Sent by e-mail only: XXXXXXXXXXXXXXX

GSK

GSK House

980 Great West Road,

Brentford, Middlesex,

TW8 9GS

T +44 208 047 5000

11 August 2023

Dear XXXXXXXX XXXXXXX

**Re: Final Draft Guidance (FDG) - belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more prior therapies [ID2701]**

Thank you for your letter of 4 August 2023, lodging an appeal against the above Final Draft Guidance (FDG).

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

**Appeal point 1(a).1: The Committee’s conclusions on the validity of belantamab UK RWE and related analyses lack transparency and are inconsistent with the focus placed on real-world data use in the NICE strategy for 2021 to 2026.**

I am not minded to refer this appeal point to the Appeal Panel under ground 1(a) (procedural unfairness). That is because the Committee discusses the NPP data at para 3.8 where it sets out the views of the company, experts and EAG and explains concerns about that data, namely:

1. The EAG considered that feasibility of a matched adjusted indirect comparison (MAIC) was not improved by using NPP;
2. NPP introduced additional uncertainty as it was less mature and included a smaller sample size than DREAMM-2;
3. the median progression-free survival was much longer in the NPP study than in DREAMM-2, which the Committee considered suggested that the population in NPP may be less likely to have disease progression and that this may favour belantamab in the company’s updated naive unadjusted comparison;
4. the extent and direction of the potential bias was unclear in the company’s naive comparison.

I consider it unarguable that the FDG provides inadequate explanation of the Committee's position in respect of the real-world evidence provided such that GSK is "unable to understand the Committee’s reasons for rejecting the naïve comparison". I cannot see what more might be required whether by section 6.1.8 of the NICE Manual or as a matter of procedural fairness. I note the company's position on confidentiality necessarily constrains the specificity that the Committee can provide in the FDG.

However, I am minded to refer a valid appeal point under ground 2 that the Committee’s conclusions on the validity of belantamab UK RWE are unreasonable in the light of the evidence submitted to NICE, noting in particular your argument that:

*"the key consideration is not whether the population in the NPP study is less likely to have disease progression than the population in DREAMM-2, but rather whether the population in the NPP study reflects the patients likely to receive belantamab in UK clinical practice (which it clearly does) and whether it is appropriate to compare patients from the NPP study with those from NCRAS"*.

Finally, with regard to your argument under (B) (that the Committee's conclusion is inconsistent with the NICE 2021-2026 strategy) I do not consider any such inconsistency would be appealable per se. That is because NICE's strategy is implemented through NICE's published methods and processes as set out in the Manual; I see no arguable point that the Committee has departed from the procedural requirements of the Manual.

**Appeal point 1(a).2: The Committee’s decision that belantamab is not suitable for use through the Cancer Drugs Fund (CDF) is procedurally unfair**

I am minded to refer this appeal point to the Appeal Panel limited to your argument under (A) that the Committee applied the wrong test under para 6.4.6 of the Manual.

I do not regard your argument under (B) (namely "The Committee’s apparent conclusion that only comparative data could sufficiently support the case for recommendation disregards the benefits of RWE") as a valid appeal point under ground 1(a). That is because nothing in your appeal supports an arguable procedural unfairness here.

I am however minded to refer your argument under (B) as a separate appeal point under ground 2 that the Committee's conclusion on managed access was unreasonable in light of the evidence.

**Appeal point 1(a).3: The Committee’s conclusion that TA897 should not be taken into account in the context of this evaluation is inconsistent with NICE’s processes and is inadequately explained**

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

**Appeal point 1(a).4: The Committee’s conclusion that it would not recommend belantamab in the 5L+ TCR MM post-POM setting due to the uncertainty in the comparative evidence is unfair, given that these limitations were largely driven by the paucity of evidence for the comparator despite being recommended by NICE and in circumstances where the effect of the decision is that patients will be forced to receive less effective treatment with less evidence of benefit**

I appreciate your concern with regard to the impact of a paucity of evidence for the comparator, however I do not regard this as a valid appeal point under ground 1(a). That is because nothing in your appeal supports an arguable departure from the requirements of the Manual or other requirements of procedural fairness.

