have been in a position to provide evidence to support use of cetuximab in these groups.

27. Professor Stevens assured the Appeal Panel that all the subgroups suggested by the Company had been considered. The principle finding, described in the Appraisal Consultation Document, was that cetuximab had no beneficial effect in those with a performance score of 80 or less. The Final Appraisal Determination only mentioned those groups of sufficient size to justify specific attention.

28. The Appeal Panel concluded that the Appraisal Committee had acted fairly in considering each of the subgroups proposed by the Company. The Company had had an opportunity to comment on any omissions during consultation on the Appraisal Consultation Document, but did not do so. The Company accepted that for these subgroups it had provided no evidence of the efficacy of cetuximab from which the Appraisal Committee could have drawn robust conclusions. The Panel considered in light of all these matters that the Institute had not acted unfairly.

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

**Merck Appeal Point 4: The basis for the Appraisal Committee's consideration of carboplatin as a comparator in this appraisal was unclear**

30. Professor Stevens stated that expert submissions from Dr Slevin to the Appraisal Committee referred both to cisplatin and carboplatin regimens. The Company submission of the decision problem examined the efficacy and cost-effectiveness of cetuximab with radiotherapy against radiotherapy alone, not against platinum-based therapies. Furthermore, the Company's submission referred to chemoradiotherapy regimens generally, not specifically to cisplatin chemoradiotherapy. There was, in any event, an evidence base for the use of carboplatin in chemoradiotherapy regimens.

31. Mr Ralston stated that the Appraisal Committee's consideration of carboplatin was unfair, because that drug had no marketing authorization for the relevant indication, there was no good evidence of efficacy, and the drug was not routinely used in the United Kingdom.

32. The Appeal Panel accepted that the decision problem did not require the efficacy or cost-effectiveness of carboplatin to be compared formally with that of cetuximab, and the Appraisal Committee had not attempted to make this comparison. Carboplatin was not licensed for this indication, but was used in current practice in the NHS, and so it was not unfair of the Appraisal Committee to consider carboplatin in the way that it was considered in the Final Appraisal Determination.

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

**Merck Appeal Point 5: There was a lack of transparency with regards assessment of relative cost effectiveness of cetuximab in subgroups identified**

34. Mr Ralston complained that the Company had had no opportunity to comment on the relative cost-effectiveness in subgroups identified. In the Company's view, the data from the Bonner trial were generally valid, and could be used in calculating cost-effectiveness in the subgroups. The efficacy would have to be reduced by 75% if the cost-effectiveness were to fall below a nominal threshold of £30,000.

35. Professor Stevens stated that, since there was no evidence of clinical benefit in any of the subgroups, it was impossible to say how much any such benefit would cost. As stated in paragraph 4.11 of the Final Appraisal Determination, the Appraisal Committee had found no evidence of clinical effectiveness, and so there was no evidence that the treatment could be cost-effective.

36. Mr Ralston accepted that the Company had had the opportunity to comment on paragraph 4.9 of the Appraisal Consultation Document, which stated clearly that the Appraisal Committee was unconvinced by the Company's evidence that the treatment was clinically effective.

37. The Appeal Panel noted that the Company had commented extensively on the Appraisal Consultation Document, but had not chosen to comment on paragraph 4.9 despite having had the opportunity to do so. The Panel concluded that the Company had been accorded ample opportunity to engage with the process and that the Institute had not acted unfairly.

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

**Mouth Cancer Foundation Appeal Point 1: The MCF's comments were submitted at the Appraisal Consultation Document stage but were not correctly attributed to the Appellant on the Institute's website, being listed under 'Other 2' on page 53 of the 54 page 'Response to consultee, commentator and public comments'. It is unclear that the MCF's comments were accorded the attention appropriate to a formal consultee to the appraisal.**

39. Dr Vinod K Joshi, for the Mouth Cancer Foundation, explained that the MCF represented the views of its members constituting a wide population of patients with mouth cancer.

