APPEAL BY MERCK SERONO UK AGAINST THE FINAL APPRAISAL DETERMINATION BY THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE FOR CETUXIMAB FOR LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

EXECUTIVE SUMMARY

Merck Serono wishes to appeal the draft determination with respect to cetuximab for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN).

The appeal is brought under all three of the grounds permitted under NICE's appeal procedures, namely: Ground 1 (Procedural Unfairness); Ground 2 (Perversity); and Ground 3 (Excess of Power):

The points of appeal under Ground 1 concern:

1. The lack of a scoping stage in the appraisal.
2. A lack of transparency in relation to the appraisal process:
    - The reasons for rejecting the subgroups considered at paragraph 4.10 of the FAD
    - The reasons for failing to consider subgroups identified by Merck Serono
    - The assessment of cost effectiveness of use of cetuximab in the identified subgroups.
    - The basis for selection of carboplatin as a comparator treatment.
    - How the Social Value Judgements Guide has been taken into account.

The points of appeal under Ground 2 concern:

3. The misinterpretation of the conclusions expressed in the EPAR for cetuximab.
4. Ethical and design issues in the proposal to run a future study of cetuximab plus radiotherapy versus chemotherapy plus radiotherapy.

We also appeal under ground three relating to the sub groups defined by NICE.

Merck Serono requests that the Appeal Panel refer this appraisal back to the Appraisal Committee for further consideration with the following directions:

1. Reconsider the scope of this appraisal.
2. Reconsider the application of the data to subgroup analyses

1. INTRODUCTION

Following consideration of NICE's draft determination with respect to cetuximab for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN), Merck Serono UK provides formal notification of its wish to appeal the Final Appraisal Determination (FAD). Merck Serono requests an oral hearing before NICE's Appeal Panel for the determination of this appeal.

The appeal is brought under all three grounds permitted under NICE's appeal procedures, namely: Ground 1 (Procedural Unfairness); Ground 2 (Perversity) and Ground 3 (Excess of Power). The points of appeal raised under each of these grounds are set out in Section 2 of this Notice of Appeal.

1.1 NICE'S appraisal of cetuximab: procedural history

In September 2005, NICE issued a press release indicating that it was proposing to develop a revised procedure for the rapid appraisal of important new drugs and health technologies. The Institute subsequently prepared a draft process for single technology appraisals (STAs), comprising a Draft "Interim" Guide to the Single Technology Appraisal Process and a Draft Specification for the Manufacturer/Sponsor Submission. Following the conclusion of the consultation process, NICE's Guide to the Single Technology Appraisal (STA) Process was issued in September 2006. There were significant differences between the draft, interim procedure, and the final version issued in September 2006.

Merck Serono was advised by the Institute in a letter dated June 2006 that an evidence submission should be presented by 2 August 2006, under the "Interim" STA Guide, which was then the subject of consultation. There was no scoping stage to the appraisal and the Interim Guide did not provide for any consideration by NICE of the "decision problem", identified by Merck Serono, prior to the submission of evidence.

The Centre for Health Economics (CHE), University of York & NHS Northern and Yorkshire Regional Drug and Therapeutics Centre was commissioned by the NHS R&D HTA program on behalf of NICE to prepare an Expert Review Group (ERG) Report. The company provided clarification of various issues raised by the ERG, in correspondence dated 31 August 2006 and 3 October 2006. This submission was considered by the ERG, before its report was completed in October 2006.

The Appraisal Committee met for the first time to consider this appraisal on 9 November 2006. Its findings were communicated to Merck Serono on 24 November which, in summary, were:

> *"As you are aware, the Appraisal Committee met to consider this appraisal on Thursday 9 November 2006.*
>
> *At this meeting the Committee was presented with extra information on cetuximab in the treatment of locally advanced squamous cell head and neck cancer. Specifically, this information consisted of the scientific discussion published by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) as part of the extension of the marketing authorisation for cetuximab. This scientific discussion is published on the EMEA website as part of the European Public Assessment Report.*
>
> *As a consequence of having been presented with this information at a late stage the Committee decided that it needed to further discuss the implications of the extra information in its next meeting which is planned for 11 January 2007."*

