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Senior Director, Patient Access

Janssen-Cilag Ltd

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Sent by e-mail only: xxxxxxxxxxxxxxxxxxxxxxxx

22 December 2022

Dear xxxxxx,

**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 1(a).1 The Appraisal Committee has failed to take into account factors other than uncertainty when defining the ICER threshold for this appraisal**.

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

**Appeal point 1(a).2 The Appraisal Committee’s conclusion that “it had not been shown if daratumumab in combination improves overall survival” disregards substantial evidence submitted by Janssen in support of complete haematological response as a surrogate endpoint for overall survival.**

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

There was no direct evidence in respect of overall survival. The committee was invited to consider complete haematological response as a surrogate endpoint and gave detailed consideration to this submission as discussed further in response to point 2.2 below.

**Appeal point 1(a).3 The fact that an expert haematologist was not invited to the first meeting of the Committee was not adequately corrected by inviting such an expert to the second meeting because issues such as the significance of complete haematologic response were not discussed**

I am 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 conclusions that “both ALchemy and EMN23-UK may be representative of UK clinical practice” are unreasonable**

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

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 Committee’s conclusion that “it had not been shown if daratumumab in combination improves overall survival” conflicts with the balance of the available evidence.**

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

The committee’s statement that “it had not been shown if daratumumab in combination improves overall survival” is accurate. There was no direct evidence in respect of overall survival. The committee was invited to consider complete haematological response as a surrogate endpoint. A clear basis for the committee’s concern in respect of overall survival data is apparent from the evidence presented to it. I note the following excerpts by way of example only:

* Janssen’s submission at page 94 of the committee papers of 20 January 2022 states that:

*Although OS data were immature at the interim analysis, these improvements in haematologic and organ response associated with the addition of daratumumab SC to BCd are expected to translate into substantial improvements in overall survival compared with BCd alone.*

* The ERG in their report to the committee of 20 January 2022 critiqued this expectation. At page 361 of the committee papers the ERG reports:

*The ERG considers that the assumption that overall survival depends only on the depth of*

*haematologic response achieved at the assessment time point of six months is overly simplistic and may bias the model predictions; however, the impact on the cost-effectiveness results is unclear.*

* The ERG further critiqued Janssen’s assumptions in modelling overall survival, at pages 373 to 375 of the committee papers of 20 January 2022. The ERG summarised the position as follows:

*The ERG has major concerns that the company’s base-case analysis, with the response assessment informed after six treatment cycles and overall survival informed by Palladini et al (2012), overestimates overall survival for UK patients with CR.*

In short, the committee was not provided with direct evidence of improved overall survival and had evidence of meaningful concerns in respect of the proposed surrogate endpoint.

I am not currently persuaded that there is an arguable case that the committee’s conclusion was unreasonable.

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