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Director – Value, Access and Pricing UK & Ireland

Incyte Biosciences UK Ltd

First Floor, Q1

The Square, Randalls Way

Leatherhead KT22 7TW

Sent by e-mail only: xxxxxxxxxxxxxxx

26 September 2022

Dear xxxxxxxx

**Re: Final Appraisal Document — Tafasitamab with Lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma [ID3795]**

Thank you for your letter of 16 September 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 because “The Committee has not taken loss of lenalidomide exclusivity and the associated impact on lenalidomide costs into account in the context of this appraisal”**

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

The basis of the appeal point, as I understand it, is that it was unfair for the Committee to rely upon costs for lenalidomide taken from the BNF in August 2022 and which relate to branded Revlimid. You say that this was unfair because Revlimid has now lost data exclusivity and “*a number of generic versions of lenalidomide have been launched on the UK market during the course of 2022*”. That being the case, you say that the Committee should have based its cost-effectiveness calculations on the generic price of lenalidomide.

The reasons why I am not minded to refer this point are as follows:

1. The Committee is required to use public list prices for technologies unless there are nationally available price reductions, in which case the reduced price should be used to best reflect the price relevant to the NHS. (Methods Guide 5.5.2)
2. The Committee can only consider evidence submitted to it at the time of the appraisal and there was no nationally available price other than the list price for branded Revlimid at the relevant time.
3. The ERG base case analysis was therefore set on the known list price.
4. The future price trajectory for generic lenalidomide was unknown at that time, and could not have been known.
5. It was therefore, in my initial view, neither unfair nor contrary to the Methods Guide for the Committee to base its cost-effectiveness conclusions on the list price of Revlimid, that being the national available price at that time.
6. In any event, there is clear evidence in the papers made available to the committee that they did consider a range of price scenarios around both the company and the ERG base cases in attempting to assess the plausible ICER range - with several price scenarios approximating to the putative discount for generic lenalidomide over its branded analogue.

**Appeal point 1a.2 NICE has failed to act fairly because “the Committee’s conclusions regarding the cost-effectiveness of tafasitamab and lenalidomide lack transparency and are therefore unfair”**

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

The Committee concluded at paragraph 3.9 of the FAD that the most plausible ICER was likely to be between the company’s and the ERG’s base-case estimates. In addition, you have stated in your appeal letter that Incyte was “*informed verbally that the ICER range exceeds the threshold of cost effectiveness that NICE would typically view as a cost effective use of NICE resources and therefore there is no requirement to provide the details*”. The basis of the appeal point, as I understand it, is that the Committee’s “*conclusions regarding the most plausible ICER*” are said to be insufficiently clear, because it is impossible for Incyte to understand whether the Committee’s conclusions are soundly based or unreasonable. In particular you say “*it is uncertain whether the Committee’s most plausible ICER is close to the company’s estimate or the ERG’s and if so where it lies”, and while “Incyte recognises that some of the net prices for medicinal products in this appraisal are confidential and that actual ICER values may not therefore be disclosed… for this appraisal to be comprehensible and the recommendations of the Committee understood, it is essential that ICER ranges, providing an indication of the Committee’s conclusions are disclosed*.”. Further, you say that Incyte cannot know (based on the information in the FAD) what it needs to do (in the Committee’s view) to achieve a positive recommendation.

The reasons why I am not minded to refer this point are as follows:

1. The Committee has explained at paragraph 9.3 of the FAD that it could not precisely set out the upper and lower bounds of the ICER range whilst preserving confidentiality.
2. The Committee has also explained at paragraph 9.3 of the FAD that the company’s and ERG’s base case probabilistic ICERs (including all the confidential discounts) were higher than the range normally considered cost-effective, even for end of life treatments.
3. The Committee further explained that, whilst it recognised the need for effective treatments, tafasitamab with lenalidomide had not been shown to be cost-effective *in any analyses* presented. (I understand from your appeal letter that the Company may not agree with this conclusion, based on the Company’s assessment of the application of EoL criteria and/or the appropriate reference price for lenalidomide, however this does not give rise to arguable unfairness in relation to this appeal point.)
4. It is therefore clear from the FAD that the Committee considered that the most plausible ICER was likely to fall between the Company and the ERG base case, and that both ends of that range are higher than the range normally considered cost-effective.
5. This is consistent with the requirements of the Methods Guide, and fairly presents a picture of the ICER range identified by the Committee, whilst preserving commercial confidentiality.
6. Further detail is also provided in the slides presented to the Committee at FAD stage, including the part 1 slides which have been seen in unredacted form by the Company.

On the basis of the above, I cannot see how the Committee’s approach could arguably be said to be unfair, and I am therefore not minded to refer this appeal point to the Appeal Panel.

**Appeal point 1a.3 NICE has failed to act fairly because “The Committee’s decision that tafasitamab and lenalidomide should not be recommended for use through the Cancer Drugs Fund in view of the lack of comparative evidence is procedurally unfair”**

I agree that this is a valid appeal point but I am minded to refer it to the Appeal Panel for consideration under ground 2.

