NOTICE OF APPEAL BY ROCHE PRODUCTS LIMITED:

BEVACIZUMAB, SORAFENIB, SUNITINIB AND TEMSIROLIMUS FOR THE TREATMENT OF ADVANCED AND/OR METASTATIC RENAL CELL CARCINOMA

1. Introduction

Roche Registration Limited is the marketing authorisation holder for Avastin (bevacizumab) a vascular endothelial growth factor inhibitor with indications including the treatment of advanced and metastatic renal carcinoma, in combination with interferon alpha 2a. The marketing authorisation originally granted under the centralised procedure on 12 January 2005, was extended by the European Commission to include this indication on 14 December 2007, following a positive opinion by the CHMP on 15 November 2007.

Roche Products Limited ("Roche") is responsible for the supply of bevacizumab in the United Kingdom.

Treatments for advanced and metastatic renal cell carcinoma were referred by the Department of Health to NICE and a Final Scope for the appraisal of bevacizumab, sorafenib, sunitinib and temsirolimus in this indication, was published by the Institute in October 2007. Submissions in relation to these technologies were provided to NICE by consultees, including Roche, by January 2008. An Assessment Report was commissioned from the Peninsula Technology Assessments Group and issued on 2 May 2008. Following consultation on the report, consultees provided comments to NICE by 20 June 2008. The Appraisal Committee met for the first time to consider this appraisal on 9 July 2008 and an Appraisal Consultation Document ("ACD") was issued on 8 August 2008. The Appraisal Committee met to consider this appraisal for the second time on 10 September 2008 and commissioned further review of the evidence by the Assessment Group. This review, produced in September, was then subject to consultation. On 4 January 2009, NICE published supplementary advice to Appraisal

Committees on appraising treatments which may extend the life of people with a short life expectancy. It is our understanding that these criteria were intended to identify those treatments that may extend life at the end of life, on the basis that such treatments may be associated with benefits which are not, or not adequately captured in the reference case. These treatments may be valued more highly by patients and therefore qualify for approval based on a higher cost/QALY threshold. The Appraisal Committee met to consider this appraisal for the third time on 14 January 2009; following this meeting, on 4 February 2009, a Final Appraisal Determination ("FAD") was issued in respect of sunitinib as first line treatment for advanced or metastatic renal cell carcinoma and a second ACD was issued a number of weeks later in respect of the other treatments, including bevacizumab. Comments on the second ACD were submitted by 4 March 2009. The Appraisal Committee met to consider this appraisal for the fourth time on 11 March 2009 and a FAD was issued on 21 April 2009.

2. Clinical Background: Renal Cell Carcinoma

Roche assumes that members of NICE's Appeal Panel will have varying knowledge of the therapeutic area under consideration and the situation of patients with advanced and metastatic renal cell carcinoma. In these circumstances, we provide here a brief outline of relevant information as background for the Panel. More detailed information is provided in Roche's submission for this appraisal provided to NICE on 16 January 2007.

Renal cell carcinoma accounts for approximately 2% of all cancers worldwide. It occurs most commonly in patients over age 50 and has a higher incidence in men than women. The prognosis for patients with renal cell carcinoma is substantially dependant on the stage of the disease at diagnosis; patients who present early when the disease is localised have a high five year survival, but for the 25-30% of patients who are diagnosed only when the disease is advanced or metastatic, the outlook is poor, with five year survival limited to approximately 10%. In the United Kingdom there were 7,380 new cases of renal cell carcinoma diagnosed in 2005 of which around 4,000 are patients with advanced and/or metastatic RCC in England and Wales.

Traditionally treatment for renal cell carcinoma has been surgery followed by immunotherapy, generally with interferon alpha. This approach has produced limited benefits in terms of improved overall survival for patients with advanced or metastatic disease. In these circumstances various innovative new agents have been developed.

