**APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION FOR ESKETAMINE NASAL SPRAY FOR TREATMENT-RESISTANT DEPRESSION**

14/06/2022

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Dear Dr Chakravarty,

**Re: Final Appraisal Determination – for ID1414 Esketamine Nasal Spray for**

**Treatment Resistant Depression**

**APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION FOR ESKETAMINE NASAL SPRAY FOR TREATMENT-RESISTANT DEPRESSION**

**EXECUTIVE SUMMARY**

Janssen brings this appeal in order to address serious procedural issues arising in this appraisal and to the reasonableness of the Appraisal Committee’s conclusions following its assessment .(“esketamine NS”) for treatment resistant depression, Janssen’s concerns and the issues raised in this appeal apply to NICE’s approach to mental health treatments generally and whether these are fair and appropriate in the context of the particular features of mental illness and its management in the NHS in England. In particular, Janssen are concerned, given the decision-making precedent arising in this appraisal, that future innovations in mental health will not appraised appropriately. Our appeal includes the following points:

Ground 1

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;

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

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

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

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

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

Ground 2

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

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

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

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

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

**INTRODUCTION**

We provide below background information in r elation to major depressive disorder (MDD), treatment-resistant depression (TRD) and esketamine nasal spray (“esketamine NS”) (Spravato), in order to assist the Appeal Panel. This summary is not intended to replace the more detailed information provided by Janssen in its original submission for the purposes of this appraisal.

**Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD)**

Depression is currently considered one of the most disabling medical conditions in the world and WHO predicts that depression will become the leading cause of disease burden worldwide by 2030. MDD is a severely debilitating, life-threatening psychiatric disorder. It is characterised by chronic, recurrent episodes of persistent low mood and/or loss of interest or pleasure in (almost) all activities. Other symptoms include sleep disturbance, fatigue, change in appetite/weight, agitation, slowness of speech, slowness of actions, diminished concentration, decreased libido, feelings of worthlessness and, in severe cases, suicidal ideation, suicide attempts and death by suicide.

TRD is a subtype of MDD; TRD is defined as a major depressive disorder that has not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

TRD predominantly affects people of working age, but it can develop at any age. It is estimated to affect more than 130,000 patients in England. At least 30% of patients with TRD attempt suicide at least once in their lifetime. The condition severely impacts patients, their carers and the wider healthcare system. The total estimated UK societal burden of TRD is £3.9 billion, the majority of which (80%) is due to carer burden and lost productivity

It is estimated that about 87% of patients with TRD do not achieve remission with the currently available oral antidepressants (OADs). It is common for patients to go through several cycles of other treatments leading to treatment resistance and chronicity of the disease over time. There is currently no pharmacological treatment, other than esketamine NS specifically approved for TRD in the UK.

Clinical trials in mental illness generally and depression in particular are challenging. Such trials are notoriously associated with high placebo rates which mean that it is difficult to determine the true treatment effect of the intervention under investigation. The European guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev. 2), describes difficulties even in the conceptual elaboration and definition of clear criteria for incomplete response and TRD. The difficulties in designing clinical trials for depression, result in a high failure rates for such trials and have led to limited new investment and innovation in the disease area. Consequently, there is a significant unmet need for treatments for patients with TRD.

**Esketamine nasal spray**

Esketamine NS is a treatment indicated for adults with TRD who have not responded to at least two different treatments with antidepressants in the current moderate to severe episode. It is taken in combination with either a serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant. ). It was granted marketing authorisation in the EU on 18 December 2019, converted, for the purposes of supply in Great Britain, to a GB marketing authorisation on the withdrawal of the UK from the EU .

Esketamine NS comes as a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril). Esketamine NS is self- administered and is to be used under the supervision of a healthcare professional. One device (for a 28 mg dose), two devices (for a 56 mg dose), or three devices (for an 84 mg dose), are to be used, with a five- minute interval between each nasal spray self-administration.

Esketamine NS is a first-in-class, pharmacological anti-depressant with a novel mechanism of action, which differs from that of approved treatment options. Whereas “OADs” chronically influence reuptake/breakdown of monoamine neurotransmitters or their respective receptor(s), esketamine NS targets the neurotransmitter glutamate and exerts its action via transient NMDA receptor blockade, enhancing glutamate release and promoting neuroplasticity.

Esketamine NS is the first antidepressant with a new mechanism of action in the field of depression in over 30 years and the first fast acting anti-depressant authorised in the UK, specifically for patients with TRD.

