

Dr Maggie Helliwell
Appeals Committee Chair
The National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
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30th September 2010

Dear Dr Helliwell

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

Thank you for your letter dated 17th September 2010 providing your initial views on the points of appeal raised by Janssen in our appeal letter dated 10th September 2010.

In this letter, we respond to your initial views before a final decision is made regarding admissibility.

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

Noted.

- 1.2. **The Appraisal Committee's reasons for limiting use of bortezomib to patients who have contra-indications to thalidomide, rather than those for whom thalidomide is clinically inappropriate, are unexplained.**

Noted.

- 1.3. **In deciding to place less weight on thalidomide studies which included a "maintenance" phase, the Appraisal Committee relied on evidence from the Assessment Group which has not been disclosed to consultees.**

While we note your comments, these do not address the principal issue raised by our appeal.

In our appeal letter, we explained that the reasons given by the Appraisal Committee in the FAD (at paragraph 4.3.4) for its decision to place little weight on thalidomide studies including a "maintenance" phase, referred to comments made by the Assessment Group (at paragraph 4.1.20). However, the Assessment Group's evidence in this respect has not been disclosed to Janssen, either in writing or at the meeting of the Appraisal Committee and we have been given no opportunity, either to understand the concerns raised by the Assessment Group or to respond to them in consultation. In circumstances where the statement reported at paragraph 4.1.20 of the FAD, appears inconsistent with the available data, it is clearly unfair that evidence from the

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Assessment Group, which has not been disclosed to consultees, has been relied upon by the Appraisal Committee in reaching its decision with respect to the reliance which should be placed upon these thalidomide studies.

- 1.4 **While the Appraisal Committee decided that the thalidomide studies which included a “maintenance” phase should receive less weight than those with no “maintenance” phase, such weighting is unexplained and appears inconsistent with NICE’s guide to the methods of technology appraisal.**

In your letter, you suggest that the point of appeal advanced by Janssen is a straightforward disagreement with respect to the weight to be given to studies including a “maintenance” phase. We do not agree with this view.

The issue raised at Point 1.4 of our appeal is that the weighting given by the Appraisal Committee, to the thalidomide studies including a “maintenance” phase, appears inconsistent with the approach set out in NICE’s Methods Guide (Section 5.3.9). While we accept that departure from the Methods Guide does not necessarily mean that an approach is unfair, a reasoned explanation is clearly required to justify such divergence. In this case, no explanation has been provided for the decision not to follow the approach set out in the Methods Guide; this is unfair.

- 2.1 **The exclusion of critical evidence from thalidomide trials has resulted in a fundamentally flawed evidence synthesis that is not a sound basis for decision making.**

Noted.

- 2.2 **The Appraisal Committee has demonstrated a lack of consistency in considering clinical experts’ opinion to inform its decision**

Noted.

In response to your comments, we accept that it is not necessarily appropriate to attach equal weight to different pieces of evidence at the same level in the hierarchy of evidence. However, in this case, the Appraisal Committee has chosen to rely on expert opinion in relation to the interchangeability of MPT and CTDa regimens, even though these opinions are inconsistent with the RCT data. In contrast, the Committee has declined to rely on expert opinion on circumstances in which thalidomide treatment is in fact clinically inappropriate, even though there is no evidence opposing those views. It is this approach to the assessment of evidence which appears arbitrary and therefore perverse.

- 2.3 **The Appraisal Committee’s conclusion at paragraph 4.3.8 of the FAD that an assessment of cost-effectiveness which assumes use of 31.5 vials of bortezomib “should be considered the most optimistic estimate for clinical practice”, is inconsistent with the available evidence.**

The Appraisal Committee’s statement, at paragraph 4.3.8 of the FAD, that an assessment of cost-effectiveness based on 31.5 vials of bortezomib is “the most optimistic”, determines the Committee’s consideration of uncertainty sounding the

ICER. By suggesting that the ICER based on treatment with 31.5 vials is the lowest possible value, the Committee indicates that all other plausible ICERs are higher. This conclusion is inconsistent with the available evidence and therefore perverse.

In your letter, you say that it does not seem necessarily perverse to regard an average quantity of treatment used in the controlled setting of a clinical trial, as optimistic in the less controlled setting of clinical practice. However, while the Appraisal Committee refers to “discussion” with the Assessment Group, no evidence to suggest that more than 31.5 vials are used on average in clinical practice, has been disclosed to Janssen. The evidence provided by the British Society for Haematology, the Royal College of Pathologists and the UK Myeloma Forum was consistent with the use of 31 vials of bortezomib. Furthermore, while the Appraisal Committee declined to consider vial sharing during the first appraisal of bortezomib, it is well known that, in practice, vial sharing occurs. In these circumstances 31.5 vials is quite clearly not the most optimistic estimate for treatment and the error by the Committee has adversely influenced its consideration of uncertainty surrounding the ICER for bortezomib.

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

Noted.

In response to your comments, we would ask the Appeal Panel to note that the Appraisal Committee declined to consider vial sharing during the first appraisal of bortezomib for multiple myeloma (TAG 129). The issue was raised by Janssen in our response to the ACD in the context of this appraisal and we would be pleased to provide relevant analyses to assist the Committee, if they are willing to consider them.

We look forward to receiving your final decision in relation to the admissibility of our points of appeal.

Yours sincerely

Senior Outcomes Research Manager