xxxxxxxxxxxxxxxx (Senior Director, Patient Access)

Janssen-Cilag Ltd

50-100 Holmers Farrm Way

High Wycombe

Buckinghamshire

HP12 4EG

Sent by e-mail only: xxxxxxxxxxxxxxxx

13 July 2022

Dear xxxxxxxxxxxxxxxx

**Re: Final Appraisal Document — Esketamine for treatment-resistant depression [ID1414]**

Thank you for your letter of 5 July responding to my initial scrutiny views. This is my final decision on initial scrutiny.

I have amended the numbering of your appeal points for ease of reference at the appeal hearing, but I refer in parenthesis to your original numbering for the avoidance of any confusion.

I consider the ground 1(a) points followed by the grounds 1(b) 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 (Original appeal point 1.1)) NICE has failed to act fairly because “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”**

1. **NICE has failed to act fairly because “The Committee is required to take into account the clinical uncertainties “inherent” to clinical trials in mental health”**
2. **NICE has failed to act fairly because “The Committee is also required to provide reasons for its conclusions in relation to the difficulties “inherent” in clinical trials for mental health”**

I note you ask that parts a and b above are considered as one appeal point and have done so.

I still understand your point to be that the Committee is required:

1. to take into account “*the clinical uncertainties inherent to clinical trials in mental health*” in the appraisal, in particular by paragraph 6.2.16 of the Methods Guide; and
2. to explain how, if at all, these clinical uncertainties were considered in the appraisal, in particular by paragraphs 6.1.4 and 6.1.9 of the Methods Guide.

I have considered your further comments. I note in particular your arguments that “*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*” and that “*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.”*

I also note your point that Janssen did ask the committee to take into account / consider the data in the context of the challenges in conducting research in mental illness.

On reflection I agree that this is a valid appeal point. In my view the starting point here must be that the burden for generating evidence of any uncertainties and for providing the appraisal committee with evidence of the implications of such uncertainties on the assessment of cost efficacy lies with the company. (See para 4.3 of the Methods Guide 2013). The committee’s role is to appraise the evidence submitted to it. Therefore so as to assist in preparing for this appeal, I expect this appeal point will focus on (1) whether / to what extent the committee took into account the evidence submitted to it on the impact of clinical uncertainties inherent to clinical trials in mental health on the assessment of cost effectiveness and (2) whether the committee was required to go beyond noting those uncertainties in para 3.1.7 of the FAD to explain whether / how they impacted the decision making in the appraisal.

**Appeal point 1(a).2 (Original appeal point 1.3) NICE has failed to act fairly because “The Committee has failed to take into account the broader social considerations in the appraisal of esketamine NS”**

Thank you for your further comments. You have clarified that “*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”.*

I consider your argument in respect of health-related benefits followed by your argument in respect of non-health objectives.

Health related benefits:

You rely on paragraph 6.3.3 of the Methods Guide, which states:

 ***“****6.3.3 Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:…*

* *Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained...”*

As you note, at initial scrutiny I stated that *“I note that SANE (patient organisation) referenced stigma associated with administration of esketamine at a mental health facility in its submission contained in the January 2020 committee papers.[[1]](#footnote-1) However no evidence was provided by the company for the committee to consider how stigma would impact either effectiveness or routine quality of life assessments. In the circumstances and 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, I am not persuaded that there is any arguable unfairness here*.”

I have considered your further comments in your response. You say that in its original submission (see page 35), Janssen provided evidence from a focus group held with patients with TRD in March 2019 indicating the disease is characterised by patients feeling embarrassed and stigmatised with *“no quality of life*” as a result. You also note that the above-mentioned submission SANE and NICE’s 2009 Clinical Guideline on Depression (CG90) refer to the stigma which may be associated with a diagnosis of depression. You argue that:

 “*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*.”

Having considered your further arguments, I remain unpersuaded that there is a valid appeal point here. As indicated in my initial scrutiny letter, it is for the company to submit evidence of any health related benefits it considers are not adequately captured in the QALY calculations; if the company considered the tools used by the committee to capture the burden on quality of life associated with the disease were inadequate it was for the company to make a case to the committee as to how such factors should be captured in the appraisal. The time for the company to make that case is during the appraisal

I accept of course that para 6.3.3 of the 2013 Methods Guide requires the committee in certain cases to take account of “w*hether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured*”. My underlining. However it is unarguable that the company did enough (by providing evidence of stigma and resultant reduced quality of life, without making any submission as to the impact of this on the appraisal) to require the committee as a matter of procedural fairness to make express reference in the FAD to the issue of stigma.