The two pivotal trials, TRANSFORM-2 and SUSTAIN-1 met their primary objectives related to short-term depression symptom control (TRANSFORM-2) and longer-term relapse prevention (SUSTAIN-1). TRANSFORM-2 was a randomised, double-blind, clinical trial to evaluate the efficacy of newly initiated OAD + esketamine NS compared with a newly initiated OAD + placebo nasal spray. The trial met the primary endpoint of a statistically significant improvement in depressive symptoms. For patients who have failed multiple previous treatments, the improvements observed with OAD + esketamine NS are clinically meaningful and translate into considerable improvements in patient’s lives. SUSTAIN-1 used a randomised, blinded withdrawal design to compare time to relapse in patients who had achieved stable remission after 16 weeks treatment with esketamine NS and were then randomised to receive esketamine NS + OAD or placebo + OAD. The results demonstrated that, for patients with TRD who experienced remission or response after esketamine NS + OAD treatment, continuation of esketamine NS + OAD resulted in clinically meaningful superiority in delaying relapse compared with OAD + placebo. The EMA’s Committee for Medicinal Products for Human Use (CHMP) concluded at the time of grant of the centralised marketing authorisation “*Overall, the clinical program can be considered comprehensive and supports the use of esketamine as an adjunctive treatment administered concomitantly with a newly initiated oral SSRI or SNRI*”.

**PROCEDURAL HISTORY OF THE APPRAISAL**

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| --- | --- |
| **Date** | **Event** |
| 1 May 2019 | Final scope for appraisal |
| 5 July 2019 | Janssen submission to NICE |
| 10 September 2019 | Evidence Review Group Report prepared by Kleijnen Systematic Reviews Ltd |
| 18 December 2019 | European Commission grants marketing authorisation for esketamine NS:  “Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode”.  [An additional indication for use of esketamine NS has subsequently been added to the marketing authorisation, but this is not relevant to the current appraisal.] |
| 7 January 2020 | Committee meeting: 1 |
| 28 January 2020 | Appraisal Consultation Document (ACD)  “Esketamine with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) is not recommended, within its marketing authorisation, for treating treatment-resistant depression that has not responded to at least 2 different antidepressants in the current moderate to severe depressive episode in adults” |
| 18 February 2020 | Responses to consultation on ACD submitted by Janssen and other stakeholders |
| 1 April 2020 | Additional response to ACD submitted by Janssen. |
| 3 April 2020 | The appraisal paused due to the fact it was not defined as therapeutically critical in light of COVID-19 |
| 5 August 2020 | Committee meeting: 2 |
| 27 August 2020 | Second Appraisal Consultation Document. Draft guidance unchanged from first ACD |
| 16 October 2020 | Responses to consultation on second ACD by Janssen and other stakeholders |
| 30 November 2020 | ERG critique of company ACD 2 responses |
| 19 January 2021 | Short response document to ERG critique of the company ACD2 responses |
| 11 February 2021 | Committee meeting: 3  Outcome not released pending discussions between NICE, NHSE and Janssen |
| 14 January 2022 | Addendum submission with additional evidence submitted to NICE/ERG |
| 7 April 2022 | Committee meeting: 4 |
| 27 May 2022 | Final Appraisal Document (FAD) issued to consultees |
| 14 June 2022 | Deadline for submission of appeal |

**GROUNDS OF APPEAL**

1. **GROUND 1a: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS FAILED TO ACT FAIRLY** 
   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**
2. The Committee is required to take into account the clinical uncertainties “inherent” to clinical trials in mental health

At paragraph 3.17 of the FAD, the Committee refers to clinical uncertainties in the clinical trials of esketamine NS and states that:

“*The Committee considered that some of these clinical uncertainties are inherent to clinical trials in mental health…*”

The Committee then listed five areas of uncertainty which it concluded fell within this category of “*inherent to clinical trials in mental health*” and stated:

“*The Committee recognised the difficulty of designing, recruiting and interpreting results from clinical trials in this disease area and that the evidence requirements of health technology assessment may be different than the licensing requirements captured through regulatory endpoints….*.”

However, while the Committee’s overall conclusions in relation to the cost-effectiveness of esketamine NS at paragraph 3.36, focus on the uncertainty of the estimates (including the matters listed in paragraph 3.17), the Committee provides no explanation of how its recognition that such matters are “*inherent to clinical trials in mental health*” has been taken into account in its decision-making in this appraisal.