40. Four members of the Mouth Cancer Foundation, Mrs Brenda Brady, Mr John Spencer, Mrs Christine Piff and Mr Mike Cummins provided the Appeal Panel with personal accounts of the suffering caused by head and neck cancer and of the very unpleasant nature of their treatments. They stressed that it was important for the Institute to take patients' views into account, but that it was unclear how it had done so.

41. Professor Sir Michael Rawlins thanked the patients for their courage in attending and for describing their experience to the Appeal Panel. He explained that NICE had the difficult task of considering the welfare of all NHS patients.

42. Professor Stevens confirmed that the Appraisal Committee considered all comments received, irrespective of their source.

43. Dr Carole Longson explained that the Mouth Cancer Foundation's comments had been transmitted electronically, which was unusual. Nonetheless, they had been identified as a 'Consultee Comment' and considered accordingly. She accepted that this was not noted in the internet-published comments on the Appraisal Consultation Document.

44. Professor Stevens stated that the decision problem did not consider the question of whether patients should be given the choice between cetuximab plus radiotherapy or platinum-based chemoradiotherapy, and no information existed to answer that question. The Committee had concentrated on the decision problem provided by the manufacturer and set out in section 1 of the Final Appraisal Determination.

45. The Company acknowledged that, in their submission to the Appraisal Committee, they had explicitly recognized that there were no data comparing cetuximab plus radiotherapy with chemoradiotherapy. At the time of the Bonner trial, chemoradiotherapy had not yet become the standard treatment for locally advanced squamous cell cancer of the head and neck.

46. Dr Joshi stressed that cetuximab had fewer serious adverse effects than cisplatin.

47. Professor Stevens noted that the Appraisal Committee clearly understood that they were assessing a treatment for a grave disease but that, however grave the disease, a treatment could only be recommended if there were good evidence that it was effective. Professor Stevens added that an appraisal of the clinical and cost effectiveness of cetuximab plus radiotherapy against chemoradiotherapy had not been within the Committee's remit.

48. The Appeal Panel concluded that, despite the Mouth Cancer Foundation's comments not being attributed correctly on the Institute's internet page, the Appraisal Committee had taken them into account appropriately as those of a consultee, and fully

understood their importance and significance. The Appraisal Committee was not able to consider issues outside the decision problem put to it by the manufacturer. The Panel concluded that there had been no unfairness.

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

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

**Merck Appeal Point 7: The Appraisal Committee's interpretation of the EPAR was incorrect**

50. Dr Rappagliosi contended that the Committee's consideration of the European Medicines Evaluation Agency's European Public Assessment Report (EPAR) concerning cetuximab had been incomplete. In particular, while it had been taken as definitive it in fact represented the summary of a scientific discussion. Only the final finding of the Summary of Product Characteristics should be considered definitive, and that stated that cetuximab was of no benefit in this indication in patients with a Karnofsky Performance Score of less than or equal to 80 and who were more than 65 years old.

51. Dr Oliver Kisker, for the Company, explained that platinum-based treatments were not the standard treatment in 1999, when the Bonner trial was set up. It was one of the largest trials in this indication, and there was a definite overall effect on survival. However, analyses of small subgroups lacked statistical power. He accepted that analysis by Karnofsky Performance Score had been pre-specified. The data in the EPAR described this analysis by Karnofsky Performance Score correctly. Furthermore other pre-specified analyses also described in the EPAR showed that there was no clear benefit in patients over the age of 65 years or in women.

52. The Company believed that the data on subgroups gave limited guidance, but that the overall conclusion of benefit from the Bonner trial could be generalized, since there was no biological reason which would support effects in one subgroup but not another. The Company argued that the Appraisal Committee should have given greater weight to the final finding of the Summary of Product Characteristics, and that if they had done so the Committee may have drawn different conclusions.

