FAO xxxxxxxx

Merck Sharp & Dohme (UK) Ltd

Sent by e-mail only: xxxxxxxxxxxxxxxx

4 April 2023

Dear xxxxxxxxxxx

**Re: Final Draft Guidance — Therapeutics for people with COVID-19 [ID 4038] [now** [**ID6261**](https://www.nice.org.uk/guidance/indevelopment/gid-ta11297)**]**

Thank you for your letter of 27 March 2023 responding to my initial scrutiny views. This is my final decision on initial scrutiny.

I consider the ground 1(a) points followed by the ground 1(b) point and then the ground 2 points.

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

**Appeal point 1(a).1; NICE has followed an ad hoc process and departed significantly from established procedures for MTAs**

In my initial scrutiny letter I set out that I was minded to refer this appeal point to the Appeal Panel, save that I was not minded to admit challenges against the NICE Manual or the Process Statement per se. I’ve considered your comments in response to that position.

Thank you for confirming MSD accepts for the purposes of this appeal that it cannot challenge the content of the Manual itself and that your argument under this point is that the procedure adopted did not adhere to the procedure and safeguards contained in the Manual (and at times, in your view, undermined those safeguards).

I note you consider the Process Statement differs fundamentally from the Manual, and MSD does not accept that the Process Statement cannot be the proper subject of an appeal, which you say “*is not a procedure that NICE is legally bound to follow in all appraisals, but rather something that NICE has chosen to follow because of the peculiarities of this particular appraisal.*” I note your position that: “*Any changes to NICE’s published processes in the Guidance Manual (which is adopted after mandatory consultation…) − no matter how procedurally unfair they might be − would then apparently be beyond the scope of an appeal and only challengeable by way of a judicial review*.”

You summarise that

“*With respect to the Process Statement, our appeal therefore asks two distinct questions:*

1. *whether the Process Statement is consistent with the Guidance Manual and upholds the procedural safeguards in the Guidance Manual; and*
2. *separately, whether the Appraisal Committee did in fact follow the Process Statement in this appraisal.”*

Having considered the additional arguments made in your letter of 27 March, I am of the view that the pertinent question for the Appeal Panel, under this appeal point, is whether NICE failed to act fairly, by following an ad-hoc process that departed from the Manual.

In considering this point, I anticipate that the Appeal Panel will wish to consider:

1. the extent to which the Committee did depart from the Manual;
2. if / the extent to which any departures potentially caused unfairness; and
3. if / the extent to which any potential unfairness was mitigated by the use of the Process Statement.

**Appeal point 1(a).2; The ad hoc process that NICE followed was inconsistent, unfair and unfit for purpose**

In my initial scrutiny letter I explained I was minded to refer this point 1(a).2 on the following limited basis: that NICE acted unfairly because it departed from published process by (1) allowing EAG to take decisions that should have remained with the Committee and (2) by allowing the EAG to make procedural and methodological changes without prior warning.

Your letter of 27 March 2023 argues for a broader appeal point.

Having considered the additional arguments made at (a)-(c) in your letter of 27 March, I agree these are valid arguments within this point 1(a).2. That is because there is a valid argument that the individual examples should be considered collectively. Whilst the incremental changes that were introduced, and which deviated from the process manual, may not be considered as significant when viewed individually there is an arguable point that the holistic effect could create unfairness in the process.

I have also considered and accept your proposal that your appeal point challenging the delegation of decisions to the EAG should sit under ground 1(b).

Accordingly, I will refer two separate points to the Appeal Panel:

Appeal point 1(a).2: NICE acted unfairly because of ad hoc process changes during the appraisal that individually or taken together led to unfairness.

Appeal point 1(b).2: NICE exceeded its powers by allowing the EAG to take decisions that should have remained with the Committee.

**Appeal point 1a.3; The Appraisal Committee’s closing its eyes entirely to relevant real-world evidence about molnupiravir proposed by MSD is procedurally unsound and led to an unfair assessment;**

**Appeal point 1a.4; The approach to real world evidence in this appraisal is inconsistent and runs contrary to the Guidance Manual and NICE’s obligation to carry out a fair and rational process.**

Thank you for confirming MSD is comfortable with combining Appeal points 1a.3 and 1a.4. I accept your amendment to the appeal point wording.

Therefore I will refer the combined point as: “*whether the Committee unfairly:*

* 1. *failed to take adequate steps to identify relevant evidence*
  2. *failed to consider relevant RWE about molnupiravir, particularly given its recognition of the “significant limitations” of the clinical evidence used in the appraisal and resulting uncertainty and the alleged particular relevance of the RWE that MSD presented, and/or*
  3. *treated RWE inconsistently.*”

**Appeal point 1a.5; The Appraisal Committee’s over-reliance on the PANORAMIC data to estimate the treatment benefit of molnupiravir and its approach to evidence synthesis were procedurally unfair**

Having considered the additional arguments made in your letter of 27 March, I agree that this is a valid appeal point under Ground 2 (unreasonableness). This is because there is a valid argument as to whether the conclusions drawn from the PANORAMIC data were unreasonable taking into account the known limitations of the data and the weight that was applied to this data set.

