Dr Mark Chakravarty

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5 July 2022

Dear Dr Chakravarty,

**Appeal against the Final Appraisal Document for Esketamine Nasal Spray for Treatment-Resistant Depression [ID1414]**

Thank you for your letter dated 21 June 2022, in which you provide your preliminary view of the admissibility of the points of appeal set out in Janssen’s appeal document submitted on 14 June 2022.

This is a complex appraisal and, in some important respects, the issues we raised in our appeal appear to have been misunderstood. We therefore provide, as you suggested in your letter, additional detail to elaborate, comment on or clarify those points of appeal (listed below) where your preliminary view was that these should not be referred to the appeal panel or should be directed to a different ground to that proposed by Janssen.

Ground 1(a)

1.1 The Committee recognises that clinical uncertainties are inherent to clinical trials in mental health but provides no explanation of how (if at all) this situation has been taken into account in its decision making

This point is central to our concerns in relation to the conduct of this appraisal and therefore to this appeal, especially, given that the way in which the clinical uncertainties are accepted by the Committee are considered in an appraisal is fundamental to a fair assessment for technologies addressing difficult to treat mental health conditions

In assessing this point of appeal, you have considered our submission as two separate sub-points. However, while our appeal simply divides the point into two parts to assist consideration by the Appeal Panel: (a) the Committee is required to take into account the clinical uncertainties inherent to clinical trials in mental health; and (b) it is required to explain how it has done so, therefore the two parts comprise the same appeal point and should be considered in that context.

We are very concerned by your preliminary view in relation to this point of appeal, which we do not believe responds to the points we have raised. You suggest, in summary, that the Committee has addressed the clinical uncertainties inherent to clinical trials in mental health by conducting theoretical modelling and sensitivity analyses. However, the Committee does not say that this is its response to the clinical uncertainties, and such an approach would be inconsistent with the purpose of theoretical modelling and the conclusions expressed in the FAD.

Theoretical modelling is a strategy required where the clinical trial or other data for an appraisal are incomplete in some way and is used in almost every appraisal conducted by NICE (see paragraph 5.7.2 of NICE’s Guide to the Methods of Technology Appraisal (2013) (the Methods Guide)). However, modelling cannot address the clinical uncertainties inherent in clinical trials in mental illness; all it can do is attempt to fill an evidence gap. In this appraisal, the Committee has repeatedly criticised both the clinical trial data and the outputs of modelling on grounds of uncertainty. The reasons for this criticism and the basis for the Committee’s conclusions regarding esketamine nasal spray (esketamine NS) are either that the clinical trial data are uncertain and should not be adjusted through modelling (e.g., paragraph 3.13 of the FAD) or that the results of modelling are uncertain because of uncertainties in the underlying clinical trial or other data (e.g., paragraphs 3.14 - 3.16 and 3.18 - 3.24 of the FAD). While you also refer to sensitivity analyses, these simply assess the extent of any uncertainty.

The uncertainty in the outputs of modelling rejected by the Committee is a direct result of the clinical uncertainties inherent to clinical trials and currently available evidence in mental health, as recognised by the Committee at paragraph 3.17 of the FAD. It is therefore impossible to conclude that the Committee has taken such difficulties into account by conducting theoretical modelling, only to reject the outputs of modelling based on the same “inherent” difficulties.

Finally, the FAD does not suggest that the Committee has used its standard modelling strategy or any other mechanism to take into account the clinical uncertainties inherent to clinical trials in mental health. The Committee should therefore be required to explain how, if at all, such matters have been considered, consistent with its obligation under paragraph 6.2.16 of the Methods Guide and the obligation of transparency at paragraph 6.1.9 and its failure to do so is a procedural deficiency in this appraisal.

A considered and fair procedure on the part of NICE, recognising the particular challenges in conducting research in mental health is essential if much needed treatments are to be developed and made available to NHS patients. However, while the Committee has recognised the inherent difficulties conducting research in mental illness, it has seemingly failed to take these into account when considering esketamine NS and this failure has impacted all aspects of this appraisal.