53. The Appeal Panel noted that Company had not provided the data that were reported in the EPAR to the Appraisal Committee, and that the published report of the Bonner trial had omitted them. The Panel concluded that the EPAR data were relevant, and accurately reflected pre-specified analyses, and that the Appraisal Committee were entitled to give to them the weight that they had and that its interpretation of them was not perverse.

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

**Mouth Cancer Foundation Appeal Point 3: The Final Appraisal Determination suggests that carboplatin, an unlicensed treatment with no clinical data to support it, be included in NICE guidance. The Committee has failed to give sufficient consideration to the side-effects (in terms of toxicity) of carboplatin and undue weight to the availability of a technology with little safety or efficacy data to support its use. This is perverse.**

55. Dr Joshi agreed some clinicians in England and Wales used carboplatin. However, it had no marketing authorization for the treatment of locally advanced squamous cell cancer of the head and neck, and there was no evidence of its effectiveness as a single agent with radiotherapy.

56. Professor Stevens disagreed with the view that there was no evidence for the value of carboplatin in this indication. It was true that it had no marketing authorization for this indication, but medicines such as this which were in continued and historic use were commonly used outside licensed indications since no commercial sponsor would apply for a marketing authorization for carboplatin in this condition. Furthermore, it was not true to say that the Bonner trial provided no evidence of the efficacy of cetuximab: rather there was a concern that the evidence pointed to a detrimental effect in those in whom cisplatin was contra-indicated who made up the population of the decision problem.

57. Professor Stevens confirmed that the decision problem framed by the manufacturer excluded consideration of the use of cetuximab in patients who were suitable for treatment with cisplatin, some of whom might prefer treatment with cetuximab and radiotherapy.

58. Dr Peter Clark accepted that it was uncertain whether carboplatin and cisplatin were of equal efficacy. Both are used for chemoradiotherapy in the United Kingdom. In fact, paragraph 4.10 of the Final Appraisal Determination refers to 'carboplatin-*based* chemoradiotherapy.' There was evidence for the efficacy of carboplatin plus fluorouracil and in the Appraisal Committee's view that combination could be and was used as an alternative to cisplatin-*based* chemoradiotherapy. Carboplatin had fewer adverse effects than cisplatin, but was more likely to suppress the bone-marrow. Therefore, cisplatin was the preferred treatment. The Appraisal Committee accepted that cetuximab plus radiotherapy caused less severe adverse effects than either of the platinum-based chemoradiotherapy regimens.

59. Professor Stevens admitted that the Appraisal Committee had not considered the potential adverse effects of fluorouracil when noting that patients who had contraindications to cisplatin would be able to be treated with carboplatin-*based* chemoradiotherapy.

60. The Appeal Panel considered that the Appraisal Committee had not given appropriate consideration to the issue of whether a chemoradiotherapy regimen of carboplatin alone was as effective as cisplatin, or that a regimen consisting of carboplatin plus fluorouracil would necessarily be suitable for the population identified in the decision problem in whom cisplatin was contra-indicated. The Panel found that, as a result, the Committee's conclusions were perverse in proposing a 'carboplatin-*based'* regimen for those in whom cisplatin was contra-indicated.

61. The Appeal Panel therefore upheld the appeal on this point.

**The Royal College of Radiologists Appeal Point (A): The guidance fails to distinguish adequately between patient performance status and patient comorbidity**

62. Dr Nick Slevin, for the Royal College of Radiologists, estimated that about 60% of patients in whom cisplatin treatment was unsuitable could benefit from cetuximab. He had no firm evidence for this figure which was based on his considered professional opinion. The Company knew that cetuximab had been used in Scotland, where the Scottish Medicines Consortium had approved its use in certain circumstances, but it did not know what proportion of patients had received it.

63. Dr Slevin agreed that active co-morbidities – for example, active angina – would reduce a patient's Karnofsky Performance Score. It was necessary to make a judgment on the risks of chemoradiotherapy in patients with pre-existing illness, and in a patient with active angina the risk would be high. He agreed though that there were instances where it was difficult to know what Karnofsky Performance Score to assign to an individual patient.