Following this meeting, an Appraisal Consultation Document (ACD) was issued in January 2007. The preliminary recommendations in the ACD provided that:

> *"Cetuximab in combination with radiotherapy is not recommended for patients with locally advanced squamous cell cancer of the head and neck."*

The responses to consultation on the preliminary guidance in the ACD consistently expressed the view that the preliminary guidance was inappropriate. The Appraisal Committee met for a second time to consider cetuximab on 15 March 2007 and following this meeting a Final Appraisal Determination (FAD) was issued on 4 May 2007. The preliminary guidance contained within the FAD states:

> *"This guidance on the use of cetuximab in combination with radiotherapy, for patients with locally advanced squamous cell cancer of the head and neck, is based on evidence submitted by the manufacturer. The evidence submitted was insufficient to enable a recommendation to be made on the use of cetuximab in combination with radiotherapy, as an alternative in patients for whom chemoradiotherapy is inappropriate.*
>
> *Cetuximab in combination with radiotherapy is not recommended for patients with locally advanced squamous cell cancer of the head and neck"*

2. GROUNDS FOR APPEAL

Merck Serono's appeal is brought on grounds of procedural unfairness and perversity. The points of appeal under these grounds are set out below.

2.1 Detailed Points of Appeal

2.1.1 Appeal Point 1: Procedural unfairness

The lack of a scoping stage to this appraisal:

This appraisal was not defined by a scope and included no requirement for the Institute to consider the manufacturer's definition of the "decision-problem" prior to the submission of evidence. This has precluded a fair consideration of cetuximab.

A proper scoping stage is now recognised by NICE as a requirement for a fair appraisal procedure and has been included in the final version of its STA process guide. However, the fact that NICE's appraisal of cetuximab has proceeded under the interim STA procedure, without the benefit of a scope or confirmation of the decision-problem, has resulted in an appraisal that is procedurally unfair. The scope of the appraisal was unclear to Merck Serono and the company's subsequent definition of the decision problem has been criticised by the Appraisal Committee (see paragraphs 3.6 and 4.2 of the FAD). If a formal scoping exercise had been carried out, NICE's approach to issues fundamental to this appraisal would have become clear prior to the submission of evidence. In particular, Merck Serono would have had an opportunity to make representations regarding: the interpretation of Karnofsky Performance Status (KPS) and, "fitness" to receive chemoradiotherapy; the clinical trial data from the Bonner study in the context of the KPS status of participants; and the appropriate selection of comparator treatments for the purposes of this appraisal.

- As indicated in its evidence submission to the Institute, Merck Serono believes that this appraisal should have considered the clinical and cost effectiveness of cetuximab based upon the whole population of patients assessed in the Bonner study. The study was not powered to detect differences in survival based on subgroup analyses, including by reference to KPS scores and the company believes that the product showed benefit across the full trial cohort However, if the appraisal had been subject to proper scoping, NICE's disagreement with that fundamental premise would have been made clear, allowing Merck Serono a fair opportunity to focus its submissions to the Institute appropriately.

- In particular, had the appraisal been scoped and the Institute's position with respect to the Bonner trial been made clear, Merck Serono would have been prompted to submit further analyses of the trial data demonstrating the efficacy of cetuximab and radiotherapy in patients with a KPS of 80. It is important to note that Merck Serono has evidence of extended subgroup analyses, which were made available to the CHMP that prove that cetuximab demonstrates efficacy in a broader patient population (defined by reference to KPS) than that inferred in the EPAR. (These data are provided, for illustrative purposes at Appendix I to this notice of appeal).

- Furthermore, a scoping stage would have permitted early consideration of key issues surrounding the identification of patients inappropriate for chemoradiotherapy, despite a KPS of 90 or greater, suggesting "clinical fitness". Confusion with respect to this issue has prejudiced cetuximab in the context of subgroup analyses, as addressed at paragraph 4.10 of the FAD.

- It is clear that there is substantial disagreement and controversy with respect to the comparators selected by the Appraisal Committee for the purposes of this appraisal (particularly carboplatin, which is not licensed in this therapeutic area and, in respect of which, there are no demonstrative data in this indication) and the circumstances in which they should and should not be used. These issues would have been considered and addressed prior to the submission of evidence had a proper scoping stage been included in this appraisal.

A manufacturer's submission is its principal opportunity to present structured evidence to influence the outcome of an appraisal. After this point, the direction of an appraisal has often been determined and the opportunities for delivering further material to the Appraisal Committee are limited. The prejudice is particularly marked in an appraisal such as this, where there was no opportunity for Merck Serono to provide a response to the full ERG report before this was considered by the Appraisal Committee. The lack of a scoping exercise to guide the focus of the appraisal and identify areas of controversy at the outset has therefore resulted in substantial unfairness to Merck Serono and cetuximab as described above.

2.1.2 Appeal Point 2: Procedural unfairness

NICE's has failed adequately to explain why it has rejected use of cetuximab treatment in the subgroups considered.

At section 4.10 of the FAD, the Appraisal Committee, considered the use of cetuximab in certain patients for whom cisplatin-based chemoradiotherapy would be inappropriate namely:

- Patients with active peripheral, cerebral or coronary vascular disease and any form of myelosupression;
- Patients with contraindications to cisplatin (conditions predisposing the patient to thrombocytopenia, impaired renal function, impaired hearing and peripheral neuropathy); and
- Patients who have received previous cisplatin therapy for any malignancy.

Whilst Merck Serono believes that each of these subgroups include patients for whom cetuximab has benefits, the Appraisal Committee rejected usage in such patients for reasons that are unclear. This lack of transparency has prejudiced Merck Serono in its ability to understand and respond to the conclusions reached by the Appraisal Committee.

(a) Active peripheral cerebral or coronary vascular disease and any form of myelosupression

The Appraisal Committee concluded that patients with active peripheral, cerebral or coronary vascular disease and any form of myelosupression, would always have a Karnofsky Performance Status ("KPS") of less than 90. Therefore, in view of the Committee's finding at paragraph 4.8 of the FAD that there is no evidence that cetuximab plus radiotherapy is effective in such patients, the Appraisal Committee concluded that the product should not be recommended in this subgroup. However, the Appraisal Committee has not adequately explained why it concluded that patients within this subgroup would have a KPS of less than 90 or why the clinical data would not support use of cetuximab in such patients.

- First, we have explained earlier in this document why we believe the reasoning of the Appraisal Committee in relation to its finding of a lack of benefit associated with cetuximab therapy in patients with KPS below 90, was deficient. The clinical trial data from the Bonner study demonstrate that cetuximab produces substantial benefits in patients with KPS of 80, as well as those with a KPS of 90 and above. The lack of transparency with respect to the Appraisal Committee's conclusions at paragraph 4.8

of the FAD also result in an absence of clarity in relation to their rejection of cetuximab in patients with active peripheral, cerebral or coronary vascular disease and particularly its conclusion that patients with KPS of 80 will derive no benefit from cetuximab treatment.

- In addition, the Appraisal Committee has provided no explanation for its conclusion that patients with active peripheral, cerebral or coronary vascular disease and any form of myelosupression, would always have a KPS of less than 90. We do not believe that this is necessarily the case. The description of a KPS of 90 is *"able to carry on normal activity; minor signs or symptoms of disease".* The presence of the identified diseases is therefore entirely consistent with a KPS of 90 and the basis for the contrary conclusion of the Appraisal Committee requires explanation.

- Finally, the Appraisal Committee asserts that there are no robust data justifying use of cetuximab in patients with the identified diseases with KPS of 90 or above. Whilst, as explained above, Merck Serono believes that the limitation to patients with a KPS of 90 is inappropriate, there is no biologically plausible reason to conclude that cetuximab would be less efficacious in patients with the identified diseases, than in the entire Bonner cohort and in these circumstances we would ask the Appraisal Committee to explain why it believes that data limited to these subgroups (presumably each of these subgroups separately) are necessary in order to establish efficacy.

In summary, for the reasons set out above, Merck Serono believes that the Appraisal Committee should be required to explain the basis for its conclusion that patients with the identified diseases would always have a KPS of 90 or greater and that cetuximab treatment should not be recommended for use in this group.

(b) Patients with contraindications to cisplatin (conditions predisposing the patient to thrombocytopenia, impaired renal function, impaired hearing and peripheral neuropathy

The Appraisal Committee rejected use of cetuximab in patients with contraindications to cisplatin on the basis that they had either been excluded from the Bonner trial (criteria for eligibility included normal haematopoietic and renal function) or affected patients could be treated with carboplatin (those with impaired hearing, peripheral neuropathy or risk of thrombocytopenia). However, the evidence relied upon by the Appraisal Committee and its reasons for these conclusions are unclear.

- The Appraisal Committee asserts that patients with impaired hearing or peripheral neuropathy may receive carboplatin treatment. However, the SmPC for carboplatin lists both ear and labyrinth disorders and mild peripheral neuropathy under "undesirable effects". In both cases, the onset of symptoms during cisplatin therapy, may produce persistent or worsening symptoms associated with further platinum based treatment. Again, there is no evidence that cetuximab is either neurotoxic or ototoxic. Therefore, in view of the warnings provided in the SmPC for carboplatin, it is unclear why the Appraisal Committee concluded that carboplatin based therapy was a valid alternative for cisplatin in patients with impaired hearing or peripheral neuropathy.

- The Appraisal Committee concluded that patients with conditions predisposing them to thrombocytopenia should be excluded from cetuximab therapy because normal haematopoietic function was one of the inclusion criteria for the Bonner trial and that, furthermore, patients at risk of thrombocytopenia could be treated with carboplatin. However, myelosuppression is listed as an undesirable effect of both cisplatin and carboplatin therapy in the SmPCs for both products and the basis for the statements by the Appraisal Committee are unclear. There is no evidence that cetuximab is myelosupressive.

- Again, the Appraisal Committee asserts that there are no robust data justifying use of cetuximab in patients with contraindications to use of cisplatin and a KPS of 90 or above. As stated under (a) above, there is no biologically plausible reason to conclude that cetuximab would be less efficacious in patients for whom cisplatin is contraindicated than in the entire Bonner cohort and in these circumstances we would ask the Appraisal Committee to explain why it believes that data limited to these patients (presumably each of these contraindications separately) are necessary in order to establish efficacy.

Again, for the reasons set out above, Merck Serono believes that the Appraisal Committee should be required to explain the basis for its conclusion (a) that patients with contraindications to cisplatin may use carboplatin or (b) that robust trial data supporting use in each subgroup is required before a recommendation may be made.

(c) Patients who have received previous cisplatin therapy for any malignancy

The Appraisal Committee rejected use of cetuximab in patients who had previously received cisplatin therapy for any malignancy on the basis that patients who had received chemotherapy was in the previous 3 years were excluded from the Bonner trial and that those treated more than 3 years previously could receive further platinum therapy. However,

the Appraisal Committee provided no explanation for its apparent conclusion that patients who had received chemotherapy with cisplatin within the previous 3 years, might in some way respond differently to cetuximab from the complete Bonner cohort and Merck Serono is unaware of any biological mechanism to explain it. Cetuximab's mode of action is dissimilar to that of cisplatin and failure to respond to platinum based chemotherapy would not be expected to be predictive of cetuximab response. In these circumstances, we believe that cetuximab therapy would be appropriate for patients who had received cisplatin chemotherapy within the previous 3 years and that the Appraisal Committee should be required to explain its reasons for rejecting use of the product in this subgroup of patients.

2.1.3 Appeal Point 3: Procedural unfairness.

The Appraisal Committee's Failure to Consider the Sub Groups Proposed By Merck Serono is unfair

The Appraisal Committee has failed to consider use of cetuximab in important subgroups of patients where the product would be expected to offer benefit, despite asking Merck Serono to identify such subgroups. In August 2006, the Appraisal Committee requested the company to propose patients for whom chemoradiotherapy would be inappropriate. Merck Serono complied with this request, in a letter to NICE on the 31st August. However the Appraisal Committee has provided no reasoning to explain why these subgroups of patients have been rejected for cetuximab therapy and has seemingly failed to give them any consideration at all.

Merck Serono believes that two of these subgroups, in particular, should receive proper consideration by the Appraisal Committee and that the Committee's failure in this context is unfair. Our reasons are set out below:

- *Patients with PEG (feeding) tubes inserted and those who have a significant risk of aspiration due to nausea or vomiting induced by cisplatin treatment which can lead to infection in an immunocompromised patient.*

The association of nausea and vomiting with cisplatin treatment represents a serious complication of therapy. The risks of such effects in the patients identified above may be unacceptable and result in such patients being denied treatment for their condition. In these circumstances, Merck Serono does not understand why the Appraisal Committee has seemingly failed to consider the situation of such patients in the FAD.

- *Patients with SCCHN aged <40 should not be treated with chemoradiotherapy due to:*

    a. *long term risks of secondary malignancies.*

    b. *long term risk of ototoxicity.*

2.1.4 Appeal Point 4: Procedural unfairness

The basis for the Appraisal Committee's consideration of carboplatin as a comparator in this appraisal is unclear.

The Appraisal Committee has concluded that carboplatin should be considered an appropriate comparator in this appraisal for patients unable to tolerate cisplatin based chemoradiotherapy. However, carboplatin has no marketing authorisation for this indication and Merck Serono has been unable to find any sufficiently powered randomised controlled trial evidence to support its use in patients with LA SCCHN or to assess the benefits, if any, that patients may derive from therapy.

In section 4.10 of the FAD, the Appraisal Committee states:

> *"The Committee was aware that although carboplatin does not have a UK marketing authorisation for the treatment of locally advanced squamous cell cancer of the head and neck, it is being used to treat this condition in UK clinical practice and has an evidence base for its use in chemoradiotherapy. The Committee concluded that because carboplatin-based chemoradiotherapy can be given as an alternative to cisplatin-based chemoradiotherapy in the group of patients for which there is an evidence base, it could not recommend cetuximab as a treatment for patients with contraindications to cisplatin."*

The evidence base referred to by the Appraisal Committee has not been identified and Merck Serono has therefore been prejudiced in its ability to respond to this conclusion of the Committee. However the limited data for carboplatin in this indication found by Merck Serono, are not of high quality and permit no firm conclusions to be drawn regarding the outcomes of such treatment. In these circumstances the company cannot understand the basis upon which the Appraisal Committee was able to assess the relative clinical and cost effectiveness of carboplatin as compared to cetuximab, without which no conclusions regarding its usage may properly be drawn.

2.1.5 Appeal Point 5: Procedural unfairness.

Lack of transparency with regards assessment of relative cost effectiveness of cetuximab in sub groups identified

There is a lack of transparency as to how the Appraisal Committee has addressed issues of clinical effectiveness and potential cost effectiveness for the subgroups of patients defined in section 4.10 of the FAD. In section 4.9 of the FAD, the Appraisal Committee states:

> *"The Committee also heard from the clinical specialist that those patients for whom chemoradiotherapy is contraindicated would represent a higher-risk population with shorter median survival than for those for whom chemoradiotherapy was an option. It concluded that the absolute benefit, and therefore the cost-effectiveness of treatment, in this subgroup might be expected to be considerably less than suggested by the economic modelling."*

However, there is no explanation in the FAD as to the Appraisal Committee's conclusions with respect to the clinical effectiveness of cetuximab in patients for whom chemoradiotherapy is contraindicated and no indication as to the advice given by the clinical specialist as to whether his comments related to all patients within the subgroups defined at paragraph 4.10 of the FAD (including say those with impaired hearing or peripheral neuropathy) and the basis for his submission. Furthermore, the FAD gives no indication as to how, if at all, the cost effectiveness of cetuximab treatment in patients within the defined subgroups was assessed following the advice of the clinical specialist and the statements at paragraph 4.9 of the FAD.

The cost per QALY presented by Merck Serono compared cetuximab plus radiotherapy with radiotherapy alone and produced an incremental cost effectiveness ratio (ICER) of £6390 per quality-adjusted life year (QALY). This ICER is based upon extrapolation of study data beyond the study period to a patient life time. When this extrapolation is ignored and the timeframe of the analysis is changed from a lifetime to the period of the trial follow-up, then the incremental cost per QALY gained is £19,951. Given these calculations provided by Merck Serono, the efficacy of cetuximab would have to be reduced by 75% of that stated, to prove to be an inefficient use of NHS resources with an ICER exceeding a £30K threshold.

