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██████████
Senior Outcomes Research Manager, Haematology and Metabolics
Janssen-Cilag Ltd

17 September 2010

Dear ██████████

Final Appraisal Determination: Bortezomib and thalidomide for the first line treatment of multiple myeloma

Thank you for lodging Janssen-Cilag'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 Failure to disclose the economic model is unfair

A valid ground one appeal point.

1.2 The appraisal committee's reasons for limiting use to patients who have contraindications to thalidomide are unexplained

A valid ground one appeal point.

1.3 In deciding to place less weight on thalidomide studies which included a maintenance phase, the committee relied on evidence not disclosed to consultees.

I note that the committee rejected these studies in the ACD, and gave a reason for doing so. You considered this was incorrect, and made comments on this together with a graph illustrating your argument. The committee evidently considered this material, but was unpersuaded by it.

Whatever the rights or wrongs of that as a substantive conclusion, it seems to me the issue was raised with you, you had a chance to comment, and the comments were considered. Fairness does not require you to have a further chance to comment, if your first comments are not found sufficiently persuasive.

I am therefore minded not to allow this point to go forward to an appeal hearing.

1.4 The reduced weighting for studies with a maintenance phase is unexplained and appears inconsistent with NICE's guides to the methods of technology appraisal.

I note first that departure from the methods guide is not necessarily unfair of itself.

It seems to me this is a straightforward disagreement with the weight to be given to these studies, albeit presented in terms of the reduced weight being "unexplained" rather than too little. That has to be a matter for the committee (subject, maybe, to the weight not being perversely little).

I am therefore minded not to allow this point to go forward to an appeal hearing.

Ground two

2.1 The exclusion of critical evidence from thalidomide trials has resulted in a fundamentally flawed evidence synthesis

A valid ground two appeal point.

2.2 The appraisal committee have demonstrated a lack of consistency in considering clinical experts opinions

With some misgivings, I agree this is a valid ground two appeal point. I would point out that the premise, if it is a premise, that all evidence at the same level in the hierarchy of evidence should carry similar weight, is unsustainable. But I am assuming you will argue that the specific evidence you say was ignored could not rationally have been ignored, and on that basis I am allowing the appeal to go forward.

2.3 A conclusion that use of 31.5 vials of Bortezomib should be considered the most optimistic estimate for clinical practice is inconsistent with the evidence.

It is unclear to me whether you are at issue with the committee at all here. They use the language of a "most optimistic" estimate, but do appear to model the use of 31.5 vials, you prefer to point out that 31.5 vials was the actual average found in a clinical trial, and should have been a "base case" but you are not, I think, arguing that some lesser figure than 31.5 should have been in play? It is hard to see how that argument could be made, on your own trial data.

In short, although I can follow your argument that there was a misunderstanding in the assessment report, it seems to have been corrected by the time of the FAD. Whether 31.5 is called "optimistic" or a "base case", could you help me by pointing out the consequent perversity in the FAD itself?

I should say I am also struck that the committee's description of 31.5 as optimistic was in relation to clinical practice. It does not seem necessarily perverse to regard an average found in the controlled setting of a clinical trial as optimistic in the less controlled setting of clinical practice.

I am therefore minded not to allow this point to go forward to an appeal hearing.

2.4 Failure to consider vial sharing is inconsistent with available evidence and other appraisals

Again with some misgivings, I agree this is a valid ground two appeal point. I note that you do not seem to have provided the committee with any analysis of vial sharing and there appears to have

been little evidence on the point. Subject to the comment that ground two relates to "guidance which cannot reasonably be justified in the light of the evidence submitted", I agree this is a valid ground two 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 days from the date of this letter, **no later than Friday 1 October**. 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