64. Professor Stevens accepted that there were, possibly, conditions that prevented patients from being treated with cisplatin, but did not reduce the Karnofsky Performance Score below 90. Mild sensori-neural deafness was an example. The Appraisal Committee had concluded that carboplatin-based therapies could be used in those patients. In his view, that left a tiny fragment of the patient population, essentially zero, who might benefit from cetuximab but were unable to receive cisplatin or carboplatin. Professor Stevens felt that the Committee could not recommend cetuximab in circumstances where the advice was now relevant only to a negligible number of patients and where there was still an absence of any robust data to support a recommendation in that minute population.

65. With regard to those who were unfit for cisplatin, Dr Slevin agreed that carboplatin was an available alternative treatment. However, there was little evidence for the value of carboplatin alone in making tumours more sensitive to radiotherapy (the principle behind chemoradiotherapy); most of the evidence came from trials of carboplatin plus fluorouracil. He accepted that his statement of the data from Pignon's meta-analysis, and the statements of the European Society for Medical Oncology and of Cancer Care Ontario, quoted in the report of the Evidence Review Group, all spoke of 'platinum-based therapies,' and that this was the evidence placed before the Appraisal Committee.

66. The Appeal Panel could imagine examples of patients who would be unsuitable for treatment with cisplatin but who would nevertheless benefit from cetuximab. The Appraisal Committee had argued that such patients could be treated with carboplatin but had reached such conclusion without appropriate consideration of evidence for the efficacy of carboplatin alone, nor for the safety or toxicity of carboplatin plus fluorouracil. The Appeal Panel considered that their conclusion in this regard was perverse.

67. The Appeal Panel therefore upheld the appeal on this point.

**The Royal College of Radiologists Appeal Point (B): There is considerable ignorance in the Committee around radiotherapy fractionation issues**

68. Dr Slevin accepted that the Committee had wished to be fully informed on the issue, but that it was not crucial to the determination. The Committee confirmed that they had understood the expert evidence offered by Dr Slevin on this issue.

69. The Appeal Panel found that the Committee had given these issues due weight in its consideration.

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

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

71. None of the Appellants sought to pursue an appeal point under this ground.

**Conclusion and effect of the Appeal Panel's decision**

72. The Appeal Panel has upheld the appeal under Ground 2 on two points: the Mouth Cancer Foundation's point 3 and the Royal College of Radiologists' point (A).

73. The Appeal Panel noted with considerable disappointment that during the course of this appraisal Merck Serono failed to disclose potentially important data to the Institute despite several requests to do so. The Panel's consideration of this appeal, as ultimately reflected in paragraph 72, together with the Appraisal Committee's review of the evidence for this submission has been hampered in large part due to this failure by Merck Serono. So as to avoid any misunderstanding the Panel requests and expects Merck Serono to engage fully with this appraisal and make available to the Institute the following:

    - Median survival data with their 95% confidence intervals, derived from the Bonner study, for each of the following KPS scores – 100, 90, 80, 70 and less;

- Any other data in its possession that would enable the Appraisal Committee to assess the clinical and cost effectiveness according to the decision problem defined by the Company.

74. The Appeal Panel requests that the Appraisal Committee reassess the evidence for the clinical and cost-effectiveness of cetuximab in patients who meet (in whole or in part) the criteria defined by Merck Serono.

75. Additionally, the Appeal Panel requests that the Appraisal Committee in performing their reassessment have due regard for the Institute's positive duties arising from anti-discrimination legislation to eliminate unlawful discrimination of all forms and to promote equality of opportunity between persons, and particularly but without limitation consider whether the Institute's guidance has been formulated in a manner which ensures these aims are achieved.

76. People currently receiving cetuximab for locally advanced squamous cell cancer of the head and neck should have the option to continue therapy until they and their consultants consider it appropriate to stop.

77. 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.