Non-health related benefits:

In respect of non-health related benefits, para 6.3.3 of the Methods Guide states:

***“****6.3.3 Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:...Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21).”*

In turn, paragraphs 6.2.20-6.2.21 state:

“6.2.20 *In general the Committee uses the most plausible ICER as the primary consideration when making judgements about the acceptability of technologies as a cost-effective use of NHS resources. However, its overall conclusions are also affected by the following additional considerations:*

* *Whether or how its judgements have a bearing on broader social considerations to the extent that these are covered by NICE's principles on social value judgements.*
* *Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services, or are associated with significant benefits other than health, only when requested specifically by the Department of Health as part of the remit.*”

6.2.21 *The concept that underlies the Committee decision-making is that of the opportunity cost of programmes that could be displaced by the introduction of new technologies. This way, NICE seeks to maximise the health benefit gained from a fixed NHS budget. This principle is correct if the sole purpose of the health service is to improve health. While this may be the primary purpose of the NHS, it is acknowledged that care delivered by the NHS could have other benefits that are considered socially valuable but are not directly related to health and are not easily captured in a cost per QALY analysis. Techniques exist to consider the trade-off between health benefits and non-health benefits quantitatively. These techniques require that all relevant criteria are identified in advance, quantified and then weighted to reflect aspects of social value in a way that can be regarded as legitimate by all stakeholders. At present the introduction of such techniques into the Committee's decision-making is considered unsuitable. Therefore the Committee will take non-health objectives of the NHS into account by considering the extent to which society may be prepared to forego health gain in order to achieve other benefits that are not health related.”*

You appear to accept that the second bullet point of para 6.2.21 applies only “*when requested specifically by the Department of Health as part of the remit.”* I say no more about this.

I understand your appeal point in respect of non-health benefits relies on the first bullet point of para 6.2.20 above and NICE's principles that guide the development of NICE guidance and standards (which states: *“Some conditions, for example, sexually transmitted diseases and drug dependency, are associated with stigma. NICE does not consider that stigma itself is a reason for altering its normal approach to assessing cost effectiveness. However, NICE is aware that stigma may affect people’s behaviour in a way that changes the effectiveness of an intervention and that the relief of stigma may not always be captured by routine quality of life assessments. Therefore, NICE expects its advisory bodies to take these considerations into account.”).*

My initial scrutiny response letter explained why I was unpersuaded of any arguable unfairness here. Having considered your response letter I remain unpersuaded. First, as with health related benefits, the burden rests with the company to make a case for how any non-health benefits should be captured in the appraisal, and to do so at the time of the appraisal. It is (again) unarguable that the company did enough in this appraisal to require the committee as a matter of procedural fairness to make express reference in the FAD to the issue of stigma as a non-health benefit that was not adequately captured by its usual tools. Further, while para 6.2.20 permits the committee to consider non-health benefits of treatment that are not captured in routine quality of life assessments, this is in exceptional cases only (as explained at para 6.2.21). That is for a good reason, i.e. to minimise the value judgments as between different patient groups that can arise when taking account of non-health benefits. I do not think it would be arguable to equate the stigma that may be associated with TRD with the stigma that may be associated with sexually transmitted diseases or drug dependency either in kind or degree.

I therefore see no arguable unfairness in the Committee’s consideration of the non-health benefits associated with use of esketamine.

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

**Appeal point 1(b).1 (Original appeal point 1.2): NICE has failed to act fairly because “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”**

Already accepted as a valid appeal point under ground 1(b) and “*limited* *to whether the committee’s application of NICE’s procedures in this particular appraisal discriminates against people with TRD”*.

Thank you for your further comments, where you state “*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*.”

For the avoidance of doubt, the limitation referred to in my initial scrutiny letter was intended to make clear that the remit of the appeal panel is to consider whether the committee applied NICE’s procedures (as applicable at the time of the appraisal) properly in this particular appraisal and is not to determine allegations against the lawfulness of NICE’s processes themselves. In other words, the appeal can look at the application of the processes in a specific appraisal, but not the content of the processes themselves. Any such general complaint would have to be made to NICE corporately.

**Appeal point 1(b).2 (Original appeal point 1.5): NICE has exceeded its powers because “The Committee conducted an assessment of the safety of esketamine NS, despite recognising that this falls outside the remit for the appraisal”**

I note your additional comments concerning this appeal point and confirm the entire point as put in your original appeal letter will be referred to the appeal panel under ground 1(b).

**Appeal point 1(b).3 (original appeal point 1.6) NICE has exceeded its powers because “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”**

I note your additional comments concerning this appeal point and confirm the entire point as put in your original appeal letter will be referred to the appeal panel under ground 1(b).

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

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

I have considered your further comments. I note your original point was illustrated by two examples of allegedly unreasonable conclusions drawn by the Committee in relation to the health state costs and that you say both are relevant to the same over-arching concern (ie that the committee’s conclusions in relation to the health state costs relevant to this appraisal are unreasonable). I note you say this should be considered as one appeal point and have done so.

These points relate to paragraph 3.32 of the FAD (explaining the committee’s conclusion that “Healthcare resource use costs are highly uncertain and contribute to the economic model’s uncertainty”). I explained in my initial scrutiny letter why paragraph 3.32 is in my view well-reasoned: the data is clearly presented and the challenges were well understood by the committee.

In your response you emphasise the appeal point raises a “very substantial issue”, as you note the TRD costing study represents the best available evidence on costs for the purposes of this appraisal. You assert that “NICE unreasonably refuses to accept the best available evidence on the costs of treating affected patients”.

NICE has not refused to accept this evidence, though it has concluded the evidence still leaves high uncertainty. I understand your argument to be, in essence, that because the TRD costing study is the best available evidence, it must be unreasonable for NICE to conclude that the costs are nonetheless highly uncertain. I disagree with that logic. I appreciate the difficulty this presents for patients with TRD and possibly other forms of mental illness (and I have referred appeal point 1(b).1 to the appeal panel for consideration of whether there is any discrimination against that group in this appraisal) but it is unarguable that no reasonable committee could have reached the view that the costs evidence is highly uncertain (even if based on the best available evidence).

I therefore remain unpersuaded this is a valid appeal point under ground 2 and will not refer this to the appeal panel.

**Appeal point 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”**

I note your additional comments and in particular your view that the committee’s conclusion was not limited to a discussion of whether it was appropriate to adjust the efficacy estimates of the placebo arm in the trials but rather was “viewed as one limitation of the clinical evidence submitted in this appraisal”. I note also your point that “no adjustment of efficacy estimates was made for the purposes of the sub-group presented at the fourth meeting of the Appraisal Committee.”

I accept that the discussion at para 3.13 of the FAD may not have been relevant to the final sub-group under consideration for the reasons you have provided. I also accept that your appeal point is not directed at appealing the conclusion at para 3.13. However, I remain of the view that it is clear from the FAD that the committee were considering this the issue (i.e. that “blinding could be an issue in the trials”) squarely within the discussion of whether in respect of the full patient population it was appropriate to adjust the efficacy estimates of the placebo arm in the trials. There is no suggestion in the FAD that the committee put emphasis on this conclusion when determining its recommendation.

The possibility that unblinding could be an issue is a legitimate consideration that was discussed in an appropriate way.

I therefore still see no arguable unreasonableness here and will not refer this point to the panel.

I note that you state in your response letter that if I “propose to exclude this point of appeal on other grounds”, you will be pleased to respond to me in relation to such matters. I have excluded this appeal point for the same reasons as set out in my initial scrutiny so I expect that you will have no more to say in this regard, however for the avoidance of doubt my decision at final scrutiny is final and there is no further opportunity within NICE’s appeals process for you to respond to the points I have made. The same applies in respect of all the points that I have decided not to refer to the panel.

**Appeal point 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”**

As with appeal point 2.2 above, I explained at initial scrutiny why I did not consider it arguable that the committee’s conclusion at para 3.13 of the FAD that “any response from trying the new oral antidepressant is difficult to separate from the treatment effect of esketamine” is unreasonable, in light of its context.

Again I understand that your appeal point is not directed at the conclusion at para 3.13 of the FAD that it was not appropriate to adjust the efficacy estimates of the placebo arm in the trials, however again it is clear from the FAD that the committee were considering this issue in that context, i.e. this was a narrow response to the issue raised by the company of adjusting the efficacy estimates of the placebo arm for the wider population. While it may no longer have been relevant to the final subgroup under consideration, I see no unreasonableness in including this response to the suggested adjustments in the FAD.

Again there is no suggestion in the FAD that the committee put emphasis on this conclusion when determining its recommendation or that this was (as you allege) “viewed as a further limitation in the clinical evidence submitted in this appraisal” with wider implications for the recommendation.

Finally, again I consider it was a legitimate consideration for the committee to recognise that it is difficult to separate any effect of the new oral antidepressants administered in the clinical trials from the effects of esketamine, such that while the trial can show any difference between esketamine and placebo it does not necessarily map easily on to how esketamine would be administered in clinical practice. I consider this was discussed in an appropriate way under para 3.13 giving rise to no arguable unreasonableness. I will not refer this point to the panel.

**Appeal point 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”**

Already accepted as a valid appeal point.

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

I have considered your further comments under this point 2.5. You say:

*“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”.*

I remain unpersuaded that point 2.5 is a valid appeal point, for the same reasons explained in my initial scrutiny letter. Having considered your further arguments I still see no arguable point under ground 2 that the recommendation is unreasonable in the light of the evidence submitted to NICE. The committee cannot be required to accept that recommendations in a clinical guideline (whether produced by NICE or otherwise) represents real life NHS practice. Rather it must (and properly did) take into account all the relevant evidence on clinical practice, e.g. from experts and patients. To ignore that evidence in favour of an assumption that treatment changes recommended by CG60 must represent real life NHS practice would clearly be unacceptable. I will not refer this appeal point to the panel.

**Appeal point 2.6 (Original appeal point 1.4): NICE has exceeded its powers because “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”**

Already accepted as a valid appeal point under ground 2 (not ground 1(b) as originally put in your appeal letter). I explained in my initial scrutiny letter that I was minded to limit this point 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) but that I did 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.

I have considered your further comments, and in particular that you say:

*“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).”*

Nothing in your response suggests to me that your original appeal point was misunderstood. I grasp your argument that by expressing a view on whether esketamine NS with an SSRI or SNRI is more effective than placebo with an SSRI or SNRI for this population the committee “assumes the role of the regulator and conflicts with the marketing authorisation for the product”.

Having considered your response, I still disagree that there is an arguable 1(b) point here and confirm this issue will be referred to the appeal panel as a ground 2 point for the reasons I explained in my initial scrutiny letter.

As you say, 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 is at para 1 of the FAD:

“***Why the committee made these recommendations***

*The company positioned esketamine nasal spray for people who have had at least 3 antidepressants before, with or without another treatment like lithium or an antipsychotic medicine. This is narrower than the marketing authorisation, and also how clinical experts advised esketamine would likely be used in NHS practice.*

*The clinical trial evidence suggests that for people who have had at least 3 antidepressants with or without another treatment, esketamine with an SSRI or SNRI could be more effective than placebo with an SSRI or SNRI. But this is very uncertain, because this evidence only considers a small number of people from the full trial population. The long-term effects of esketamine are also uncertain because the trials were short.*

*Also, the trial evidence excluded people with characteristics of depression like psychosis or suicidal ideation with intent. This limits how well the evidence applies to the NHS, because people having treatment for depression in the NHS may have psychosis or suicidal ideation with intent.*

*The clinical uncertainty means the economic modelling is also uncertain, including:*

* *how treatment-resistant depression was modelled*
* *how long people would take esketamine for*
* *the costs of using esketamine in the NHS.*

*The limitations in the clinical evidence and economic model mean it is not possible to determine a reliable cost-effectiveness estimate. Esketamine is unlikely to be an acceptable use of NHS resources, so it is not recommended. Further research is recommended to address some of the uncertainties.”*

I see no “inconsistency” or usurping of the licensing authority’s role here. Provided the subgroup is within scope of the appraisal (as this subgroup was) then, as a public body tasked with carrying out health technology appraisals, it is clearly the case that NICE must reach its own view on the evidence and not simply adopt that of the licensing authority, provided NICE does so for its own proper purposes, and not for the purposes of the licensing authority. Reaching a view in respect of this subgroup in the context of a technology appraisal is clearly not the same as “disputing the grant of marketing authorisation” for that subgroup, which the committee did not do. Whether the committee’s view was reasonable in light of the evidence (in particular the evidence from the licensing authority) will be considered by the appeal panel.

Conclusion

Therefore the valid appeal points are:

* 1(a).1 (original appeal point 1.1);
* 1(b).1 (original appeal point 1.2);
* 1(b).2 (original appeal point 1.5);
* 1(b).3 (original appeal point 1.6);
* 2.4;
* 2.6 (original appeal point 1.4) as it relates to whether the 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 is reasonable in light of the evidence (in particular the evidence from the licensing authority).

Where there are multiple appellants, NICE shares the valid appeal grounds of each appellant with the other appellants to assist with preparation for the hearing.

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

National Institute for Health and Care Excellence

1. <https://www.nice.org.uk/guidance/gid-ta10371/documents/committee-papers> [↑](#footnote-ref-1)