Bevacizumab is a first in class innovative humanised monoclonal antibody directed towards vascular endothelial growth factor, which inhibits development of blood vessels required for tumour growth.

A major clinical trial of bevacizumab with interferon alpha compared with interferon alpha alone, demonstrated substantially improved progression free survival associated with the combination regime. Adverse effects were higher in the bevacizumab arm of the trial, which may be partly due to the fact that treatment was longer in these patients than in those that received interferon alpha monotherapy. However, most bevacizumab related effects were of low severity. Whilst acknowledging the limitations of making comparisons across clinical trials, an indirect comparison with sunitinib suggested that the tolerability of bevacizumab and interferon alpha was, at least, no worse than that of sunitinib.

3. Notification of intention to appeal the Final Appraisal Determination

After careful consideration of the FAD issued by NICE in respect of bevacizumab, sorafenib, sunitinib (second line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma, Roche provides formal notification of its intention to appeal the conclusions of the Appraisal Committee.

This appeal is advanced under Grounds 1, 2 and 3 as permitted under NICE's procedures. Roche requests an oral hearing before NICE's Appeal Panel for the determination of this appeal.

4. Points of Appeal under Ground 1: Procedural Fairness

(1) The decision of the Appraisal Committee is improperly based on the overall affordability of treatments for renal cell cancer.

At paragraph 4.3.9 of the FAD, the Appraisal Committee describes its application of the supplementary advice issued by NICE on appraising life-extending, end of life treatments ("NICE's Supplementary Advice"). While the Committee determined that bevacizumab plus interferon alpha satisfied three of the four criteria listed in NICE's Supplementary Advice, the Committee concluded that the regime did not satisfy the fourth criterion, namely the requirement that *"the treatment is licensed or otherwise indicated for small patient populations"*. For this reason, the Committee concluded that the Supplementary Advice should not apply to bevacizumab plus interferon alpha therapy and therefore the regimen was not recommended by the Committee for use in NHS patients.

However, while NICE is empowered to appraise the clinical and cost effectiveness of health technologies referred to it by the Secretary of State, it is not permitted to determine whether a technology should be recommended for use in NHS patients, based on an assessment of the overall affordability of that technology (i.e. the total resources that would be required should a positive recommendation be made). The fourth criterion listed in NICE's Supplementary Advice is not related to clinical effectiveness or cost effectiveness of the technology under consideration; the wording suggests that it is simply a matter of overall affordability. For this reason, a decision based on the fourth criterion is contrary to NICE's procedures and falls outside the powers delegated to NICE by the Secretary of State. It is our belief that the small patient population criterion does not reflect the stated purpose for the Supplementary Advice, namely to take into account the additional benefits associated with treatments which may extend life at the end of life, on the basis that these are not or not adequately captured in the reference case. Such treatments may be valued more highly by patients and

should therefore qualify for approval based on a higher cost/QALY threshold than other medicines.

The fact that NICE is not permitted to base its decisions on the overall affordability of a particular technology has been made clear since the inception of the Institute. This situation was confirmed by the Secretary of State for Health speaking in the House of Commons on 8 March 2000:

> *"There are clearly two separate sets of decisions to be made. One is about effectiveness. It is right and proper that NICE should look at clinical and cost effectiveness side by side …. there is a separate set of decisions which, in the end, I take. I take decisions about affordability. Those are my decisions. That is right and appropriate and I will be held to account for them. When NICE comes up with recommendations, we will of course consider what it says. That is the right thing to do."*[1]

Therefore NICE must not consider matters of affordability unless the Institute has been given specific guidance regarding the resources that would be available to fund a particular technology, from the Secretary of State or the Welsh Assembly Government. There is no indication that NICE has received any such guidance from the Secretary of State or from the Welsh Assembly Government in relation to this appraisal.

The position is also addressed in NICE's procedural guides. The 2004 version of NICE's Guide to the Methods of Technology Appraisal ("the Methods Guide") stated at paragraph 6.2.6.2:

> *"the Appraisal Committee does not consider the affordability of the new technology but does take account of how its advice may enable the more efficient use of available health care resources".*

[1] House of Commons Hansard Debates, 8 March 2000, column 1023.

Interestingly, the wording of this provision has been modified slightly in the 2008 version of the Methods Guide which states, at paragraph 6.2.14:

> *"The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. The Committee does take account of how its advice may enable the more efficient use of available health care resources. In general, the Committee will want to be increasingly more certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases. Therefore, the Committee may require more robust evidence on the effectiveness and cost effectiveness of technologies that are expected to have a large impact on NHS resources".*

There is, however, no indication that any change in how NICE carries at its work is intended by these modifications or that the power or authority of the Institute has altered in any way following the 2008 issue of the Methods Guide.

Therefore the decision that the Supplementary Advice should not apply to bevacizumab plus interferon alpha therapy was based on the overall affordability of the technology under consideration using the small population criteria as a proxy for affordability, contrary to NICE's procedures, and standards of fairness.

For the avoidance of doubt, this point of appeal is also raised under Ground 3: Excess of Powers, and Roche would ask the Appeal Panel to consider it also on that basis.

(2) <u>The Appraisal Committee's interpretation of the Supplementary Advice on appraising life extending end of life treatments lacks transparency and is unfair.</u>

In applying NICE's Supplementary Advice, specifically the fourth criterion limiting the advice to treatments "licensed or otherwise indicated for small patient populations", the assessment of whether a population may be viewed as "small" is unclear and Roche has been prejudiced in its ability to participate in the consultation process in this appraisal in circumstances where the approach to be followed by the Appraisal Committee has not been explained. During the public session of the Appraisal Committee meeting on 14th January it was apparent that there were significantly different views being expressed between Committee members regarding how this particular criterion should be interpreted including differences of opinion between the Chair and the Vice Chair of the Committee.

(a) In this appraisal, the Appraisal Committee considered not only the patient population with advanced or metastatic renal cell carcinoma, eligible for treatment with bevacizumab plus interferon alpha, it also took into account all other patients for which regimes including bevacizumab are licensed. Paragraph 4.3.9 of the FAD states:

> *"The Committee was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4,000. However, the Committee understood that it should take into account the cumulative population for each product in considering the strength of any case, for justifying decisions which employ, in whole or part, the supplementary criteria for appraising life extending, end of life treatments. It noted that bevacizumab was licensed for a number of other indications involving much larger patient groups"*.

No explanation is given for the Appraisal Committee's belief that it should take into account the cumulative population for each product, including all indications for which a bevacizumab regimen is licensed and the approach followed by the Appraisal Committee is not understood by Roche.

The wording at section 1 of the Supplementary Advice emphasises the importance of developing treatments "for small groups of patients who have an incurable illness". The focus accordingly is on the requirement to support innovative treatments for rare cancers on the basis that the benefits of therapy associated with end of life treatments may not adequately be captured using standard appraisal methods. Such an imperative has nothing to do with whether or not the technology under consideration may, as part of the same or a different treatment regimen, be indicated for other cancer treatments. It should of course be noted that the various indications involving bevacizumab each require combination therapy with different agents so that the "treatment" in each case is not the same. Furthermore each indication requires its own extensive and costly development programme and if, as suggested by the wording of the Supplementary Advice, the intention is to encourage the development of innovative treatments for rare cancers, the fact that a treatment may be used for another malignancy is entirely irrelevant.

(b) During the course of the meeting of the Appraisal Committee on 11 March 2009, [redacted] went still further in suggesting that cumulation of different patient populations was appropriate when assessing criterion four of the Supplementary Advice, stating that all populations in which the product would be used worldwide, should be taken into account. While it is unclear from the FAD whether the Appraisal Committee ultimately relied on such an approach, it is inconsistent with that followed in relation to the FAD for sunitinib for the first line treatment of advanced and/or metastatic renal cell carcinoma and also with the FAD for lenalidomide

for the treatment of multiple myeloma in people who have received at least one prior therapy.

(c) During the consultation process Roche submitted that it was inappropriate to cumulate populations of patients receiving bevacizumab for different indications in view of the fact that use of the technology for other indications in the UK was very limited as a result of negative recommendations from NICE. In response, the Appraisal Committee stated *"that this point did not override its view that bevacizumab is licensed for a relatively large population across its range of indications"*. No reason for this conclusion is provided and it is unclear why the obtaining of any EU marketing authorisation for indications that are not the subject of the current appraisal has any relevance in the context of the Appraisal Committee's consideration of renal cell carcinoma patients, particularly in circumstances where there is no material use in such indications in the UK.

(d) It was also suggested during the course of the Appraisal Committee meeting that where a technology is licensed in several cancer indications, NICE would consider the first indication for which an authorisation was received under the Supplementary Advice (subject to it satisfying the listed criteria) but that subsequent indications would be subject to cumulation with the first and therefore likely to be excluded on the basis that the small patient population criterion was not satisfied. (By way of example, while sunitinib is already licensed for renal cell carcinoma, licenses are also imminent for additional use in GIST and in breast cancer.) If this is correct, and Roche requires clarification as to NICE's position in this respect, the result is arbitrary and unfair. The rationale for the Supplementary Advice is not connected with the order in which a marketing authorisation for various indications may be obtained, and the effect of such an approach may be to influence regulatory strategy so that

an authorisation is sought first for the clinical indication that may be expected to benefit most from the Supplementary Advice rather than in an indication where the efficacy appear greatest. It appears arbitrary and unfair that patients with renal cell cancer should be denied access to a treatment simply because of the ordering of the application for licences for different indications for that treatment.

(3) The basis for the Appraisal Committee's conclusions with regard to the tolerability of bevacizumab plus interferon alpha are unclear.

At paragraph 4.3.8 of the FAD, the Appraisal Committee states that:

> *"it considered that there would be disutility associated with the high toxicity, poor tolerance and issues with the administration of bevacizumab plus interferon alpha, that had been highlighted by clinical specialists and patient experts, and that this disutility had not been incorporated into the cost effectiveness estimate of bevacizumab plus interferon alpha compared with interferon alpha".*

However, [redacted], the clinical expert who provided a written statement to the Committee, made no mention of increased toxicity associated with bevacizumab and the three patient experts similarly did not raise this as an issue. Their views are consistent with the results of the clinical trials which suggest that overall the tolerability of bevacizumab and interferon alpha appears at least no worse than that of sunitinib.

Furthermore, in the public part of the Appraisal Committee meeting on 11th March, there seemed to be agreement that the adverse event profile and tolerability of bevacizumab and interferon alpha appeared to be at least no worse than that of sunitinib and the Assessment Group assumed the same quality of life for both sunitinib and bevacizumab in their base case model.

In these circumstances, it is impossible to understand the conclusions of the Appraisal Committee in the absence of proper identification of the evidence relied upon at paragraph 4.3.8. Currently, it is unclear what material formed the basis for the conclusions expressed by the Appraisal Committee and a strong inference is raised that these simply constituted anecdotal reports which may not form the basis of credible scientific guidance issued by NICE.

5. Point of Appeal under Ground 2: Perversity

Roche considers that the conclusions reached regarding the side effect profile of bevacizumab plus interferon alpha are inappropriate given the evidence that has been presented to the Appraisal Committee.

In the second ACD, the Committee made the following comments regarding the adverse event profile of bevacizumab plus interferon alpha:

- Section 4.3.5:
  However, it was mindful of the adverse effects associated with the combination of bevacizumab and IFN-alpha

- Section 4.3.7:
  'it noted there were more participants in the bevacizumab arm of the trial than the IFN-α arm that were censored. The Committee considered that this was likely to be caused by a greater number of participants withdrawing from bevacizumab plus IFN-α treatment than IFN-α plus placebo treatment, which could be because of adverse effects of bevacizumab plus IFN-α treatment '

In Roche's response to the ACD, whilst fully acknowledging the importance of public comments on adverse events, the importance of assessing this against the level 1 clinical

evidence available was highlighted. Roche submitted robust clinical trial data relating to tolerability and adverse events from the randomised, double-blind, placebo controlled study for review by the Committee and made the following points:

- When taking into account the different duration of therapy, the adverse event profile and associated treatment withdrawals for the combination of bevacizumab plus interferon alpha was similar to that observed for interferon alpha alone.

- No detailed consideration of the adverse event profile for sunitinib appeared in the sunitinib FAD, even though the Committee commented in Section 4.1.12 of the sunitinib FAD that '*The frequency of adverse events associated with sunitinib is comparable to that associated with IFN-a monotherapy.'* Furthermore, the Committee's comments appeared to be based on an immature dataset that was inconsistent with a more mature published dataset that was available at the time of the original submission in January 2008.

- Whilst acknowledging the limitations of cross-trial comparisons, indirect comparison of the adverse event data from the two pivotal studies showed that the adverse event profile and tolerability of bevacizumab plus interferon alpha appeared at least no worse than that of sunitinib.

As such Roche felt that the Committee had been inconsistent in its evaluation of the two different technologies within the MTA, and requested a re-evaluation of this issue.

In the public part of the Appraisal Committee on 11th March, there appeared to be agreement that the adverse event profile and tolerability of bevacizumab plus interferon alpha appeared to be at least no worse than that of sunitinib. Whilst the Assessment Group assumed the same quality of life for both sunitinib and bevacizumab in their base case model, in the FAD for sunitinib the Appraisal Committee appeared to utilise anecdotal evidence to suggest an increase in quality of life over the base case, whereas in

the FAD for bevacizumab the Committee assumed a reduction in quality of life also based on anecdotal evidence, contradicting the more robust clinical trial data submitted:

"It considered that there would be disutility associated with the high toxicity, poor tolerance and issues with the administration of bevacizumab plus IFN-α, that had been highlighted by clinical specialists and patient experts, and that this disutility had not been incorporated into the cost-effectiveness estimate of bevacizumab plus IFN-α compared with IFN-α. Taking these concerns that had been highlighted into account the Committee agreed that the ICER was likely to be an underestimate and therefore the Committee concluded that the lowest plausible ICER estimate was £53,800 per QALY gained".

The conclusions regarding the adverse event profile for bevacizumab plus interferon alpha are perverse based on the totality of the evidence base submitted.

6. Points of Appeal under Ground 3: Exceeding Powers

We would like to request that the Appeal Panel consider our points from Ground 1 in relation to the negative decision of the Appraisal Committee regarding bevacizumab being improperly based on overall affordability under Ground 3 also.

7. Conclusions

In the above circumstances it is clear that there remains substantial uncertainty regarding the application of NICE's new Supplementary Advice to the Appraisal Committee regarding the appraisal of life-extending, end of life treatments. Roche would respectfully request that the Appeal Panel should clarify the approach to be followed by the Appraisal Committee when considering the Supplementary Advice, in particular, the application of the fourth criterion relating to small patient populations.

As indicated above, we believe that the approach followed by the Appraisal Committee in this appraisal, which allowed the Committee seemingly to base a decision on grounds of overall affordability and to cumulate all indications for the various bevacizumab containing regimens irrespective of whether or not such treatments are in fact used in the UK, is inconsistent with the purpose for which the Supplementary Advice was issued and creates results which are arbitrary and unfair.

Following the clarification of the Supplementary Advice, Roche requests that the appraisal should be returned to the Appraisal Committee for further consideration in the light of that information and for consultation when the issues of lack of transparency, highlighted above, have been addressed.