At paragraph 3.38, the Committee refers to underinvestment in mental health services. It states that:

“*The Committee understood the NHS has a responsibility to deliver parity of esteem for physical and mental health and considered the uncertainties around current mental health service provision in its decision. It acknowledged the funding issues in mental health and the limited new treatment options………However, it recalled that NICE’s remit from the Department of Health and Social Care for this technology appraisal was to appraise the clinical and cost effectiveness of esketamine within its licensed indication. The Committee concluded that equity of access could not be addressed as part of this appraisal”.*

The Committee’s reference to “equity of access” in this context is not understood. However, to the extent that the Committee may be relying on the remit from the Department of Health and Social Care to justify an approach which does not take into account the inherent challenges in developing new treatments in mental health, this would be inconsistent with NICE’s processes. This is not a situation where the Committee is being asked to deviate from its remit. The issue is simply the approach to be followed by the Committee when assessing the clinical and cost effectiveness of an innovative new treatment and, in particular, how it takes account of the recognised difficulties “inherent” in mental health, in the context of procedural fairness and section 6 of NICE’s Guide to the Methods of Technology Appraisal (2013). including the provision at paragraph 6.2.16, stating “*the Committee is aware that the evidence base will necessarily be weaker for some technologies….*”.

1. The Committee is also required to provide reasons for its conclusions in relation to the difficulties “inherent” in clinical trials for mental health

Paragraphs 6.1.4 and 6.1.9 of NICE’s Guide to the Methods of Technology Appraisal (as well as general standards of transparency as an element of procedural fairness) require the Committee to explain its assessment of the evidence and provide reasons for its conclusions, including, in this case, the “inherent” difficulties in conducting research on technologies for the treatment of mental illnesses. Paragraph 6.1.9 states:

“*The credibility of the guidance produced by the Institute is dependent on the transparency of the Appraisal Committee's decision-making process. It is crucial that the Appraisal Committee's decisions are explained clearly with reference to all the available evidence, and that the contributions of clinical specialists, commissioning experts, patient experts and the views of people who responded to consultation during the appraisal are considered”.*

In summary, in the context of the Committee’s conclusions at paragraphs 3.17, 3.36 and 3.38 of the FAD and its recognition of the “inherent” clinical uncertainties in conducting research in treatments for mental health, the Committee is required to explain how this situation has been taken into account when reaching its conclusions on the use of esketamine NS, in accordance with procedural fairness and section 6 of the Methods Guide, in view of the inevitable clinical uncertainties associated with research in this area. Its failure to do so in the FAD is inconsistent with rigorous decision making and precludes any determination of whether the approach followed by the Committee in this respect is fair and reasonable.

* 1. **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**

People with mental illness suffer from a disability, a protected characteristic for the purposes of the Equality Act 2010.

It is well recognised[[1]](#footnote-1), including by the Committee in this appraisal, that the development of new treatments for mental illness (including TRD) is associated with inherent difficulties. Some of these challenges have been listed by the Committee at paragraph 3.17 of the FAD. The nature of such challenges means that any data generated in relation to a new treatment are likely to be associated with uncertainty, resulting in a potential barrier to patients accessing such therapies. It is material in this context that esketamine NS is the first breakthrough in depression treatment in over 30 years.

NICE’s standard approach to technology appraisal. including the way it addresses uncertainty, has been developed and used almost exclusively in therapeutic areas other than mental health and, to date, NICE has issued technology appraisal guidance in respect of only one health technology indicated for the treatment of depression[[2]](#footnote-2). If therefore, patients with mental illnesses are deprived access to new treatments relative to patients with physical illnesses because NICE’s procedures favour physical illnesses and are not capable of taking account of the clinical uncertainties inherent to clinical trials in mental health, this is discriminatory.

It is Janssen’s position that NICE’s current procedures may be interpreted and applied so that the assessment of clinical and cost effectiveness is non-discriminatory to patients with mental illness, such as TRD and the resulting guidance does not breach NICE’s equality duties. However this requires not simply an explicit recognition of the inherent challenges and uncertainties associated with research in treatments for mental illness (as has been done in this appraisal) but that NICE’s procedures do not discriminate against people with mental illness due to aspects of their disability which mean that it is more challenging to conduct clinical trials for these conditions than for physical illnesses. Failure to adopt and apply procedures which fairly measure and reflect the clinical and cost effectiveness of health technologies indicated for mental illnesses as well as health technologies indicated for physical illnesses continues the progressive undermining of and underinvestment in mental health services in England, despite the requirement for parity of esteem[[3]](#footnote-3) and conflicts with NICE’s duties under the Equality Act 2010.

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

At paragraph 3.37 of the FAD, the Committee notes Janssen’s view that TRD has a substantial societal burden, mostly because of time off work, but refers to NICE’s Guide to the Methods of Technology Appraisal (2013) which states at section 5.19 that the reference case perspective on outcomes should be that of the NHS and personal social services.

Similarly, at paragraph 3.38, the FAD refers to the need for further investment in mental health services and “*noted that this context could be considered in the decision for esketamine…*”, before concluding that its remit from the Department of Health and Social Care was limited to the appraisal of clinical and cost effectiveness of esketamine.

However, both paragraphs 6.2.21 and 6.3.3 of NICE’s Guide to the Methods of Technology Appraisal require NICE to consider:

* non-health benefits associated with use of a health technology, which are considered to be socially valuable; and
* where there are strong reasons to believe that the benefits of treatment in terms of health related quality of life have not been adequately captured

In the context of the current appraisal, there is no evidence from the FAD that such benefits 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. In particular:

1. The Committee seems to have concluded incorrectly that, in circumstances where the reference case perspective for this appraisal should be that of NHS and personal social services. it was precluded from taking into account the societal benefits of treatment for TRD, which disproportionately affects people of working age and impacts productivity of both patients and carers; and
2. While NICE’s statement of the principles that guide the development of its standards states under “Principle 9: Aim to reduce health inequalities”:

“*However stigma may affect people’s behaviour in a way that changes the effectiveness of an intervention and routine quality of life assessments may not capture the benefits of treatment. Our advisory committees should take both these factors into account”*.

And NICE’s Clinical Guideline on Depression (CG90) states at paragraph 1.1.1.1:

*“….be aware that stigma and discrimination can be associated with a diagnosis of depression”.*

However, there is no indication that the Committee has considered the potential stigma associated with a diagnosis of TRD in the context of this appraisal, including in its consideration of whether the quality of life assessments are likely to have captured the associated benefits of treatment.

In summary, despite recognising the very substantial difficulties associated with development of new mental health treatments, the societal burden associated with TRD and the huge clinical need for new treatment options, the Committee has seemingly failed to comply with its obligation to take into account the broader societal benefits associated with treating TRD and the requirements of NICE’s own Principles Document in its decision making. Alternatively, if the Committee has taken such matters into account, it has failed to explain its reasoning and how they have influenced the Committee’s conclusions relating to esketamine NS, given the importance of mental health treatments and the fact that the current provision of mental health services is accepted to be inadequate. This omission is contrary to NICE’s processes and is procedurally unfair.

**GROUND 1b: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS EXCEEDED ITS POWERS**

* 1. **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**

At paragraph 1 of the FAD, the Committee refers to the group of patients who have received at least three prior treatments (who form part of the licensed indication for use of esketamine NS) and states:

“*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.”*

However it is not a matter for the Committee to determine whether OAD + esketamine NS is more effective than OAD + placebo. This is an efficacy decision to be determined by the regulator, whose responsibility it is to assess the benefit risk balance for a medicinal product across the eligible patient population, based on the available evidence, before deciding whether a marketing authorisation should be granted and, if so, the scope of that authorisation. It is self-evident that a medicinal product which is no more effective than placebo, but is nevertheless associated with a risk of side-effects, can never have a positive benefit risk balance and will not be granted a marketing authorisation. The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) considered the data for OAD + esketamine NS in the full licensed population, which included the subgroups considered in this appraisal, in the context of the application for a marketing authorisation and concluded that the benefit risk balance for the product was positive. CHMP stated:

“*Short- and long-term efficacy of esketamine on top of an SSRI or SNRI in TRD patients has been established*” (EPAR page 172).

The role of the Committee is not to duplicate the work of the regulator (i.e. whether there is benefit that outweighs potential risks), but to determine magnitude of benefit relative to a relevant comparator and to assess cost-effectiveness. In this appraisal however, the Committee has:

(a) reached conclusions on the existence of benefit that assume the role of the regulator and conflict with the conclusions of the regulator; and

(b) provided no explanation for diverging from the conclusion of the regulator, that OAD + esketamine NS demonstrate superior efficacy to OAD + placebo across the entire population of patients eligible for treatment in accordance with the marketing authorisation, including patients who have received at least three prior treatments. .

The fact that the Committee has questioned the existence of any benefit associated with esketamine NS therapy relative to placebo, despite the conclusions of the regulators and the existence of the marketing authorisation does not only exceed the powers of the Committee and NICE itself but is indicative of the unfair approach to consideration of data from clinical trials of treatments for depression as illustrated in this appraisal.

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

The Appraisal Committee have carried out a detailed assessment of the safety of esketamine NS assuming the role of the regulator and, we suggest, taking into account irrelevant issues in the context of their remit.

(a) Consideration of safety at the fourth Committee meeting

The fourth meeting of the Appraisal Committee to consider esketamine NS took place on 7 April 2022. At that meeting a slide deck was presented, which addressed, at slides 23 and 24,the safety profile of esketamine NS, even though safety is not an issue to be considered by the Committee, save to the extent that safety impacts health related quality of life or costs. Slides 23 and 24 did not however address quality of life or costs but considered the overall safety of esketamine NS, which is a matter for the regulatory authorities and not for NICE. Starkly, slide 24 concluded with the following question to be addressed by the Committee:

*“Is the safety profile acceptable?”*

Consistent with the content of the slide deck, the Appraisal Committee spent a considerable period during the public part of the meeting discussing the safety profile of esketamine NS unrelated to quality of life or costs (Janssen estimates approximately an hour was spent in this way).

Janssen is particularly concerned by the fact that the slides were modified at some point after the meeting, to remove the question on slide 24 quoted above, so that this is not present on the version of the slide deck published on NICE’s website.

Copies of both versions of slide 24 are attached as an Annex to this letter.

(b) Consideration of safety in the FAD

At paragraph 3.18 of the FAD, the Committee considers the safety profile of esketamine NS, reflecting the discussion at the fourth Committee meeting before stating:

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

Consistent with the final sentence of Paragraph 3.18, the Appraisal Committee is not a safety committee and conclusions on safety are a matter for the regulators. In these circumstances, it is contrary to NICE’s procedures for a detailed discussion on safety to appear in the FAD (unless such discussion relates to associated quality of life or costs, which is not in the case here). There is accordingly no basis for such a consideration of the safety profile of esketamine NS by the Committee in the context of this appraisal and the fact that such consideration took place and is documented in the FAD falls outside the remit of the Committee and the powers of NICE.

Overall, the fact that the Committee gave extensive consideration to the safety profile of esketamine NS, both at the Committee meeting and in the FAD, raises a strong inference that such matters were taken into account by the Committee when reaching its conclusions regarding the technology. These concerns are not removed by the fact that the slide deck presented to the Committee was modified after the Committee meeting and that the FAD recognises (after describing the Committee’s concerns in detail) that they should not be taken into account by the Committee because it is then unclear why this assessment is included in the FAD at all.

* 1. **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**

Section 4 of the FAD includes three recommendations for research:

* How clinical data from regulatory trials in depression could appropriately be used in health technology assessment and decision modelling;
* The long term course of TRD, its natural history and health related quality of life in the long-term; and
* Healthcare resource use of people with depression, including which patients use services such as hospitals and crisis resolution home teams.

All of these research recommendations relate to generic issues concerning depression/ TRD in general and are not specifically related to esketamine NS. It is Janssen’s position that the inclusion in the FAD of research proposals relating to depression in general fall outside the remit of this Committee.

As indicated in NICE’s Guide to the Processes of Technology Appraisal (2018) applicable to this appraisal, states “*The technology appraisal processes are designed to provide recommendations, in the form of NICE guidance, on the use of new and existing medicines, products and treatments in the NHS*” but do not suggest that technology appraisal guidance looks more broadly at the management of diseases. Similarly, NICE’s Guide to the Methods of Technology Appraisal (2013) addresses at section 6.4 the research recommendations that may be made in the context of a technology appraisal, namely “*that the technology is used only in the context of research or while the technology is recommended as an option, research is also conducted*”. In both instances, the research envisaged by section 6.4 relates to the technology under appraisal and not to the disease area in general.

The general disease area research recommendations made by the Committee fall outside the powers of this Committee in the context of technology appraisal guidance for esketamine NS. We are also aware that no research recommendations (general disease related or otherwise) were made in relation to vortioxetine (TA367) (the only health technology indicated for a depression indication where NICE has issued technology appraisal guidance) and, while NICE’s Clinical Guideline on Depression (CG90) does, quite properly, include various recommendations for disease area research, none of these recommendations reflect those suggested in the FAD for esketamine NS..

