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17 December 2010

Dear Karen

Final Appraisal Determination: Everolimus for the second line treatment of advanced and/or metastatic renal cell carcinoma

Thank you for lodging Novartis's appeal against the above Final Appraisal Determination.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

- Ground 1: The Institute has failed to act fairly
- Ground 2: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted.
- Ground 3: The Institute has exceeded its powers.

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am

satisfied that your points contain the necessary information and arguably fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

I can confirm that there will be an oral hearing of the appeal.

Initial View

Ground one

1.1. **NICE's failure to disclose to Novartis the modified economic model upon which its guidance is based, lacks transparency and is unfair**

The points you raise here are highly detailed. I note from the *BMS* case to which you refer that a mere failure to have provided your modified model back to you (if such a model exists) is not necessarily unfair. The unfairness arises only if "information can only be properly supplied by handing to the manufacturer the fully executable model as modified". As you are no doubt aware in the BMS case itself no modified model was provided, and that was not held to have been unfair.

I am minded to refer this issue to the appeal panel, but in view of the factual complexity of the issues you raise I am concerned to do so in a way which allows the appraisal committee fairly to prepare for the hearing, and which will allow the appeal panel to deal with the issues correctly on the day. This means that the issues must be comprehensively set out in writing in advance.

Before I refer this issue on, then, I would be grateful if you could provide a full statement of all of the complaints you are making under this ground, together with all of the supporting material on which you rely. My intention is that this will form the case which the committee must meet. I would like this to take the form of a document, perhaps based on the material at para 1.1 in your letter, which sets out each factor on which you wished to comment but which you say was not made sufficiently clear, and then for each such factor, (1) the material you had, (2) the material you were provided with, and (3) the material you say existed but you were not provided with, explaining if it is not obvious why the material you were not provided with was necessary for you to make informed comment notwithstanding the material you did have or were given.

I would be grateful if you would relate each such factor to the timeline of the appraisal, so that the panel can see which issues were in play before or during consultation, and which have been introduced at other times.

I would also be grateful if you would provide all of the contemporaneous documentation in which you raised these issues with NICE.

Although I am assuming you will be able to satisfy me on this point and so am minded to refer this issue to an appeal hearing, I will reserve my final decision until I have had the chance to review these materials.

1.2. The lack of transparency in relation to the extrapolation of data on OS associated with everolimus therapy using a Weibull curve is unfair

This appeal point appears very closely related to point 1.1, and I would be grateful if you could provide the same information requested above. Although I am presently minded to refer this issue to an appeal hearing, I will reserve my final decision until I have had the chance to review these materials.

1.3 The lack of opportunity afforded to consultees to scrutinise and comment on the ERG's "exploratory" analyses (modifications to Novartis' model) which form the basis of the recommendations in the FADs dated June 2010 and November 2010 constitutes procedural unfairness.

I agree this is a valid appeal point, which can be reduced to your comment that [fairness required that] "*NICE should either have requested consultation on the ERG report before the meeting of the Appraisal Committee on 12 May 2010 or should have issued a second ACD for consultation following that meeting"*

Ground two

2.1 The reasons given by the Appraisal Committee for refusing to consider the investigation of uncertainty surrounding the hazard ratio for overall survival (OS) based on a more clinically plausible range, carried out by Novartis, are inconsistent with the request from NICE to investigate a plausible range and the evidence. This therefore constitutes perversity

This seems a simple disagreement on the evidence. The appeal point seems to me to turn on whether the only reasonable view is that your cut offs, derived from the results of your clinicians survey and the ITT analysis in the RECORD 1 trial, had to be preferred to those modelled using the RPSFT method. I am not sure how this can ever be more than a disagreement between experts, and if so, how the appeal panel can be asked to reach a view.

Before I take a final view, could you provide me with details of how your clinicians survey was conducted, focusing especially on the measures taken to avoid bias in the results? If you could also address my concern that this amounts only to an expert disagreement that would also be very helpful.