I will refer the point under Ground 2, and anticipate that the Appeal Panel will want to consider your arguments that:

* *The PANORAMIC study data had clear limitations in their relevance and generalisability, so making comparisons between, and synthesising, PANORAMIC data with data from other randomised-controlled trials considered in the appraisal was unsound.*
* *The Appraisal Committee itself acknowledged the limitations of the PANORAMIC study in its FDG.*
* *Despite its awareness and acknowledgment of the lack of generalisability and limited relevance of the PANORAMIC data, the Appraisal Committee used these in a flawed evidence synthesis process and invested the results of such with unduly significant weight in its ultimate decision not to recommend molnupiravir.*
* *In light of the clear deficiencies in the evidence synthesis process using the PANORAMIC study that were presented to and acknowledged by the Appraisal Committee, its influential conclusions developed on such shaky foundations cannot reasonably be justified.*

**Appeal point 1a.6** **The Appraisal Committee’s blanket capping of the efficacy levels of all treatments, without due consideration of each individual case, resulted in considerable bias and unfairness against molnupiravir**

Thank you for confirming that MSD accepts my admitting this appeal point under Ground 2.

**Appeal point 1a.7; NICE unduly focused on mortality and hospitalisation rates to assess clinical benefit rates and failed to give due consideration to other outcome measures, thereby creating bias against molnupiravir.**

In my initial scrutiny letter I explained I was minded to refer this point under ground 1a on the limited basis that it is arguably procedurally unfair that the appraisal departed from the final scope by omitting virological outcomes from the consideration of outcome measures; but that I was also minded to refer your argument (originally under point 1a.7(2), that “*The true benefits of molnupiravir were inadequately assessed in the MTA and omitted from the EAG’s economic model*”) under ground 2.

I explained why I was not minded to refer the remainder of your arguments under this point. Your letter of 27 March 2023 explains why you disagree with that initial conclusion.

Having considered the additional arguments made in your letter of 27 March 2023, I agree these are valid arguments within this point 1(a).7. I agree that there is a valid argument as to whether the Committee focused exclusively on hospitalisation and mortality outcome measures, at the expense of a systematic assessment of other relevant outcome measures.

Having referred this point in full under ground 1(a), I am satisfied that there is now no need for an additional referral under ground 2, in respect of this appeal point.

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

**Appeal point 1(b).1 NICE has breached its legal obligations under human rights and equalities laws**

Having considered the additional arguments made in your letter of 27 March 2023 I confirm my initial view that this is a valid appeal point.

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

**Appeal point 2.1; By evaluating evidence selectively, inappropriately, and in a methodologically unsound and unfair manner, the Appraisal Committee’s conclusions in respect of molnupiravir are necessarily unreasonable in light of the available evidence**

Having considered the additional arguments made in your letter of 27 March 202 I remain of the view that this appeal point should not proceed to an oral hearing.

My understanding of your position is that the cumulative effect of procedural changes is unfair, and that the unfairness (as you see it) leads to unreasonableness because the decision ‘lacks a rational basis or foundation and simply does not add up’. Your arguments as to unfairness fall to be considered under appeal 1(a).2, which I have agreed to refer to the Appeal Panel in full. I cannot see a possible scenario in which your appeal point 1(a).2 fails, but this appeal point 2.1 succeeds, or vice versa. Accordingly, I confirm my view that this appeal point will not be referred to the Appeal Panel.

**Appeal point 2.2; The Appraisal Committee’s administration cost assumptions for molnupiravir and nirmatrelvir plus ritonavir are unreasonable**

Having considered the additional arguments made in your letter of 27 March 2023, I agree that this is a valid appeal point. I have taken into consideration your arguments that your challenge is made on the basis that the administration costs used by the committee were demonstrably wrong based on the evidence that was available at the time of the appraisal, and therefore this decision was unreasonable.

Conclusion

Therefore the valid appeal points are:

* 1(a).1: NICE failed to act fairly, by following an ad-hoc process that departed from the Manual.
* 1(a).2: NICE acted unfairly because of ad hoc process changes during the appraisal that individually or taken together led to unfairness.
* 1(a).3: NICE acted unfairly because the Appraisal Committee unfairly:
  + failed to take adequate steps to identify relevant evidence
  + failed to consider relevant RWE about molnupiravir, particularly given its recognition of the “significant limitations” of the clinical evidence used in the appraisal and resulting uncertainty and the alleged particular relevance of the RWE that MSD presented, and/or
  + treated RWE inconsistently.
* 1(a).7: NICE acted unfairly because the Committee unduly focused on mortality and hospitalisation rates to assess clinical benefit rates and failed to give due consideration to other outcome measures, thereby creating bias against molnupiravir.
* 1(b).1: NICE has breached its legal obligations under human rights and equalities laws
* 1(b).2: NICE exceeded its powers by allowing the EAG to take decisions that should have remained with the Committee
* 2.2: The Appraisal Committee’s administration cost assumptions for molnupiravir and nirmatrelvir plus ritonavir are unreasonable]
* 2.3 (originally 1(a).5): the recommendation is unreasonable in light of the conclusions drawn from the PANORAMIC data, which were unreasonable taking into account the known limitations of the data and the weight that was applied to this data set
* 2.4 (originally 1(a).6): The Appraisal Committee’s blanket capping of the efficacy levels of all treatments, without due consideration of each individual case was unreasonable.

Finally, I confirm that NICE would, should it become necessary, confirm its view to the Court that the limitation period for any judicial review challenging a decision not to refer a proposed appeal point to the Appeal Panel, starts running only on conclusion of this appeal process.

NICE shares the valid appeal grounds of each appellant with the other appellants to assist with preparation for the hearing. These will be included in the appeal papers when they are circulated.

NICE will be in contact with you regarding the administration of the appeal, which will be held orally.

Yours sincerely

Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence