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Director of Research and Advocacy

Myeloma UK

22 Logie Mill, Beaverbank Business Park

Edinburgh EH7 4HG

Sent by e-mail only: xxxxxxxxxxxxxxxxxxxxxxxxxx

22 December 2022

Dear xxxxxxx,

**Re: Final Appraisal Document — Daratumumab in combination for the treatment of adult patients with Light-Chain (AL) amyloidosis**

Thank you for your letter of 16 December 2022, lodging an appeal against the above Final Appraisal Document (FAD).

Introduction

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

* 1(a) NICE has failed to act fairly, or
* 1(b) NICE has exceeded powers;
* (2) the recommendation is unreasonable in the light of the evidence submitted to NICE.

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, are arguable, and 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 will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn.

***Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly***

**Appeal point 1a.1 NICE has failed to act fairly by not taking into account the advice and experience of haematologists at every stage of the appraisal process.**

I am minded to refer this appeal point to the Appeal Panel.

**Appeal point 1a.2 NICE has not acted fairly by failing to allow the National Amyloidosis Centre to nominate its own clinical expert for committee meetings**

I am minded to refer this appeal point to the Appeal Panel.

**Appeal point 1a.3 In making the assessment that preceded the recommendation, NICE has failed to act fairly by neglecting to consider inequalities of healthcare provision caused by its decision.**

I do not consider this a valid appeal point.

The existence of geographical inequalities in existing healthcare provision is not a factor that the committee is required to consider under NICE’s Guide to the methods of technology appraisal 2013 (the “**Methods Guide 2013**”). This point can therefore be considered as a challenge against the appraisal process itself as set out in the Methods Guide, rather than against the final draft guidance, and as such would fall outside the scope of an appeal.

Accepting for the sake of argument that existing health inequalities can properly be considered as part of the evaluation process in this appraisal, I nevertheless still consider that you have not put forward an arguable case under ground 1a (or any other ground). MyelomaUK has not identified health inequalities beyond the simple fact that provision may vary on a regional basis. Differing regional or local approaches to commissioning and provision are commonly found in instances where NICE evaluates a technology. No argument has been put forward as to why regional variation gives rise to particular unfairness for patients living with AL amyloidosis as compared to other conditions where such variation is seen or why the approach taken by the committee in this appraisal is procedurally unfair.

Such inequalities as may be related to current differences in approach to the management of AL amyloidosis are not attributable to NICE.

I am therefore not minded to refer this appeal point to the Appeal Panel.

***Ground 2: the recommendation is unreasonable in the light of the evidence submitted to NICE***

**Appeal point 2.1 The Appraisal Committee’s conclusion that “both Alchemy and EMN23-UK may be representative of UK practice” is unreasonable in light of the evidence submitted.**

I am not minded to refer this appeal point to the Appeal Panel.

That is because, despite the points you make in your letter, I consider the committee had a sufficient basis on which to conclude that both Alchemy and EMN23-UK may be representative of UK practice. I note for example the following extract from the ERG Report at page 346 of the committee papers of 20 January 2022:

*In contrast to the two studies used in the CS, the ALchemy study reports a large prospectively collected dataset (n=1194) comprising of UK patients recruited by the NAC. The NAC is predominantly a tertiary referral service open to all NHS patients in England and Scotland with suspected or proven amyloidosis, treating around 80% of UK patients. The ERG’s clinical advisors estimate this study reports around two-thirds of all UK AL amyloidosis patients assessed between February 2010 and August 2019. Consequently, it is likely to be the cohort that most closely reflects the current UK clinical population and treatment context. In addition, the study reports overall survival for haematologic response assessed at 1, 3, and 6 months. This captures both the assessment points addressed in the CS model plus 1-month assessment of response, which the ERG’s clinical advisors suggest is becoming an increasingly common point at which treatment decisions are made.*

Further, there is a clear explanation in para 3.10 of the FAD of the committee’s conclusion on this point. I have identified no evidence in your appeal letter or otherwise to support an arguable case that the committee’s conclusion was unreasonable.

I therefore am not currently persuaded that it is arguable that the committee’s conclusion on this point cannot reasonably be justified from the evidence presented to it.

**Appeal point 2.2 The Appraisal Committee’s conclusion that “Potential confounding factors between haematological response and overall survival are not appropriately explored” is unreasonable in light of the evidence submitted**

I am not minded to refer this appeal point to the Appeal Panel.

That is because I consider the committee had a sufficient basis on which to conclude that potential confounding factors between haematological response and overall survival were not appropriately explored. I note for example the following excerpt from page 13 of the committee papers of 2 December 2022:

*In Appendix 4 of the ACD response, the company presented multivariate analyses of 11.4 month median follow-up data from the ANDROMEDA trial to assess the impact of baseline patient characteristics on overall survival for patients who achieved a CR at three months and six months.*

*However, the plots presented by the company in Appendix 4 suggest a failure to adequately estimate the parameters of interest, so no conclusion can be made. Many of the HRs presented do not have appropriately estimated confidence intervals, almost all are estimated at 0, or extremely high (with values in the millions also presented). The ERG cannot comment on these results as they do not appear to be adequately estimated.*

*The company also cites clinical advice that any confounding between haematologic response and the overall survival predictions in ANDROMEDA would not be meaningfully impactful. Given the lack of reliable results from the statistical analysis, this is still an area of uncertainty.*

The committee explains its conclusion at paragraph 3.12 of the FAD, noting the position of the ERG. I have identified no evidence in your appeal letter or otherwise to support an arguable case that the committee’s conclusion was unreasonable.

I therefore am not currently persuaded that it is arguable that the committee’s conclusion on this point cannot reasonably be justified from the evidence presented to it.

**Appeal point 2.3 The Appraisal Committee’s conclusion that “Some utilities derived from ANDROMEDA EQ-5D-5L data lack face validity and comparison with utilities from ALchemy is preferred” is unreasonable in light of the evidence submitted.**

I am not minded to refer this appeal point to the Appeal Panel.

That is because the committee clearly had a basis on which to query the face validity of utility values from ANDROMEDA. As stated at paragraph 3.15 of the FAD:

*The ERG identified that utility values from the group with a very good partial response were lower than utility values from the combined partial and no response group.*

The committee’s conclusion as to the validity of the ANDROMEDA utility values is also supported by the ERG’s position as described at pages 576 to 577 of the committee papers of 20 January 2022.

I note that the committee queried whether utility values could be obtained from the Alchemy data at this time, but then established that this was not possible. The committee did not therefore insist on the provision of information which was unavailable to Janssen.

I therefore am not currently persuaded that it is arguable that the committee’s conclusion on this point cannot reasonably be justified from the evidence presented to it.

**Appeal point 2.4 (referred to as 2.5 in your appeal letter) The Appraisal Committee’s conclusion that “an acceptable ICER is £20,000 per QALY gained” is unreasonable in light of the evidence submitted.**

A valid appeal point; however I consider this properly falls under ground 1(a) (not ground 2) as it goes to whether the committee has fairly applied the criteria for determining an acceptable ICER value under the Methods Guide 2013.

Conclusion

The above sets out above my initial views on all of your appeal points.

In respect of your points which I am not minded to refer on you are entitled to submit further clarification and/or evidence to me **no later than 17 January 2023** and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held which is likely to be held remotely.

Once I have made my final decision, and where there is more than one appellant, each appellant will receive the valid appeal points of the other appellants and their redacted appeal letter. This is to enable appellants to avoid duplication at the hearing where there are overlapping appeal points. If the appeal letter and/or responses to scrutiny contain confidential information, please ensure you have provided a version with this information redacted by **24 January 2023.**

Ordinarily appeals are conducted on the basis of the appellants’ written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be before the panel that you would wish to rely on you must let the NICE Appeal team know by return of letter, indicating what the material is, why it is desirable to submit it, and when it will be available, by no later than **18 January 2023**. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

Yours sincerely

Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence