Sent by e-mail only: XXXXXXXXXXXXXX

FAO XXXXXXXXXXXXXXX

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Pfizer

18 August 2023

Dear XXXXXXXXXXXXXXXX

**Re: Final Appraisal Document — Voxelotor for treating haemolytic anaemia caused by sickle cell disorder (SCD) (ID1403)**

Thank you for your letter of 11 August 2023, lodging an appeal against the above Final Draft Guidance (FDG).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: "It was procedurally unfair for the Committee not to give, at any point during the appraisal process, any indication of what it considered to be the plausible cost-effectiveness of voxelotor."**

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

**Appeal point 1(a).2: "It was procedurally unfair for the Committee not to inform Pfizer, in sufficient time in advance of ACM2, of the estimates generated by the exploratory scenario analyses of the external assessment group (‘EAG’)."**

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

**Appeal point 1(a).3: "In a situation where the Committee considered there still to be multiple sources of uncertainty by the time of ACM2, it was unfair nevertheless to proceed directly to the publication of the FDG with no opportunity for a further ACM or to explore suggestions such as managed access."**

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

I understand the appeal point to raise two distinct arguments:

1. That it was procedurally unfair not to proceed to a third Appraisal Committee Meeting ("ACM") where there were uncertainties that remained unresolved. You appear to rely on an expectation that this would happen, based on NICE's previous practice.
2. That it was procedurally unfair not to provide further opportunity to consider a Managed Access Agreement after the second ACM.

In regard to the first argument, I note your reference to section 5.2.1 of the NICE Health Technology Evaluations Manual (the "[Manual](https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741)") which states:

*"it is not possible to set absolute timelines for all stages of the evaluation. The length of time needed for each stage can vary depending on the nature of the particular evaluation."*

I am aware of no procedural requirement in the Manual or otherwise on the Committee to proceed to a third ACM where uncertainties remain. It is clear from the FDG that the Committee considered the uncertainties that remained and took these into account, concluding that any plausible ICER was highly uncertain but likely to be above the suitable range (FDG paragraph 3.20). This approach was open to the Committee as a matter of procedural fairness. There can be no assumption by a company that, rather than incorporate any remaining uncertainties into its decision-making, a Committee will proceed to a third Committee meeting to seek to explore them further. I can see nothing in the Manual or conduct of previous Committees that could arguably support that proposition. I therefore am not persuaded that there is a valid appeal point in relation to your argument that the Committee should have convened a third ACM as a matter of procedural fairness.

In regard to your second argument, the Manual states:

*"5.5.21 A company may opt to make a managed access proposal for any medicines that may be considered eligible through the Cancer Drugs Fund or the Innovative Medicines Fund. Early engagement with NICE about a managed access proposal is encouraged to allow exploration of the potential for further data collection to address significant uncertainties in the evidence. Multiple touch points within the evaluation process provide opportunities for NICE, the company and other stakeholders to identify if a medicine may be suitable for managed access, and that a managed access proposal could be submitted, including:*

*• At scoping, during the decision-problem stage where the company is considering making a managed access proposal.*

*• At submission, a managed access proposal as part of the company's submission.*

*• At technical engagement (if held) when significant uncertainties are highlighted, and a managed access proposal could be submitted.*

*5.5.22 Managed access proposals should be submitted at the evidence submission stage…"*

It is clear that the onus is on the company not only to indicate its interest in exploring an MAA but to make a proposal. I can see nothing in the Manual or otherwise that arguably creates a procedural obligation for the Committee to invite the company to make a proposal in the period following the second ACM before publication of draft guidance.

Furthermore, at the first ACM meeting on 7 December 2022, the Committee noted that you had not put forward a manged access proposal and that:

*"To consider a recommendation with managed access, the committee need a managed access proposal (requested as part of the company submission) along with a feasibility assessment from NICE (normally expected approximately 4 weeks prior to the committee meeting)".*

Therefore, I consider it unarguable that the Committee have acted unfairly by providing inadequate opportunity or notice for you to submit a managed access proposal.

I note that you have argued in your appeal letter (paragraph 23-27) that it was unrealistic and unfair for you to submit a managed access proposal before the second ACM. I have considered these reasons but remain unpersuaded that this is a valid appeal point. In regard to your first and second points as to why the company did not put in a proposal, the Manual and guidance provided by the Committee in the first ACM slides clearly set out expectations in regard to submitting a managed access proposal. I disagree that this was a "different approach" or that the Committee failed to convey its position clearly to the company with reasonable notice.