2.2 The approach of the Appraisal Committee to the possibility of uncertainty in the assessment of cost effectiveness is inconsistent with that followed in other appraisals and is therefore perverse.

In a recent appeal decision, the appeal panel responded to a similar point in these terms:

The Appeal Panel found the reference to other appraisals unhelpful. The possibility and extent of vial sharing depended on the characteristics of the product, its indications, and the arrangements made for treating patients. A relatively stable product available only in large vials for a relatively common condition treated at large treatment centres lent itself to vial sharing. An unstable product available in small vials and used for rarer conditions in small centres did not lend itself to vial sharing. The importance of vial sharing would therefore differ from one appraisal to another.

My understanding, (and I was a member of the appeal panel in question), was that the appeal panel was laying down a general rule that bare inconsistency arguments were not plausible, because each appraisal would ordinarily differ too much from any other for detailed consistency to be a reasonable expectation. In this case, you are comparing the very end point of this appraisal, encapsulating all the data, uncertainty, and special considerations in the appraisal, with two others, encapsulating different data, uncertainty and special considerations. It seems to me at present that it will not be possible to argue with any hope of success that these two other appraisals are so closely related to this appraisal that the differences in conclusion you detect are unreasonable.

I am therefore minded to reject this appeal point, but before doing so would appreciate your comments on why the two appraisals you cite should be seen as binding on this appraisal.

2.3 Due to the heterogenous nature of the studies and the patient populations included in the Delea meta-analysis referred to in sections 3.6, 4.5 and 4.10 of the FAD dated November 2010, reliance of the Appraisal Committee on the ratio of PFS:OS of 1:1.4 to quantitatively justify the survival gain of 5.9 months from the ERG's analysis is perverse, as the results from this analysis are unlikely to represent so specifically the OS gain conferred by everolimus.

I agree this is a valid ground two appeal point

2.4 The Appraisal Committee has disregarded the available evidence for OS in patients who receive BSC

This appears to me to be a simple disagreement on the evidence. I cannot see that the Committee can be said to have disregarded the evidence you cite, rather, it appears to have considered the available evidence but had concerns about the uncertainty surrounding it. The committee specifically refer to the ERG estimate varying from observed clinical practice, but conclude that differential survival, which is the important issue, was more plausible.

I am minded to reject this appeal point.

2.5 The estimates of mean OS associated with BSC alone, relied upon by the Appraisal Committee are inconsistent and do not reflect the referenced calculations of the ERG

The Committee do not seem to rely on an estimate of 10.8 months at para 4.7 of the FAD, they attribute that figure to the ERG. I have not been able to trace your reference to a figure of 10.08 in a table 2 of the ERG report dated 27 April 2010, the ERG report available on NICE's website is dated 30 November 2009 and table 2 does not contain the figure referred to. I am also concerned that this is

not a relevant issue, as the key figures are surely the incremental difference in overall survival, which you do not challenge here (although it is challenged at 2.3 above). What then does this challenge add to point 2.3?

I would be grateful for elaboration on these points before reaching a decision.

2.5 Reliance of the Appraisal Committee on a mean probabilistic ICER to justify the decision not to recommend everolimus is perverse as the mean probabilistic ICER will vary from one run to another.

It cannot be the case that use of probabilistic sensitivity analyses per se is unreasonable. My understanding is that they are a widely accepted technique and, although it may be they have strengths and weaknesses which could be the subject of discussion between expert statisticians, I cannot agree that an appeal to the NICE appeal panel on the grounds of reasonableness has any prospect of success.

I am minded to reject this appeal point.

Conclusion

As I am minded to rule that at least some of your appeal points are valid, I will pass your appeal to the Appeal Panel for consideration.

If you wish to make any further comment on the points that I have indicated that I do not, at this preliminary stage, view as valid please provide to me this within 10 working days from the date of this letter (omitting the 2-week Christmas holiday period), no later than **Monday 17 January**. I will then reach a final decision on the validity of those points.

Yours sincerely

Maggie Helliwell
Appeals Committee Chair
National Institute for Health and Clinical Excellence