I consider that your arguments under this point may be supportive of a ground 2 point, but I am not yet persuaded by your appeal letter that this is an arguable point. If you wish to bring an appeal point under ground 2 (that the Committee's conclusion that it would not recommend belantamab in the 5L+ TCR MM post-POM setting due to the uncertainty in the comparative evidence is unreasonable in light of the evidence) then I invite you to do so in your response to this letter, explaining why you consider the Committee's judgment in respect of this sub-group was flawed and bearing in mind that the Committee is obliged to consider both clinical and cost efficacy when exercising its judgement as to whether a technology can be recommended.

**Appeal point 1(a).5: The Committee has failed to fairly consider belantamab in the original (5L+ TCR) or revised positioning (5L+ TCR post-pomalidomide subpopulation) in which belantamab offers significant benefits to UK patients with a high unmet need**

I do not regard this as a valid appeal point.

Having "recognised that belantamab may offer significant benefits to some individuals" at 3.10 of the FDG, the Committee stated that "it was not possible to define this subgroup of people who would be expected to have greater clinical benefit than the broader eligible population." I understand that this is a factually accurate statement. Similarly I accept for the purposes of this letter that it is factually accurate for GSK to state in your appeal that "there are no approved therapies with a validated biomarker to predict which patients may respond to therapy."

That the above two statements are factually accurate does not in itself create an arguable procedural unfairness.

If (as I understand it) you consider that this potential subgroup can be identified quickly following commencement of treatment, then there are ways that response can be modelled to inform subgroup analysis, such as through stopping rules. It was for the company to provide that modelling to demonstrate to the Committee that the technology would be cost effective if used in this way. I see no procedural obligation on the Committee that has arguably been breached.

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

**Appeal point 2.1: The Committee’s conclusion in relation to the data from the DREAMM-3 are unreasonable in the light of the evidence submitted.**

I am minded to refer this appeal point to the Appeal Panel limited to your argument under (B) (that the Committee’s conclusions regarding the DREAMM-3 subgroup data as being the most relevant to this decision problem are unreasonable).

I do not regard your argument under (A) (that the Committee’s conclusion at 3.9 of the FDG that "the DREAMM-3 ITT population results were relevant to its decision making" is unreasonable) as a valid appeal point. That is because the FDG shows that:

1. the Committee was aware of the points you raise in your appeal and understood the limitations of DREAMM-3 in the context of this appraisal; but
2. nonetheless considered it had relevance for its decision-making, for the reasons at paras 3.9-3.10, i.e. that DREAMM-3 was a single comparative study between belantamab and a comparator providing PFS results in both treatment arms. See in particular para 3.10:

"Despite these limitations, [the Committee] agreed with the EAG that the randomised subgroup data from DREAMM-3 may be less biased than the single-arm, non-randomised evidence presented by the company (see sections 3.4 to 3.8). It discussed how the effectiveness data was likely to be more comparable in DREAMM-3 because it came from a single study rather than 2 independent studies. The Committee also discussed that DREAMM-3 provided progression-free survival results for both treatment arms, so there is no need to use a proxy measure…"

While the points you raise (i.e. that the DREAMM-3 ITT population does not reflect the licensed indication for belantamab, the patients eligible for treatment, or the decision problem for this appraisal) arguably limit the degree of relevance or weight given to the DREAMM-3 data, I am not persuaded that they support an arguable point that the only reasonable view was that the DREAMM-3 data had no relevance whatsoever.

**Appeal point 2.2: The Committee’s failure to recognise belantamab as an innovative intervention with benefits not captured in the economic modelling is inconsistent with the innovation passport granted by MHRA, the evidence submitted by GSK and stakeholders’ comments in response to the consultation on the draft guidance and is therefore unreasonable.**

I do not regard this as a valid appeal point. I respond to your arguments in turn.

Your argument under (A) appears to be that it was unreasonable for the Committee to conclude that "all additional benefits of belantamab had already been taken into account" and it "did not identify any additional benefits of belantamab not captured in the economic modelling" because the MHRA had granted belantamab an innovation passport. I am unpersuaded that the MHRA's assessment (which is by a different body applying different criteria and not subject to NICE's methods and processes set out in the NICE Manual) could arguably render the Committee's conclusion unreasonable. For the same reasons I disagree that there is any arguable duty on the Committee to provide an "explanation for diverging from MHRA’s assessment" and in any event that would not support an appeal point under ground 2.

Your argument under (B) appears to be that "more weight should be given to the innovative nature of belantamab", noting that it would be the first BCMA targeted therapy within the NICE pathway and citing comments from stakeholders. Assuming that belantamab is innovative, the argument at (B) does not identify any benefit arising from that innovation that arguably renders the Committee's conclusion that "all additional benefits of belantamab had already been taken into account" in the modelling unreasonable.

Your argument under (C) is that it is unreasonable for the Committee to conclude that it "did not identify any additional benefits of belantamab not captured in the economic modelling" because: (1) belantamab "would improve patients’ QoL by bringing hope to a group who otherwise are left with poor treatment options which may negatively impact their and their family’s mental health" and (2) "the burden on caregivers and impact on their QoL is not reflected in the QALY calculations". I am not persuaded that these points support arguable unreasonableness in the Committee's conclusion. That is because (as you acknowledge in your appeal letter) any positive psychological impact could have been captured in the QALY calculations and modelling, as could any substantial effects on carers' health-related QoL (see in particular sections 4.2.7 and 4.3.17 of the NICE Manual). It was for the company to submit evidence of these QoL benefits and include them in its modelling, had it wished to do so. I can see no arguable case that the Committee's conclusion was unreasonable in light of the evidence submitted to NICE.

At (D) you appear to argue that the following points are not captured in the economic modelling (and thus it was unreasonable for the Committee to conclude that "all additional benefits of belantamab had already been taken into account") :

1. That belantamab benefits some patients because it is not used with combination steroids which may have toxic side effects. As with my response to (C) above, this could have been captured in the QALY calculations and modelling, and it was for the company to submit evidence of the benefits. Your appeal does not identify evidence submitted to NICE in light of which the Committee's conclusion was arguably unreasonable.
2. That belantamab is the only antibody treatment to be licensed for MM that targets the BCMA. The Committee was clearly aware of this (see para 3.1 of the FDG). Your appeal does not make an arguable case for why this factor is so distinctive and/or substantial as to amount to an "uncaptured benefit" arising from the innovative nature of the technology that the Committee unreasonably failed to acknowledge or give appropriate weight at para 3.21 of the FDG.
3. The clinical need of patients with triple-class refractory MM after 4 or more treatments. The Committee was, again, aware of this (see para 3.1 of the FDG), and again your appeal does not make an arguable case for why this factor is so distinctive and/or substantial as to amount to an "uncaptured benefit" arising from the innovative nature of the technology that the Committee unreasonably failed to acknowledge or give appropriate weight at para 3.21 of the FDG.

Should you wish to pursue this point, I invite you to explain what you consider the Committee was bound to do (as a matter of reasonableness) in respect of the factors at (2) and (3) any why you consider the Committee's approach rendered its recommendation unreasonable in the light of the evidence submitted to NICE.

**Appeal point 2.3: The Committee’s conclusions on the severity modifiers in the 5L+ TCR post-POM subgroup are unreasonable given the evidence indicating the applicability of a 1.7 severity weight.**

I am minded to refer this appeal 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, 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 25 August 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 29 August 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

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Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence