FAO xxxxxxxxxx

Merck Sharp & Dohme (UK) Ltd

Sent by e-mail only: xxxxxxxxxxxxxxxxx

14 March 2023

Dear xxxxxxxxx

**Re: Final Draft Guidance — Therapeutics for people with COVID-19 [ID 4038]**

Thank you for your letter of 7 March 2023, lodging an appeal against the above Final Draft Guidance (FDG).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 1a: 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**

I am minded to refer this appeal point to the Appeal Panel, save for any challenge against NICE’s published processes (i.e. the Manual and Process Statement) themselves, as opposed to the Committee’s compliance with the processes set out in those documents. That is because I consider if an appellant wishes to challenge the processes set out in the Manual and Process Statement (i.e. the steps that the Manual requires and the sequencing and timing set out in the Process Statement), as opposed to the committee’s compliance with those processes, then that is outside of the scope of the appeals process and would be a matter for NICE.

I am mindful of the company’s view that alleged departures were caused by NICE’s resequencing and/or shortening of NICE’s usual timelines in accordance with the Process Statement. That resequencing and/or shortening in itself cannot in my view be the subject of an appeal point, however I am minded to agree that an Appeal Panel can properly explore whether the approach taken departed from the requirements of the Manual and Process Statement.

My initial view is that the appeal point to put to the Appeal Panel should therefore read:

“*NICE has failed to act fairly because it has departed significantly from the requirements of the Manual and/or the Process Statement. In particular:*

* *the Appraisal Committee and the External Assessment Group (“EAG”) are said to have applied a less rigorous standard and methodology of review than is required under a conventional MTA, as set out in Appendix 1 of MSD’s letter.*
* *the Process Statement for ID4038 committed the EAG to carrying out a systematic evidence review, in accordance with the Guidance Manual. In practice, it is said that the process for gathering and reviewing was selective and any additional evidence submitted by consultees did not receive proper attention or review at different appraisal stages that could have facilitated engagement between companies and NICE.*”

To assist your review and response to my initial view, my more detailed response to your arguments under the ground are as follows:

1. *“ID4038 has not simply been a “re-sequenced” MTA (without conceding that it is open to NICE to re-sequence an MTA), but rather has followed an ad hoc, light touch programme which departs so significantly from the established procedures for technology appraisals under the NICE Health Technology Evaluations Manual (the “Guidance Manual”) that it cannot in truth be called an MTA at all.”*

I am not minded to refer an argument that the appraisal was not an MTA at all. This is outside of the scope of the appeals process and would be a matter for NICE. The same applies to your arguments that:

* 1. *“the output of an appraisal process that does not follow published procedures cannot deliver a “technology appraisal recommendation” under law and would not carry the same legal effect as such. One must question what the legal effect of ID4038 is and whether it should be promulgated as an “MTA””;*
	2. *“MSD further questions at what point NICE reviewed and approved the departures from the conventional MTA process; whether this was consulted upon and formalised; and what safeguards it put in place to ensure that the methodology and standard of review remained unaffected”; and*
1. *“the ad hoc process followed has led to the Appraisal Committee and the External Assessment Group (“EAG”) applying a less rigorous standard and methodology of review than is required under a conventional MTA*.”

I consider you make an arguable point here in relation to specific departures from NICE’s published processes, i.e. as set out in Appendix 1 to your letter. The first two bullet points on page 4 of your appeal letter appear to duplicate Appendix 1 – as to which see my comments below. I do not consider the third bullet point (at the top of page 5) is arguable as it is too general.

1. *“notwithstanding NICE’s commitment to follow “all the steps” of an MTA, the Process Statement issued on 28 September illustrates some key gaps…”*

I am not minded to refer your arguments relating to the content of the Process Statement p*er se* to the Appeal Panel. The committee is required to follow the process as set out in the Manual and the Process Statement. A challenge against the Process Statement itself would be outside of the scope of the appeals process and would be a matter for NICE.

1. “*The Process Statement for ID4038 required committed* [sic] *the EAG to carrying out* [sic] *a systematic evidence review, in accordance with the Guidance Manual*.’

I am minded to refer this point to the Appeal Panel, noting it appears to duplicate Appendix 1.

1. *Please also refer to the table attached at Appendix 1 to this appeal letter for a summary of further departures from NICE’s usual MTA process - Appendix 1 – “Key Departures from NICE’s Usual MTA Process”*

I am minded to refer the arguments you have raised in Appendix 1 to the Appeal Panel to assess whether the committee has departed from the Manual in the Appraisal, save that I do not consider any argument against NICE’s published processes themselves to be valid. In particular, I do not consider your following points arguable:

* your comment under “Invitation for evidence submissions” that there was a shorter window of 28 days for evidence submission, as this was specifically provided for in the Process Statement;
* your comment that the EAG reported without receiving any evidence submissions from consultees, as again this is provided for in the Process Statement.

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

I am 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. It will be for you to persuade the Appeal Panel that this did in fact happen and that it resulted in unfairness. I set out more detailed reasons below.

First, where your arguments here overlap with appeal point 1(a).1, (e.g. as to the evidence submission and review) and challenge NICE’s compliance with its published processes, I have considered them above and they will be heard within 1(a).1.

Secondly, I understand your argument under this point 1(a).2 to be that you have provided a “single set of examples” that you consider “*demonstrates a central flaw and unfairness of approach. NICE departed from its set procedures, replacing these with an ad hoc approach that created gaps, inconsistencies, and unsound comparisons*.” As set out above, if an appellant wishes to challenge the processes set out in the Manual and Process Statement (i.e. the steps that the Manual requires and the sequencing and timing set out in the Process Statement), as opposed to the committee’s compliance with those processes, then it seems to me that is outside of the scope of the appeals process and would be a matter for NICE.

Thirdly, I consider the following three arguments under this appeal point are additional to your arguments under 1(a).1. I set out my initial view on these arguments below:

1. *“First, the Appraisal Committee has over-delegated responsibilities that it must retain. It is NICE’s (and therefore the Appraisal Committee’s) responsibility to ensure the appraisal follows a fair and robust process – this is not the EAG’s role; nor is the EAG expert in these matters. To give the EAG free rein as to the scope of admissible evidence, how to scrutinise it, what to reject, and to take other shortcuts to improve efficiency is wrong.*

I consider it arguable that NICE acted unfairly because it departed from published process by (1) allowing EAG to take decisions that should have remained with the Committee.

1. *“Second, leaving the EAG to make procedural and methodological changes and simply notify these to NICE leaves consultees entirely in the dark. How could companies and others meaningfully follow and contribute to an evidence review process without knowing what would and would not be reviewed, when, and to what standard?*

I consider it arguable that NICE acted unfairly by allowing the EAG to make procedural and methodological changes without prior warning.

1. “*Further, the Protocol states that:* “[i]t is anticipated that re-running of models may be required as new evidence emerges, for example if studies reporting new data on the efficacy of interventions, potentially to new variants of SARS-CoV-2, are published, however, this will be dependent on when the MTA is taken to a NICE Appraisal Committee.” *This suggests that the procedure would be open to considering new data as and when it emerged, which led to a legitimate expectation that all new data would be considered (or, possibly, only data whose exclusion would impact on the main conclusions. The confusion here, and the difficulty of being sure what will or will not impact on the main conclusions, highlights how unfair this process was)”.*

I am not minded to refer this argument within 1a.2 as I do not consider it arguable as a standalone point. I have referred your arguments relating to the quality of the evidence review **in fact** under point 1a.1 and 1a.3.

**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.**

I am minded to refer your appeal points numbered 1a.3 and 1a.4 together to the Appeal Panel as a single appeal point.

I consider that the combined appeal point can be summarised as covering whether the Committee unfairly:

1. failed to take adequate steps to identify evidence outside the public domain,
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.

I invite you to explain in your response to this letter, if there is any good reason for distinguishing between 1(a).3 and 1(a).4.

**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.**

I am not minded to refer this appeal point as I see no arguable ground 1(a) point here. I consider the Committee was entitled as a matter of procedural fairness to handle the PANORAMIC data as it did.

**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.**

I am not minded to refer this appeal point under ground 1(a) as again I see no arguable case of procedural unfairness; I will however refer this as a ground 2 point as I consider it arguable that the Committee’s approach of a blanket cap on efficacy levels was unreasonable.

**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.**

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

I am not minded to refer the remainder of the point for the following reasons.

I note you say that “The central issue in this appeal ground is whether hospitalisation and mortality ought to have held such primacy over other outcome measures” and MSD submits that the Appraisal Committee’s approach is “irrational, procedurally unsound and leads to bias against molnupiravir” for four reasons set out in your appeal letter.

I consider it clear that the committee’s focus on mortality and hospitalisations stems from the fact that they are the key drivers for cost-effectiveness and therefore play a key role in driving the appraisal outcome. Page 3 of the FDG explains ‘*The cost-effectiveness estimates are highly dependent on how well each treatment works compared with standard care, and hospitalisation and mortality rates*.’ Whilst it is acknowledged by the committee that the changing circumstances around COVID-19 were driving other benefits this does not significantly impact on the overall cost effectiveness which was driven by mortality and hospitalisation. The committee set out their reasoning and the key drivers of cost-effectiveness in paragraph 3.21 of the FDG. I therefore disagree with your point (3) that *“the Appraisal Committee’s reasons for pursuing a narrow focus on hospitalisation and mortality in preference to other outcome measures is unexplained*”.

Even if I accept your arguments at (2) and (4) that “the true benefits of molnupiravir were inadequately assessed in the MTA and omitted from the EAG’s economic model” and “The assessment does not take into account a range of uncaptured benefits for molnupiravir”, I do not see that this creates any procedural unfairness in the Committee deciding to apply greatest weight to the measures which they consider drive the cost effectiveness in this appraisal.

I will however refer your argument under your point 1(a).7(2) (“*The true benefits of molnupiravir were inadequately assessed in the MTA and omitted from the EAG’s economic model*”) as a valid ground 2 point.

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

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

I am currently minded to refer this appeal point; but would be grateful for further explanation from you before reaching my final decision.

In summary, I understand your argument here to be as follows:

1. nirmatrelvir plus ritonavir, which is recommended within its licensed indication for mild Covid-19, is contra-indicated for some patients with protected characteristics
2. mindful of this, the Committee explored alternatives and recommended sotrovimab within its licensed indication where nirmatrelvir plus ritonavir is contraindicated.
3. Sotrovimab is a more intrusive treatment than nirmatrelvir plus ritonavir, has different side effects, and ‘IV therapies [such as sotrovimab] can be associated with increased infection, anaphylaxis and infusion-related reaction risks’.
4. This breaches:
	1. article 14 of the ECHR (which you say is engaged because articles 2, 3 and 8 are also engaged) by discriminating against patients who are unable to receive nirmatrelvir plus ritonavir
	2. the PSED, on the basis that NICE ‘ought to have robustly assessed the feasibility of other treatment options that reduced inequalities of treatment.
	3. Section 29 EA 2010 on the basis that NICE should have made the ‘reasonable adjustment’ of “conducting a thorough assessment of molnupiravir as an alternative to nirmatrelvir, including a robust assessment of all available evidence.”

Please can you explain whether the success or failure of this ground overlaps completely with your grounds under appeal point 1a? Put another way, on your analysis is it inevitable this ground will succeed if the Appeal Panel upholds one of your appeal points alleging procedural failings in the way that the Committee approached evidence relating to molnupiravir, and is it inevitable that this ground will fail if the Appeal Panel dismisses all of those grounds? It currently seems to me that this is the case.

***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.**

I am not minded to refer this appeal point to the Appeal Panel. That is because I consider your reasoning that any recommendation made following numerous alleged procedural errors must be unreasonable *per se* is flawed. I do not accept the proposition that procedural errors must result in substantively unreasonable decisions so I do not consider you have set out an arguable ground 2 point in your appeal letter.

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

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

As to your point (a) (unreasonably high administration cost for molnupiravir), the FDG para 3.26 acknowledges the challenge to the CMDU deployment costs used in the appraisal and sets out the approach taken by the committee. Whilst the FDG acknowledges that ‘*future delivery may be in primary care, which would likely reduce these costs’* , such hypothetical scenarios cannot be used as a basis for cost modelling. In my view the committee rightly took into account the current administration costs to the NHS at the time of the appraisal and it is not arguable that it is unreasonable to use current administration costs to inform cost modelling.

Your point (b) (unreasonable underestimation of the administration cost of nirmatrelvir plus ritonavir), complains that the FDG does not take into account the time required to ensure nirmatrelvir plus ritonavir is not prescribed to patients who are contraindicated or where there may be DDIs. I see no arguable unreasonableness here; nothing in your appeal letter explains why the Committee’s approach to the administration cost was beyond the bounds of what was reasonable on the evidence.

Furthermore, I do not consider that the Committee’s chosen approach on these points could have influenced the outcome of the appraisal, given the Committee considered molnupiravir “has limited effectiveness at treating mild COVID-19 compared with standard care” and molnupiravir was “*not recommended because [it is] unlikely to be effective at treating COVID-19* *and it is not possible to reliably estimate [its] cost effectiveness*” (pages 3-4 of the FDG).

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 28 March 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 March 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

Mark Chakravarty

Non-Executive Director

National Institute for Health and Care Excellence