We address below the specific points raised in your letter under part (a) and part (b) of our appeal document.

Your response to part (a)

Your preliminary view that part (a) is not a valid appeal point is based on a conclusion that the Committee has responded to the uncertainties in the data relating to esketamine NS by conducting theoretical modelling, consistent with paragraph 6.2.16 of NICE’s Guide to the Methods of Technology Appraisal (2013) (the Methods Guide). However, as indicated above, theoretical modelling is a standard strategy where the available data are incomplete or unreliable and is used by NICE in almost every technology appraisal. The Methods Guide states at paragraph 5.7.2: “*Modelling provides an important framework for synthesising available evidence and generating estimates of clinical and cost effectiveness in a format relevant to the Appraisal Committee's decision-making process. Models are required for most technology appraisals*”.

Importantly, neither paragraph 6.2.16 of the Methods Guide (which deals with the approach of the Committee to uncertainty), nor paragraph 5.7.2 (which deals with modelling) suggests that theoretical modelling can resolve all uncertainties where there are inherent difficulties in generating reliable data as a result of the disease area itself. Paragraph 6.2.16 simply provides that the Committee is likely to consider more favourably technologies where the evidence is underpinned by the “*best-quality clinical data”* than ones where the evidence is based on the theoretical modelling. Paragraph 6.2.16 concludes by stating

*“However, the Committee is aware that* ***the evidence base will necessarily be weaker for some technologies****, such as technologies used to treat patients with very rare diseases”* [emphasis added]

The Committee recognised the existence of some of the inherent difficulties in conducting trials in mental health as required by paragraph 6.2.16 of the Methods Guide, but then focused at length on perceived uncertainties in the clinical data and the outputs of modelling when considering esketamine NS (there are at least 33 references in the FAD). It is therefore clear that the Committee did not conduct theoretical modelling in order to take into account the inherent difficulties conducting research in mental illness and there is no indication to the contrary in the FAD.

Your response to part (b)

Your preliminary view that part (b) is not a valid appeal point is based on your conclusion that the Committee addressed the inherent difficulties in conducting clinical trials in mental health through modelling. However, while the Committee addressed uncertainties in the available data through modelling, consistent with its standard approach, this does not address the issue advanced in this point of appeal; the Committee repeatedly expressed the view that the outputs of the modelling required in this appraisal resulted in uncertainty (e.g., paragraphs 3.18 - 3.24, of the FAD), and such uncertainty was a direct result of the inherent difficulties identified at paragraph 3.17.

Finally, you refer to previous consultations in this appraisal and suggest that “*no point has been taken previously as to the committee’s approach to the inherent uncertainties in this area*”. While we do not believe that the lack of a specific challenge by Janssen would justify the Committee breaching its obligation of transparency under paragraph 6.1.9 of the Methods Guide, your suggestion that Janssen has not previously raised the issue is incorrect. Janssen has in fact repeatedly referred to the challenges in conducting research in mental illness and asked the Committee to take these into account in conducting this appraisal. (The precise reference to inherent uncertainties was introduced by the Committee for the first time in the FAD.) By way of example:

* “In mental health and depression trials specifically, many trials fail to show a statistically significant efficacy outcome of the active drug compared with placebo…This demonstrates the challenge of conducting a successful trial in the field of depression, mainly caused by the high placebo effect of clinical trial participants. This challenge is also acknowledged by the CHMP.” [Clinical trials in the field of depression in perspective, Company submission Section B.2.1.3]
* “*The clinical data for ESK-NS should be considered in the wider context of the unique challenges of conducting clinical trials in this therapeutic area*” [Key point 1, Janssen response to second ACD]
* “*The results of the ESK-NS clinical trial programme should be considered within the context of clinical trials in depression. There are specific difficulties in conducting trials in this therapeutic area, as recognised by the EMA…*” [Key point 1, Janssen response to ACD]

1.2 Conducting an appraisal of esketamine NS using a procedure which fails to take into account the particular challenges investigating new treatments for depression, discriminates against people with this condition

You have agreed that this is a valid appeal point but suggest that it should proceed under Ground 1(b). You also say: “*So as to assist in preparing for this appeal, this appeal point 1.2 is limited to whether the committee’s application of NICE’s procedures in this particular appraisal discriminates against people with TRD*”.

We do not understand your letter to be suggesting that any part of the appeal point as drafted in our appeal document of 14 June should not be admitted. On that basis, we are willing to proceed as you propose.

1.3 The Committee has failed to take into account the broader social considerations in the appraisal of esketamine NS

This point of appeal relates to the Committee’s consideration of the non-health benefits associated with use of esketamine NS and whether the benefits of treatment in terms of health-related quality of life (HRQoL) have been adequately captured in the appraisal of the evidence. Both of these elements are of particular importance in considering health technologies indicated for the treatment of mental illness, which is associated with a substantial societal burden and challenges in capturing the benefits of treatment in standard tools for measuring HRQoL. It is therefore necessary as a matter of procedural fairness that the Committee considers these elements when reaching its conclusions.

You say that you are not persuaded by Janssen’s view that there is no evidence that such matters have been taken into account by the Committee or, if they have been taken into account, how such matters are reflected in the overall conclusions set out in the FAD. You raise two points in support of this conclusion.

* Paragraph 1.4.4 of the Methods Guide states that the Committee will take into account the Institute’s guidance on social value judgments, as described in the Institute’s document “Social Value Judgments; principles for the development of NICE”. This recognises at Principle 9 the impact of stigma and the fact that routine quality of life assessments may not capture the benefits of treatment in this context. However, you say in your letter that, while stigma was referenced by another consultee, Janssen had provided no evidence addressing how stigma would impact either effectiveness or routine quality of life assessments. You conclude that, “in the absence of evidence that the Committee ignored submission evidence indicating that its assessment of the change in the quality of life inadequately captured the health gain”, you are not persuaded there is any unfairness.

However, in its original submission (see page 35), Janssen provided evidence from a focus group held with patients with TRD in March 2019, which indicated that “*the limitations in effective treatment options result in the clinicians offering similar treatments over and over again, and that is not helping, and even more discouraging [for the patients]*”. In addition, these patients mentioned that it feels like their disease is ‘endless’ as they have no hope that additional treatment(s) will be effective, making them anxious to start another treatment. The disease is characterised by patients feeling embarrassed and stigmatised about their disease and living isolated lives, with *“no quality of life*” as a result.

However, in addition to the submission from a consultee referenced in your letter, NICE’s own 2009 Clinical Guideline on Depression (CG90) refers to the stigma which may be associated with a diagnosis of depression. This certainly constituted material that should have been taken into account by the Committee when considering whether all the benefits of treatment with esketamine NS had been captured in the QALY calculation.

Nevertheless, there is no indication in the FAD that the Committee gave any consideration to this issue and the statement at paragraph 3.39 of the FAD: “*The committee concluded that it had not been presented with robust evidence of additional benefits not captured in the QALY calculations*”, is simply unrealistic. The implications of the treatment of TRD, such as relief of stigma, are clearly not captured by standard health related quality of life measures and to refuse to consider such matters in the absence of “robust evidence” is clearly unfair.

* You say, in your letter, that costs or benefits incurred outside the NHS and personal social services or associated with significant benefits other than health, are to be taken into account only when expressly requested by the Department for Health and Social Care in its remit. However, this addresses only a situation where costs other than those relevant to the NHS and personal social services are to be taken into account.

Irrespective of any direction given to NICE in its remit, paragraph 6.3.3 of the Methods Guide expressly requires the Committee to consider in every case “*whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured*”. Appraisals where such changes have not been adequately captured are likely to include those, such as treatments for TRD, where there are significant benefits associated with successful treatment in addition to health. However, there is no evidence that such matters have been considered by the Committee in preparing the FAD in this appraisal.

Ground 1(b)

1.4 The Appraisal Committee’s conclusion that it is very uncertain whether esketamine NS with an SSRI or SNRI is more effective than placebo with an SSRI or SNRI assumes the role of the regulator and conflicts with the marketing authorisation for the product

Your letter indicates that this is a valid appeal point, but you consider that it should be brought under ground 2, rather than ground 1(b) because you say that it goes to the reasonableness of the Committee’s decision. You additionally express the view that the appeal point should be limited to “*whether the committee’s conclusion that the evidence is “very uncertain” is reasonable in light of the evidence (in particular the evidence from the licensing authority)*” and say that you “*do not consider it arguable that the Committee exceeded NICE’s powers by reaching a conclusion as to effectiveness, notwithstanding that that conclusion is arguably inconsistent with the view of the EMA’s CHMP in the licensing context*”.

We are concerned that this point of appeal may have been misunderstood. The issue raised here is the fact that regulators are responsible for assessing the efficacy of a technology (i.e., whether the product works at all); if a product does not produce a benefit, its benefit risk profile will inevitably be negative, and it will not be granted a marketing authorisation. In contrast, NICE is tasked with considering clinical effectiveness (i.e., the scope and magnitude of clinical benefits associated with use of a heath technology) and cost effectiveness (i.e., whether the cost of such benefits is acceptable) in general limited to licensed medicines used within the scope of their marketing authorisations as determined by the regulators.

In this case, however, the Committee has considered the efficacy of esketamine NS in a subpopulation within the marketing authorisation and expressed the view that it is “very uncertain” whether esketamine NS with an SSRI or SNRI is more effective than placebo with an SSRI or SNRI. This situation is therefore different from those where the Committee has adopted a different approach to the regulators in terms of acceptance of evidence (e.g., R (Servier Laboratories Ltd) v NICE & Anor [2010] EWCA Civ 346) because the Committee is essentially disputing the grant of a marketing authorisation covering this population of patients with TRD, a matter that falls outside its powers. For this reason, we believe the point should properly proceed under ground 1(b).

1.5 The Committee conducted an assessment of the safety of esketamine NS, despite recognising that this falls outside the remit for the appraisal

This point of appeal and the fact that the Committee assessed the safety of esketamine NS outside its remit is demonstrated by (a) the consideration of safety at the Appraisal Committee meeting on 7 April 2022 and (b) the assessment of safety at paragraph 3.18 of the FAD. However, the issues raised overlap between (a) and (b) and it is therefore important that they are considered together.

(a) the consideration of the safety at the Appraisal Committee meeting on 7 April 2022

In relation to part (a) you express the preliminary view that this “subpoint” is admissible, but should be moved to Ground 1(a) and limited to consideration of whether it was unfair for the Committee not to explain why the wording “*Is the safety profile acceptable*?” were removed from slide 24 presented at the Committee meeting and the implications of this, if any. You say that you do not consider it arguable that the Committee exceeded NICE’s powers by considering the safety profile of esketamine NS, as you disagree with Janssen’s view that such assessment did not take place in the context of consideration of associated health related quality of life or costs.

We fundamentally disagree with your preliminary view. While the revision of the slide deck raises very serious procedural issues, which we assume are being investigated by NICE, these form part of Janssen’s appeal only because the revision of the slide deck confirms that NICE was aware that its consideration of the safety of esketamine NS, fell outside NICE’s remit and therefore sought to conceal the evidence of such consideration.

Janssen’s concern, as we have explained, is the fact that the Committee engaged in a protracted and inappropriate discussion of the safety of esketamine NS at the meeting and that the Committee was asked to address an improper question as recorded on slide 24, contrary to NICE’s remit. The resulting assessment of the safety of esketamine NS by the Committee assumed the role of the regulator, and it is likely that this inappropriate discussion influenced its conclusions. Furthermore, while you say that, contrary to Janssen’s view (which was based on its attendance at the meeting) that the assessment of the safety profile of esketamine NS at the meeting of the Appraisal Committee did not take place in the context of consideration of associated HRQoL or costs, the basis for your view is unclear, in circumstances where Committee slides 23 and 24, which deal with the safety profile of esketamine NS, include no reference to these matters and consider exclusively the safety of esketamine NS as a therapy.

(b) the assessment of safety at paragraph 3.18 of the FAD

You express the preliminary view that this sub-point should not proceed to a full appeal hearing because you do not accept Janssen’s assessment that the discussion at paragraph 3.18 of the FAD is unrelated to HRQoL or costs.

We disagree with your preliminary view. Paragraph 3.18 includes no references to health-related quality of life or costs. Furthermore, after setting out regulatory information including references to the summary of product characteristics for esketamine NS, to the controlled drug regime, to a registry set up by the MHRA and to the risk management plan which forms part of the marketing authorisation for esketamine NS, paragraph 3.18 concludes by stating:

“*The Committee concluded that it was not a safety committee and could not make recommendations about safety”.*

In contrast, paragraph 3.28 of the FAD, which addresses disutility associated with adverse effects carries out a separate analysis and does not cross refer to the matters described in paragraph 3.18. Paragraphs 3.31 and 3.32 which address costs do not consider the matters covered by paragraph 3.18.

In the above circumstances, we are very concerned by the suggestion that this point of appeal should not be permitted to proceed to a hearing under Ground 1(b) in its entirety, as presented by Janssen. It is absolutely clear that NICE as well as Janssen recognised that the consideration of safety at the meeting of the Committee on 7 April 2022 was inappropriate. This is demonstrated by the serious procedural irregularity demonstrated by an alteration made to the Committee slides after the meeting but prior to publication and by the statement at the end of paragraph 3.18 of the FAD. Janssen is entitled to challenge a decision made in such circumstances and it would plainly be wrong (and contrary to the interests and credibility of NICE) for the implications of this issue to be suppressed or for there to be any attempt to exclude this point of appeal from full consideration at an appeal hearing.

1.6 The recommendations for research included in section 4 of the FAD relate to depression and treatments for depression in general, rather than specifically to esketamine NS

We note that you consider this to be a valid point of appeal.

However, you suggest that this point should proceed under Ground 1(a) rather than Ground 1(b). Your reason for this preliminary view is that you say the point is directed to whether or not NICE has followed its own procedures in making the research recommendations, namely paragraph 6.4 of the Methods Guide.

However, paragraph 6.4 relates to recommendations for use of the technology under appraisal in research. That is not relevant to the appraisal of esketamine NS. No research recommendation was made in relation to esketamine NS and the recommendations which are the subject of this point of appeal relate to research in mental health generally and TRD in particular. It is Janssen’s position that the Committee had no power to make such recommendations in the context of an appraisal of esketamine NS (whether under paragraph 6.4 of the Methods Guide or anywhere else) and we therefore consider that the point was properly brought under Ground 1(b).

You express the preliminary view that it is not relevant that no research recommendations were made in relation to vortioxetine or that the research recommendations made in NICE’s Clinical Guideline on depression do not reflect those suggested in the FAD for esketamine NS. However, this cannot be correct. NICE generally seeks to achieve consistency in its recommendations both as a matter of fairness and also in the context of credibility. In this case, the recommendation under consideration does not relate to a specific product (where it might be possible to justify differences in approach) but to a common disease area. In these circumstances if different research recommendations are made (or not considered to be necessary) in different documents issued by NICE, with no explanation for such differences, this impacts the overall merits and credibility of the various guidance documents. We therefore believe that the inconsistency with these other decisions by NICE committees is highly relevant to our appeal.

Ground 2

2.1 The Committee’s conclusions in relation to the health state costs relevant to this appraisal are unreasonable

In presenting this point of appeal, Janssen provided two examples of the unreasonable conclusions drawn by the Committee in relation to the health state costs relevant to this appraisal. Both of these are relevant to the same over-arching concern and the two examples should therefore be considered together rather than as individual sub-points.

In relation to the first part of this appeal point, you say that you do not regard the approach of the Committee as unreasonable, because “*it is perfectly possible to consider that data comprising “average” or “mean” costs is the best data on cost to the NHS, while also noting that within that data set there is a patient population driving those averages, such that - depending on the relevant patient population - the data set will be more or less relevant in determining the impact of a particular use of a particular drug in NHS*”. However, the principal objection of the Committee seems to have been that the available data on costs were higher than they would have liked, even though the TRD costing study was conducted in a UK population and in circumstances where treating patients with TRD (including where patient crises are managed in an inpatient setting) is necessarily costly and the results will be skewed by the high-cost patients. The data from the TRD costing study were obtained from the charts of real NHS patients. These patients therefore exist and are relevant; excluding them from any assessment of costs would be unrealistic. The Committee’s sole criticism of the TRD costing study, that the design meant that people who were seen more frequently in the psychiatric outpatient clinic were more likely to be included in the study, was invalid. The results of the TRD costing study were supported by the results of the CRIS database analysis, using a different database and a different methodology (see Janssen submission addendum, section 3.2, pages 25-26).  The design of the CRIS database analysis, which incorporates all patients with TRD, produces results consistent with the TRD cost study (with similar high costs in some patients with TRD) and mitigates the risk of selection bias associated with the TRD cost study. In these circumstances, the Committee has no real basis for dismissing the results of the TRD cost study, save that they simply disliked the findings, concluding, without evidential support and contrary to the evidence submitted, that the costs seemed implausibly high. This is not reasonable.

In considering the second part of this point of appeal, which relates to the generalisability of the costs study to a UK population, you again refer to the fact that the data in the TRD costing study were skewed by a few high-cost patients (those who would be hospitalised.) You conclude that the costs are not necessarily generalisable because the people who incur the most costs are not necessarily those who would receive esketamine NS because of the precautions applicable to its use in people with psychiatric comorbidities and the lack of evidence that esketamine NS would be beneficial in people for whom hospital costs are largest. However, all people included in the TRD costing study were eligible for treatment with esketamine NS in accordance with its marketing authorisation and reflecting the clinical trial programme and there is accordingly no basis for the issues raised by the Committee.

You also say that you see no arguable unreasonableness in the Committee’s view that further research is needed to understand the costs associated with TRD and hospitalisations generally.

The NHS does not routinely collect data on costs and outcomes in mental health and, in contrast to oncology and rare diseases where treatment for individual patients is generally provided at one centre, mental health patients are treated for a range of different conditions by various agencies and healthcare professionals. The difficulties are illustrated by the response from the NHS when Janssen proposed a managed access agreement (MAA), incorporating data collection, as a way to address some of the Committee’s concerns in the context of this appraisal. Following discussions with NHS England and NICE, it became clear that collecting data through an MAA would be challenging to implement given the structure of commissioning at a local level within the NHS and the limited infrastructure to allow for routine data collection in mental health currently. Even a bespoke data collection system would present unacceptable burdens on the NHS. In these circumstances, the NICE team, NHS England and Janssen agreed that the best opportunity to collect the data of interest to the Committee would be real world evidence in the context of baseline commissioning of esketamine NS.

The TRD costing study was conducted in UK patients eligible for treatment with esketamine NS, the results have been confirmed by the CRIS database analysis and they therefore represent the best available evidence on costs for the purposes of this appraisal. In these circumstances, the Committee’s refusal to rely on these data and its request for further research, even though it is unclear what further research could be conducted, given the studies carried out by Janssen and the fact that NICE, NHS England and Janssen have investigated and found further research not to be feasible from an NHS perspective. The result of NICE’s conclusions is that patients with TRD and other forms of mental illness are effectively barred from new treatments, because NICE unreasonably refuses to accept the best available evidence on the costs of treating affected patients.

This is a very substantial issue, relevant not only to esketamine NS, but also to other treatments for TRD and should not be excluded from consideration by the appeal panel.

2.2 The Committee’s concerns that the clinical trials of esketamine may not have been adequately blinded are based on speculation only and conflict with the available evidence

In your letter you explain your understanding of this point of appeal as directed towards the decision of the Committee at paragraph 3.13 of the FAD, that it was not appropriate to adjust the efficacy estimates of the placebo arm in the trials. However, this was not the focus of our appeal, there is no reference to adjustment of the efficacy estimates in our appeal document and no adjustment of efficacy estimates was made for the purposes of the sub-group presented at the fourth meeting of the Appraisal Committee.

The Committee’s concerns regarding the adequacy of blinding of the esketamine NS clinical trials were viewed as one limitation of the clinical evidence submitted in this appraisal. This point of appeal is directed towards that conclusion which, for the reasons given in our appeal document, is unreasonable.

The reasons given in your letter for rejecting this point of appeal are directed towards a misunderstanding of the issue we had raised. We hope, following clarification that our appeal is directed towards a different issue, you agree this point should proceed to a full hearing. However, if you propose to exclude this point of appeal on other grounds, we will be pleased to respond to you in relation to such matters.

2.3 The Committee’s conclusion that it is difficult to separate any effect of new oral antidepressants administered in the clinical trials from the effects of esketamine is unreasonable

Your preliminary view of this appeal point is similar to your assessment of appeal point 2.2 and, again, you suggest that this point of appeal is directed towards the decision of the Committee at paragraph 3.13 of the FAD, that it was not appropriate to adjust the efficacy estimates of the placebo arm in the trials. However, as with appeal point 2.2, the issue of efficacy adjustments was not the focus of our appeal, there is no reference to adjustment of the efficacy estimates in our appeal document and no adjustment of efficacy estimates was made for the purposes of the sub-group presented at the fourth meeting of the Appraisal Committee.

The Committee’s conclusion that it is difficult to separate any effect of the new oral antidepressants administered in the clinical trials, from the effects of esketamine NS was viewed as a further limitation in the clinical evidence submitted in this appraisal. For the reasons set out in our appeal document, that conclusion is unreasonable.

As with appeal point 2.2, the reasons given in your letter for rejecting this point of appeal are directed towards a misunderstanding of the issue we had raised. We hope, following this clarification, that you agree that point 2.3 should proceed to a full hearing. However, if you propose to exclude this point of appeal on other grounds, we will be pleased to respond to you in relation to such matters.

2.4 The Committee’s conclusions regarding potential uncertainty and generalisability of relapse rate data and long-term outcomes of depression are unreasonable in light of the available evidence

Your view that this is a valid appeal point is noted.

2.5 The Committee’s conclusions regarding treatment changes conflict with NICE’s Clinical Guideline on Depression and are therefore unreasonable

You express the preliminary view that this point should not be permitted to proceed to a full hearing on the basis that, you say: “*the Committee is not bound to accept CG90 as evidence of clinical practice; rather the CG90 is a broader guideline on depression that makes recommendations for ideal practice*”.

NICE aims to ensure consistency, where possible, between its various outputs. The reasons for this are obvious; lack of consistency would undermine the credibility of all of NICE’s guidelines and guidance and indicate that these are not soundly based on evidence. It may be that there are reasons why a committee would choose to issue recommendations that are inconsistent with those issued by another NICE directorate. However, in those circumstances it is clearly necessary for the inconsistency to be explained and justified, failing which the inconsistency is arbitrary and unreasonable.

In this case, however, the Committee has provided no reasons for deviating from the 2009 CG90 and in those circumstances the inconsistency is unreasonable.

For the avoidance of doubt, while you say that NICE Clinical Guidelines make recommendations for “ideal practice”, the Guideline Development Manual (most recently updated in January 2022) does not reflect this statement. The Manual states that Guidelines made “*evidence-based recommendations*” and that rather than making recommendations for “*ideal practice*”, they make recommendations on *“the care and services that are suitable for…most people with a specific condition or need”.*

We hope that these additional submissions, in which we have sought to clarify our points of appeal, have satisfied you that these should be permitted to proceed to an oral hearing. We look forward to receiving your final decision in relation to the admissibility of the matters raised in our appeal.

Please do contact me if you need additional clarification.

Yours sincerely,

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Senior Director, Patient Access, Janssen-Cilag Ltd