In regard to your third point, I understand you say that the reason the company did not make a proposal was that no ICER had been provided. Whether an ICER or range should have been shared is a question that will be explored under ground 1(a).1, and you may refer under that point to the impact and consequences of the Committee not having shared this. However, I do not consider that the absence of a plausible ICER from the Committee renders its decision to proceed to publication of the draft FDG after the second ACM without exploring managed access with the company procedurally unfair.

**Appeal point 1(a).4: "Given the nature of the outstanding issues, the Committee should have ensured that a clinical and/or patient expert was invited to ACM2, to speak directly on issues where their input would have been valuable."**

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

**Appeal point 1(a).5: "The Committee should have explained more clearly, during the appraisal process, how it intended to take (or not take) the health inequalities in relation to SCD into account in its decision-making and why."**

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

I understand this appeal point to be that the Committee has failed to **explain** adequately how it intended to take (or not take) the health inequalities raised during the evaluation into account and why. It is clear that the Committee were aware of the issues relating to health inequalities that had been raised: see the responses to consultation (including the NICE response to the specific comments to which you refer in your appeal letter) and the slides from the second ACM meeting: <https://www.nice.org.uk/guidance/gid-ta10505/documents/1-2>. The Committee acknowledge health inequalities in the FDG at paragraph 3.18, concluding that:

*"it was willing to take health inequality into account in its decision making by accepting a higher cost effectiveness estimate than it otherwise would have done, despite the considerable unresolved uncertainty (see section 3.20)."*

In my view the papers demonstrate that the Committee were aware of the issues raised regarding health inequalities and explained how they were taken into account as part of the evaluation (i.e. by accepting a higher ICER). Whether this was an adequate adjustment under equalities law is an arguable appeal point which I will refer to the Appeal Panel (as your point 1(b).1)) but I can see no arguable appeal point that procedural unfairness demanded more by way of explanation.

***Ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers.***

**Appeal point 1(b).1: "The adjustment made by the Committee to reflect the health inequalities associated with SCD, while welcome, was inadequate and should not have been so limited in scope."**

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 Committee’s conclusion that there was too much uncertainty, such that it could not assess the cost-effectiveness of voxelotor, was irrational."**

I do not regard this as a valid appeal point.

I understand your appeal point to be that the Committee's decision not to provide an ICER owing to uncertainty (rather than factor that uncertainty into the most plausible ICER) was highly unusual in light of the evidence submitted to NICE and therefore required a cogent explanation. Without such explanation, you say the approach was unreasonable as it differed from the approach taken in apparently similar other appraisals. You consider there was no good reason for this approach and that all of the unresolved issues or uncertainties identified by the Committee do not constitute such a reason. The Committee's approach to two of the five issues you identify are challenged in your appeal points 2.2 and 2.3 which I consider valid (see below). Your appeal point 2.1 appears to be that the Committee's concerns about uncertainty 'ranged from greatly overstated to simply incorrect', such that the Committee's overall conclusion that the degree of uncertainty prevented calculation of a sufficiently reliable most plausible ICER was unreasonable.

I note the Committee concluded at paragraph 3.17 of the FDG that:

*"the high levels of uncertainty about the population and model inputs meant that it could not adequately assess the cost effectiveness of voxelotor, given the historic challenges associated with SCD."*

Page 2 of the FDG summarises the reasons as follows:

*"Voxelotor has the potential to address the health inequalities associated with sickle cell disease and the unmet need for effective treatments, so a higher cost effectiveness estimate could be accepted for decision making. But, the estimates for the company’s proposed second line positioning were extremely uncertain. Any estimate that could be considered sufficiently reliable for decision making would likely be above what NICE considers an acceptable use of NHS resources."*

The Committee have considered the uncertainties raised in the evaluation and concluded that they should be taken into account by accepting a higher ICER.

I accept that there may be specific arguments as to how the data was understood, which have been raised in your appeal points 2.2 and 2.3 (see further below), but I can see no arguable point that the Committee's overall approach to uncertainty (whereby it identified the issues, explained that it would accept a higher ICER than usually an acceptable use of NHS resources and explained why it was unable to calculate a most plausible ICER) was unreasonable.

**Appeal point 2.2: "The Committee misunderstood the relationship between the proposed positioning/NHS population and the trial population. It drew incorrect conclusions."**

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

**Appeal point 2.3: "To the extent that the Committee considered that the rates of RTT modelled in the voxelotor and SoC arms of the model could be the same, and relied in the FDG on that being a possibility, it was unreasonable to do so."**

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 1 September 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 4 September 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