1. **GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE**
   1. **The Committee’s conclusions in relation to the health state costs relevant to this appraisal are unreasonable**

(a) The Committee unreasonably characterises skewed data as resulting in uncertainty

At paragraph 3.32 of the FAD the Committee states:

*“The committee noted that all of the evidence considered about resource use was characterised by strongly skewed data, which introduced substantial uncertainty to estimates of non-pharmacological healthcare resource costs within the model…. The committee also noted that cost savings are driven by reducing costs in a small group of people (those who would be hospitalised)”*

NICE’s Guide to the Methods of Technology Appraisal (2013) addresses evidence on resource use and costs at section 5.5 and provides for use of “average" or “mean” costs. This approach requires consideration of all patients, regardless of whether their inclusion will “skew” the data. It is not therefore unusual for costing data to be skewed, reflecting the fact that certain “high cost” patients have been included. This is clinical reality and the mere fact that the data are skewed does not justify a conclusion that the data introduce ‘substantial uncertainty’, as described at paragraph 3.32 of the FAD. Conversely, the exclusion of patients with high costs, would conflict with the correct NHS position and this would be unreasonable.

The assertion that skewed data are necessarily uncertain is also inconsistent with conclusions reached in other appraisals and therefore arbitrary and unreasonable..

(b) The committee has unreasonably questioned the generalisability of the TRD costing study

At paragraph 3.32 of the FAD, the Committee considered the generalisability of the TRD costing study to NHS clinical practice stating that this:

“…..*was crucial to understanding whether esketamine would reduce hospitalisations and other healthcare resource use. It questioned whether the same people who are hospitalised would have esketamine, because there are precautions for its use for people with certain psychiatric comorbidities. The committee noted that cost savings are a key driver of the cost-effectiveness estimates. The committee also noted that cost savings are driven by reducing costs in a small group of people (those who would be hospitalised). But it considered there was no evidence that esketamine would be beneficial in the group of people for whom hospital costs are largest….. .It recommended further research to fully understand the costs associated with treatment-resistant depression and hospitalisations…*”

The TRD costing study was specifically conducted in UK patients with TRD in order to inform the healthcare resource use in the economic model for this appraisal. The study directly collected the healthcare resource use of actual UK patients with TRD per health state to input into the model. Furthermore the results of the TRD costing study are consistent with data obtained from the Clinical Record Interactive Search (CRIS) database at South London and Maudsley, NHS Trust and also with the DISCOVER dataset from Northwest London NHS Foundation Trust (Section 1.1 and 3.2 of company addendum, submitted in February 2022). Nevertheless, the Committee concluded that these NHS data may not be generalisable to UK clinical practice, including because the Committee relied on the inappropriate Byford study, which considers a population outside the scope of this appraisal.

Against this background, where three separate datasets obtained from NHS management of TRD in the UK all produce similar results, the conclusions of the Committee which suggest that these findings may not be generalisable to UK clinical practice are unreasonable.

In summary, the Committee has concluded that the results of the TRD costing study may not be generalisable to UK clinical practice, even though they were obtained from UK NHS practice and are supported by two other NHS databases. The apparent rejection of these data by the Committee in circumstances where they represent the best data available to the Committee is unreasonable.

* 1. **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**

At paragraph 3.13 of the FAD, the Committee considers the efficacy estimates of the placebo arms of the TRANSFORM clinical trials and concluded: (a) that trial participants “*may have had a high expectation of esketamine because it has a novel treatment mechanism*”; and (b) for participants receiving placebo “*the absence of psychoactive effects and other effects expected with esketamine could lead to negative expectations and a lower response to treatment*”.

* However patients in both groups were commenced on a new SSRI or SNRI at the same time as esketamine or placebo and these oral treatments could also produce treatment effects supporting blinding of randomisation.
* The high efficacy estimates demonstrated in the OAD + placebo arm of the TRANSFORM-2 trial and confirmed by the expert from the NICE guideline on depression (paragraph 3.13 of the FAD) are inconsistent with the Committee’s concerns at (b) above; in particular, an unusually high response in patients receiving OAD + placebo does not suggest negative expectations in these patients. The CHMP expressed similar views, stating: ‘*a higher than expected response in the oral AD + intranasal placebo arm is an opposite effect than is expected in case of unblinding’*,
* The data from Chen G et al provided to the Committee in the Janssen’s initial evidence submission in July 2019 (Chen G et al. Relationship Between the Antidepressant Effects of Esketamine Nasal Spray and Perceptual Disturbances. The American College of Neuropsychopharmacology (ACNP) 57th Annual Meeting, December 9-13, 2018 demonstrated that patients who experience dissociative symptoms achieve outcomes that are not significantly better than patients who do not experience such symptoms and that dissociative symptoms were experienced by patients on OAD + placebo as well as those on OAD + esketamine NS.

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The Committee also expressed concern in relation to blinding of trial data at paragraph 3.15 of the FAD in the context of trial participants who were randomised to receive placebo after receiving esketamine NS during the optimisation phase in SUSTAIN-1.

* While the Committee recognised that, in response to the second ACD, Janssen had submitted data showing that censoring patients from the clinical trials, who experienced dissociative symptoms and relapsed after discontinuing esketamine NS and switching to placebo, made no significant difference to the results, the Committee stated that this assessment did not address other symptoms (not specified).
* As indicated in Janssen’s response to the second ACD, the high rate of early relapse in the SUSTAIN-1 clinical trial OAD + placebo arm (45.3%) was similar to that observed after cessation of electroconvulsive therapy, from which rebound effects are not seen (Sackeim HA, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA. 2001;285(10): 1299-1307).
* In any clinical trial there is a possibility that benefits or adverse effects experienced by one group may impact blinding. However the Committee does not identify or explain the basis for its particular concerns (other than in relation to dissociative effects, which have been addressed by the data submitted by Janssen) in relation to esketamine NS.

Overall, there is no evidence to support the Committee’s concerns that the TRANSFORM-2 and SUSTAIN-1 trials were unblinded.

Importantly, the EMA’s CHMP, who assessed blinding of treatment in the clinical trials of esketamine NS for the purposes of the application for marketing authorisation concluded:

“*With respect to blinding, the investigator was not provided with randomization codes. Due to the dissociative effects with esketamine, independent remote (by phone) blinded raters for MADRS assessment were used to maintain the blinding of the studies. Furthermore, the use of a bittering agent in the intranasal placebo and the use of 3 devices in each treatment session were additional precautionary measures to ensure that blinding was maintained and as such these are considered appropriate”*.

The Committee has not seemingly considered the views of the CHMP in relation to adequacy of blinding and has provided no reasons for disagreeing with the conclusions of the regulators in this respect.

It is unreasonable for the Committee to speculate that trial results may be unreliable in the absence of any supporting evidence to that effect and in the face of a different conclusion by regulators.

* 1. **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**

The Committee states at paragraph 3.13 of the FAD

“*The Committee noted that in clinical practice, oral antidepressants would not be newly started at the same time as esketamine, because it is not clinical practice to try 2 new therapies at the same time. Therefore, any response from trying the new oral antidepressant is difficult to separate from the treatment effect of esketamine.…”.*

However, the reason why two (or more) groups are included in a clinical trial is to permit measurement of the effects of the investigational treatment relative to the comparators. Participants in both the investigational and comparator groups of the TRANSFORM and SUSTAIN trials received a new SSRI or SNRI (on the basis that failing to include a new treatment for the comparator group would have been unethical) and the difference between treatment groups can therefore be attributed to the effects of esketamine NS, received only by participants in the investigational group. This is standard trial design and in circumstances where both treatment groups received new OAD therapy, the conclusion of the Committee that it is difficult to separate the effects of the new OADs from the effects of esketamine NS, is unreasonable.

* 1. **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**

(a) Consideration of relapse rate data

At paragraph 3.21 of the FAD, the Committee criticises the relapse rate data used in the economic model on the basis that the esketamine NS arm used transitions between health states from the SUSTAIN-1 trial and the placebo arm used relapse data from the STAR\*D trial. The Committee states:

“*The Committee concluded that using different sources of data for relapse leads to potential generalisability issues and bias in the model”.*

However, this conclusion conflicts with sensitivity analyses submitted by Janssen in its initial submission in this appraisal. At section B 3.4.4.8 (page 214) of its initial submission, Janssen provided an alternative analysis which used relapse rate data from SUSTAIN-1 for both the esketamine NS + OAD group and the placebo +OAD group in the economic model. This alternative analysis found that, both the risk of relapse and loss of response for OAD in SUSTAIN-1 were higher than estimated using the STAR\*D data. Therefore the estimated ICER for esketamine NS + OAD in the alternative analysis was less than that calculated in the base case when data from STAR\*D had been used for the placebo + OAD group.

The alternative analysis therefore confirms that the base case assumptions on relapse rates are conservative and the Committee’s conclusions regarding uncertainty and generalisability are unreasonable.

(b) Long-term outcomes of depression

At paragraph 3.22 of the FAD, the Committee considers the long-term course of TRD and concludes:

“…*the company and the ERG estimated the proportion of people in the MDE [major depressive episode] health state at later stages of the model, for which there was no available evidence”*.

However, the conclusion that “*there was no available evidence*” disregards evidence submitted by Janssen and is therefore unreasonable.

* In response to the second ACD, Janssen submitted a targeted literature review, confirming the poor long- term outcomes of people with TRD. The review was provided at Appendix 1 to Janssen’s submission dated 16 October 2020 and is referenced by the Committee at paragraph 3.23 of the FAD.
* In addition, Janssen’s addendum dated February 2022 included data from a UK study conducted using the DISCOVER dataset, which estimated the length of a depression episode for people with MDD and TRD in the UK and further supported the results of the literature review.
  1. The C**ommittee’s conclusions regarding treatment changes conflict with NICE’s Clinical Guideline on Depression and are therefore unreasonable**

At paragraph 3.22 of the FAD, the Committee considers the use of subsequent treatments in the economic model and states:

“*The response and remission rates were calculated on a 4-weekly basis to be implemented per cycle in the model. This meant people moved between treatments quickly if their symptoms did not respond within 4 weeks. The committee considered that moving through treatments would not happen that quickly in clinical practice”.*

However, the assumption used in the economic model is based on NICE’s own Guideline on Depression (CG90) which expressly provides for treatment review at 2-4 weeks and treatment switch in cases where benefits are not seen. In these circumstances, the conclusions of the Committee, which are not supported by evidence or explanations, are unreasonable.

**THE DETERMINATION OF THIS APPEAL**

Janssen requests that this appeal should be determined at an oral hearing.

**REQUESTED OUTCOME FOLLOWING APPEAL**

Janssen respectfully requests the Appeal Panel to return this appraisal to the Appraisal Committee for further consideration with the following directions:

* In its appraisal of esketamine NS, the Committee to take into account the particular uncertainties inherent in conducting clinical trials for mental health disorders (such as TRD) which result from particular features of the conditions themselves and explain how this has been achieved, both as a matter of procedural fairness and in the context of the Equality Act 2010.
* The Committee to take into account the broader social considerations associated with use of esketamine NS and treatment of TRD in this appraisal, including the non-health benefits (such as the implications for work by both patients and family members) and matters that are not adequately reflected in the measurement of health related quality of life (such as the impact of stigma associated with mental illness).
* The Committee to reconsider esketamine NS without assessing either the efficacy (whether there is any benefit) or the safety profile of the product (paragraph 3.18 of the FAD to be deleted) or making recommendations for research generally in mental health all of which exceed its powers.
* The Committee to consider the evidence relating to esketamine NS in the context of its use to treat a mental health condition and the evidence which is available, including in relation to:
* The non-pharmacological health resource costs associated with treatment of TRD;
* Blinding of mental health clinical trials in general and the TRANSFORM and SUSTAIN trials in particular;
* The design of the TRANSFORM and SUSTAIN trials and distinguishing the effect of new OAD therapy from the effect of esketamine NS;
* Rate of relapse after discontinuing treatment;
* Switching between treatments; and
* Long-term outcomes of depression.

Please do contact me if you need additional clarification.

Yours sincerely,

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Senior Director, Patient Access, Janssen-Cilag Ltd



1. See for example: NICE CG90 Section 9.3, <https://www.nice.org.uk/guidance/cg90>; Wong, C. et al. (2018). Estimation of clinical trial success rates and related parameters. Biostatistics, 20(2), 273-286. doi: 10.1093/biostatistics/kxx069; Khin NA et al. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry 2011; 72: 464-72; <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-depression_en.pdf>; <https://www.ema.europa.eu/en/news/development-challenges-medicines-central-nervous-system-disorders> [↑](#footnote-ref-1)
2. Vortioxetine for treating major depressive episodes (TA367) [↑](#footnote-ref-2)
3. <https://www.centreformentalhealth.org.uk/parity-esteem>; <https://commonslibrary.parliament.uk/mental-health-achieving-parity-of-esteem/> [↑](#footnote-ref-3)