In these circumstances, we believe that the Appraisal Committee should be required to explain its conclusions regarding the cost effectiveness of cetuximab in the defined subgroups of patients.

2.1.6 Appeal Point 6: Procedural unfairness

There is a lack of transparency as to how the principles of social value judgment were applied in this appraisal.

The Appraisal Committee has failed to provide clarity as to how the Guidance for the Institute and its Advisory Committees "Social Value Judgements" ("the Social Value Guidance") was applied in the context of this appraisal.

First, the Appraisal Committee has failed to explain how Principle 4 of the Social Value Guidance has been taken into account in this case. Principle 4 provides:

> "*In the economic evaluation of particular interventions, cost-utility analysis is necessary but should not be the sole basis for decisions on cost-effectiveness",*

Given that the Appraisal Committee noted:

- the high quality of the conducted study and the fact that this demonstrated longer median locoregional control and greater median overall survival associated with cetuximab therapy
- the manufacturer economic model was acceptable and of good quality
- subgroups of patients where treatment with cetuximab would be expected to offer particular benefits (see FAD paragraph 4.10)

The application of the Social Value Judgments guidance should, we believe, have led to a positive determination by granting access to the treatment to the patients identified by the Committee.

Second, when answering to the comments of stakeholders and consultees, the Appraisal Committee failed again to clarify how Principle 12 of the Social Value Guide had been applied. Principle 12 provides:

> "*The Board consider it incumbent on the Institute and its advisory bodies to respond, objectively, to the comments of the stakeholders and consultees and, where appropriate, to change their views*".

The comments from a series of clinicians, healthcare representatives and Physicians Associations were consistently addressed with, "comment noted". However, such comments were not reflected in the FAD and no explanation for the Appraisal Committee's rejection of these views was provided.

2.1.7 Appeal Point 7: Perversity of findings

The Appraisal Committee's interpretation of the EPAR is incorrect.

At paragraph 4.8 of the FAD, the Appraisal Committee states:

"However, it noted that no clinical benefit had been demonstrated for cetuximab plus radiotherapy in patients with a Karnofsky performance score of 80 or less, based on evaluation of the principal registration trial data in the 'European public assessment report' published by the European Medicines Agency. The Committee noted that the manufacturer had stated that the Bonner trial was not designed or statistically powered to identify the subgroups of patients for whom chemoradiotherapy would be inappropriate. However, given the absence of benefit (albeit with wide confidence intervals) it could not make the subgroup of patients with a Karnofsky performance score of 80 or less the basis for a recommendation to use cetuximab plus radiotherapy. Indeed the Committee noted that the 'European public assessment report' stated that the 'overall impression of all subgroup analyses is that the add-on effect of cetuximab tends to be small or absent irrespective of outcome measure in patients with poor prognosis (estimated from median overall survival)'."

However, this reference to the EPAR is incorrect. The analyses of the Bonner study considered by the CHMP were limited to those assessing the effects of cetuximab in patients with a KPS score of 90 or more and in patients with a KPS score of 80 or below. The CHMP concluded, based on these data, that "the add-on effect of cetuximab is small in patients with poor performance status….", but, in contrast to the assertion in the FAD, it was careful not to specify a KPS score, below which the benefits of cetuximab would not be meaningful.

Analyses presented in the EPAR are limited due to the following reasons:

- The group of patients reporting 50 – 80 KPS at the baseline assessment is underpowered to assess differences in survival. Indeed, the confidence intervals associated with the 50-80 KPS are wide, suggesting that no scientific interpretation can be made.

- Data presented by the EPAR cuts the analyses as 90-100 KPS and 50-80 at the baseline assessment. This dichotomisation was done as a stratification factor, and subsequent analyses are only explorative (i.e. hypotheses generating) rather than confirmatory analyses.

- This analysis does not present survival data for patients with a KPS of 80 or 70 as a separate analysis, for example. Information is not presented to validate whether, had

the data been cut differently (such as 70-100 or 80-100 KPS), cetuximab would have proven to be effective, or not effective. [There is no information to suggest that it is biologically implausible that cetuximab would demonstrate clinical efficacy at this KPS].