The Committee concluded in paragraph 3.10 of the FAD that tafasitamab with lenalidomide did not meet the criteria for inclusion in the Cancer Drugs Fund. In part, this conclusion was based on the Committee’s assessment that further evidence on survival and response outcomes that the company plans to produce “*will not provide additional comparative evidence. The model would still rely on indirect evidence for comparator treatments, so this would not resolve a key uncertainty.*”

The bases of your appeal point, as I understand them, are that:

1. “*Based on the results from L-MIND and the decisions of the Licensing Authorities in EU and UK there was no basis for the conduct of randomised trials of tafasitamab and lenalidomide with other licensed treatments in the population of patients under consideration in this trial*”; and
2. “*a CDF recommendation would allow particular uncertainties identified by the Committee… to be addressed*”.

I cannot see any arguable unfairness arising from either of these points. The Committee’s decision that tafasitamab and lenalidomide should not be recommended for the CDF is not based on the lack of a randomised controlled trial *per se*. The FAD makes clear that the Committee reached that decision on the basis of evidential uncertainties, and its assessment that those uncertainties would not be resolved by the further evidence in view. I can see, without expressing a view on it, that the latter conclusion – that the further evidence would not address the identified uncertainties – could be argued to be unreasonable. For that reason, and on that basis, I am minded to refer this appeal point to the Appeal Panel under ground 2.

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

**Appeal point 2.1: The recommendation is unreasonable because “the Committee’s conclusion that patients eligible for treatment with tafasitamab and lenalidomide do not meet the end of life criteria does not reflect the balance of the available evidence”**

I agree that this is a valid appeal point.

**Appeal point 2.2 The recommendation is unreasonable because “the Committee’s conclusion that the company’s base case ICERs were not plausible because the model survival outputs were not consistent with TA 649 disregards the evidence generated since that appraisal”**

I am not minded to refer this point to the Appeal Panel. The appeal letter quotes the following from paragraph 3.9 of the FAD, alleging that this sets out the Committee’s entire reasons for rejecting the ICERs submitted by Incyte:

*The committee considered that the company’s base case ICERs were not plausible because the modal survival outputs were not consistent with NICE’s technology appraisal guidance on polatuzumab vedotin.*

The appeal letter argues that this unreasonably disregards the evidence generated since the appraisal on polatuzumab vedotin. However, the Committee provides additional reasoning in the next sentence of paragraph 3.9 of the FAD:

*[The Committee] acknowledged that although the ERG’s base case was more closely aligned with these survival outputs, they may overestimate survival for polatuzumab vedotin with bendamustine and rituximab (see section 3.6).*

Section 3.6 sets out extensive additional consideration and reasoning concerning the approach taken to polatuzumab vedotin with bendamustine data and in particular, to the conclusions of TA 649. Having considered that approach, the committee stated the following:

*… the committee* [ie the Committee carrying out the current appraisal] *also took into account feedback from clinical experts on outcomes observed in clinical practice submitted in response to the appraisal consultation document. These suggested that the estimates from the ERG’s base case may be overestimated, despite alignment with NICE's technology appraisal guidance on polatuzumab vedotin with bendamustine and rituximab.*

It is my initial view that the reasoning set out in paragraph 3.6 of the FAD makes clear that the Committee did not rely solely on TA649 in reaching its view that the base case supplied by the Company was not plausible, and for that reason, the appeal point is not arguable.

**Appeal point 2.3 “The Committee’s conclusion that the evidence presented did not demonstrate that tafasitamab is innovative is inconsistent with the Promising Innovative Medicine (PIM) designation by MHRA and the Committee’s own conclusions elsewhere in the FAD”**

I am not minded to refer this appeal point to the Appeal Panel. In section 3.11 of the FAD the Committee recognised that certain additional benefits of tafasitamab with lenalidomide may not be captured in the QALYs. The Committee then concluded that the technology should not be considered innovative within the meaning set out in the Methods Guide. The argument in your appeal letter, as I understand it, is that this conclusion is unreasonable because:

1. It is inconsistent with the decisions of the MHRA to designate the treatment a ‘Promising Innovative Medicine’ and of the US FDA to designate the treatment a ‘Breakthrough Therapy’; and
2. It is inconsistent with:
	1. the Committee’s recognition in paragraph 3.1 that treatment delivered in an outpatient setting would have a significant positive effect on the quality of life of patients and their families”, and
	2. the Committee having noted in paragraph 3.11 that the company submitted that uncaptured benefits include the advantage of administration in an outpatient setting.

The Methods Guide (6.3.3) explains that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factor (amongst others):

*The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure*

In this case, the Committee noted that this means that for a technology to be considered innovative *in the context of a NICE technology appraisal*, the technology should add “demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure”. This is a specific set of requirements, which go beyond what might in a general sense amount to a technology being ‘innovative’. That the MHRA and US FDA considered the technology to be innovative (or in the US FDA’s case, ‘breakthrough’) within their own definitions of those concepts is not determinative of whether or not the technology meets the test under consideration by the Committee. Therefore I can see no arguable unreasonableness here.

Further, to the extent that your appeal point challenges the Committee’s conclusion that the treatment should not be considered innovative for any other reasons, I can see no arguable unreasonableness in the Committee reaching its conclusion that the specific test set out in the Methods Guide is not met, having acknowledged that there may be some uncaptured benefits including the benefits brought by treatment in an outpatient setting. This is particularly the case given the clinical expert evidence heard by the committee, “*that tafasitamab with lenalidomide is considered to be innovative, but not necessarily a step change*”.

For those reasons, I see no arguable unreasonableness here and am therefore not minded to refer this point to the Appeal Panel.

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 within the next 10 working days, **no later than 10 October 2022** 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 **17 October 2022.**

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 **11 October 2022**. 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