**From:** xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx < xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx >   
**Sent:** 06 July 2022 02:38  
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< xxxxxxxxxxxxxxxxxxx >; xxxxxxxxxxxxxx < xxxxxxxxxxxxxxxxxxxxxx >; xxxxxxxxxxxxxx < xxxxxxxxxxxxxxxxxxxxxx >  
**Subject:** [EXTERNAL]:Royal College of Psychiatrists response to initial scrutiny letter: esketamine ID1414

Dear Dr Chakravarty,

I am writing on behalf of the Royal College of Psychiatrists in response to your Initial Scrutiny letter of 21st June to xxxxxxxxxxxxx.

Thank you for responding in detail to our comments and for accepting our Appeal point 2.1.  We look forward to discussing this further on 27th July.

We accept your rejection of our Appeal point 2.3

We disagree that Appeal point 2.2 is not valid.  Specifically, we disagree with your rejection of the final paragraph relating to stopping rules.  We wrote:

‘The vortioxetine FAD accepted that people in stable remission would stop their antidepressant after 2 years. This was accepted. The esketamine submission was that 60% would stop at 2 years but was not accepted’.

We do not agree that the Committee’s approach was rendered not unreasonable by the following explanations on stopping which are given in para 3.29 and 3.30:

1. there is limited evidence on the effect of stopping esketamine for reasons other than lack of efficacy and more data for stopping treatment for reasons other than lack of efficacy was needed to justify modelling the additional stopping guidance provided by the company
2. in clinical practice stopping treatment may not be guided by the company criteria and could include ongoing repeated or prolonged treatment based on symptom severity, particularly for the expected population in NHS clinical practice and the 3 or more treatments subgroup.

The explanation in (a) is factually incorrect and therefore cannot be used to support the idea that the Committee was being reasonable.  Specifically, the statement ‘there is limited evidence on’ does not tally with the fact that high quality data were available from the SUSTAIN2 trial (Wajs 2020) which DO record the reasons for stopping treatment (30 withdrawals, 25 Treatment emergent adverse events, 25 lack of efficacy, 10 lost to followup, 30 others, 2 death).   We do not see what further data could be required to justify an attempt at modelling.

The explanation in (b) does not reflect the reality that treatment CAN be guided by NICE in the form of stopping rules - with which clinicians will then conform. Specifically, the SUSTAIN2 and SUSTAIN1 data provide enough information for the effect of stopping at 12 months to be modelled.  SUSTAIN 3 data provides data at longer time points which are suitable for modelling.

We note that no justification is actually given by the Committee for why stopping vortioxetine at 2 years should be less problematic, or uncertain, than 60% of cases stopping esketamine at 2 years.  This further supports our contention that this was unreasonable.

We consider that stopping rules are a good way to manage uncertainty and would be useful in this circumstance.

Stopping rules will also help to overcome the perception that those with mental illness are being discriminated against compared with, for example, those with cancer for whom access to novel treatments, constrained by stopping rules, is common.

This relates to Appeal point 2.1 concerning the general approach to uncertainty.  Undue weight is put on inevitable uncertainties in what (particularly for mental health research) are actually high quality data (SUSTAIN1 and 2).  More uncertain alternatives are then modelled and rejected.

Whilst we understand your point that there is no rule of precedent between the different Committee judgements on different drugs, we do think that this inconsistency can undermine the credibility of NICE’s processes.  We also note also that precedent set by FADs does seem to play a significant role – eg in the ID3735 appeal

*‘insufficient justification was given in the FAD for adoption of an approach in the appraisal of avelumab that was not broadly consistent with previous comparable technology appraisals, and accordingly this inconsistency is unreasonable’*

Yours sincerely,

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