- The CHMP did not, in fact, present analyses considering the effects of cetuximab in patients with a KPS score of 80 or in patients with scores of 80 and above and therefore was not in a position to determine where the demarcation between high and low performance status patients should lie for this purpose.

In the context of the conclusions of the Appraisal Committee following this appraisal and while Merck Serono believes that it is not scientifically appropriate to complete subgroup analyses on research which is not sufficiently statistically powered to allow this, the company has examined the clinical trial report of the Bonner study and, can provide information on patients with KPS scores of 80. A preliminary table is attached as Appendix 1.

In summary, Merck Serono believes that the Appraisal Committee has misrepresented the conclusions of the CHMP as set out in the EPAR and that the statements made in the FAD at paragraph 4.8 are inconsistent with the results from the Bonner trial.

2.1.8 Appeal Point 8: Perversity of findings

Ethical and design issues in the proposal to run a future study of cetuximab plus radiotherapy versus chemotherapy plus radiotherapy.

The recommendations for future research at paragraph 6 of the FAD are perverse in the context of ethical objections identified by the clinical specialist.

In section 6.1 of the FAD, the Appraisal Committee states:

"The Committee recommended further research on:

- *The use of cetuximab in combination with radiotherapy compared with radiotherapy alone in patients with low Karnofsky performance score*
- *The use of cetuximab in combination with radiotherapy compared with chemoradiotherapy in patients with high Karnofsky performance score. A clinical trial on radiation therapy and cisplatin with or without cetuximab in treating patients with stage III or stage IV head and neck cancer (RTOG-0522) is currently recruiting patients."*

However, it is quite clear from comments made by Dr Nick Slevin in his evidence to the ACD that such research would not be possible.

> *"Having been Chair of the NCRI head and neck research group it would be IMPOSSIBLE to get agreement on trial design and/or funding to do a clinical trial of RT + Cetuximab versus RT + chemo as recommended in the ACD"*

In these circumstances, the recommendations included in section 6 are perverse and leave no viable option for the manufacturer in developing further research in this area for cetuximab.

2.1.9 Appeal Point 9: Excess of power

Subgroups defined by NICE in effect define treatment pathways

The subgroups defined in section 4.10 in the FAD go beyond the intentions of a technology appraisal and define treatment pathways for the treatment of LA SCCHN. Merck Serono is appealing due to an excess of power.

In a technology appraisal, the intention for the Appraisal Committee is to assess the clinical and cost effectiveness of a particular technology (or group of technologies) in a particular disease state. In defining subgroups of patients who would or would not be appropriate for cisplatin based chemotherapy, the FAD is - in effect - providing guidelines on the treatment of these patients. Interpretation of the guidance would be as follows:

- Patients with active peripheral, cerebral or coronary vascular disease and any form of myelosuppression should be treated with radiotherapy alone because it is not possible for a patient with these comorbidities to have a KPS of less than 90. or above
- Patients with particular contraindications to cisplatin should be treated with carboplatin if the patient has a KPS of 90.
- Patients who have been previously treated with cisplatin therapy for any malignancy within 3 years should be treated with further radiotherapy alone, but those treated more than three years previously should receive further cisplatin.

This content of the FAD suggests an excess of power in defining treatment pathways within a Technology Appraisal for one particular treatment.

3. REQUESTED ACTIONS

In the context of the above concerns, Merck Serono respectfully requests the Appeal Panel to refer this appraisal back to the Appraisal Committee for further consideration with the following directions:

1. Reconsider the scope of this appraisal.
2. Allow consultees an opportunity to focus their submissions in the context of the defined scope.
3. Ensure full transparency for the future progress of this appraisal, both in the context of the evidence base relied upon and the reasoning for the conclusions of the Appraisal Committee.

Merck Serono UK

May 2007

APPENDIX 1

Survival rates of RT+ cetuximab over RT alone for patient with a KPS >= 80(i.e. 100, 90, 80)

Strata	Treatment	N	% Censored	Survival Rates			Median	
				1 Year	2 Years	3 Years		95% CI
KPSGroupGe80	RT + CET	189	55.6	80.3%	65.7%	60.1%	55.2	(45.5, -)
	RT alone	191	44.0	75.6%	56.7%	46.0%	30.3	(23.5, 6.9)