Esketamine Stakeholder Meeting Outcome Statement

Wednesday 1 February 2023

Attendees

Members of the Pharmaceutical Benefits Advisory Committee (PBAC), clinicians with expertise in the management of treatment-resistant depression (TRD), representatives from health consumer organisations, Janssen-Cilag Pty Ltd (the sponsor of esketamine) and the Department of Health and Aged Care were in attendance.

Non-departmental attendees undertook confidentiality declarations and provided conflict of interest statements.

Purpose of meeting

As part of its consideration of the July 2022 resubmission for esketamine[1], the PBAC considered it would be appropriate for a stakeholder meeting to be convened to further refine the PBS restriction, discuss potential issues related to access, discuss the likely extent of use and discuss what additional information might be required to support the PBS listing of esketamine.

Background

The PBAC has considered applications for the PBS listing of esketamine nasal spray for TRD at its July 2021 and July 2022 meetings. Below are links to the Public Summary Documents (PSDs):

esketamine-psd-july-2022.pdf (pbs.gov.au)
esketamine-psd-july-2021.pdf (pbs.gov.au)

Discussion and outcomes

It was acknowledged that TRD has a significant impact on the quality of life of individuals and their families and there was a clinical need for alternative treatment options. The PBAC Chair noted that the PBAC was supportive of a further submission for esketamine and that clinical input was important for framing any resubmission.

Place in therapy and PBS restriction

- The stakeholders acknowledged the treatment of TRD is complex and the best sequence of treatments for specific patient groups is developing as clinicians gain more experience with esketamine (and ketamine).
- The stakeholders advised careful consideration by experienced psychiatrists will be required to determine if esketamine (or ketamine), repetitive transcranial magnetic stimulation (rTMS) or electroconvulsive therapy (ECT) are appropriate treatment options for individual patients, noting patients may sequence through the different treatments. It was noted treatment choice was needed and was dependant on a patient's age,

[1] Esketamine is the S-enantiomer of racemic ketamine

treatment preferences, treatment history, severity of symptoms and location (i.e., metropolitan or rural/ remote).

- The stakeholders noted the availability and patient cost of accessing treatments can be factors in treatment choice.
- The place in therapy of esketamine (and ketamine) versus ECT was discussed. Comments made include:
    - Comparative clinical trials of ECT versus ketamine suggest ECT might be more effective than ketamine[2], especially in patients over 50 years of age.
    - Esketamine and ECT have different adverse events profiles, such that patients may have a preference for one over the other.
    - Esketamine may be a useful treatment option prior to ECT for some patients.
    - ECT may be more effective than esketamine (and ketamine) for some patients with severe TRD
    - Esketamine may be the preferred treatment option in younger patients.
- The place in therapy of esketamine versus rTMS was discussed. Comments made include:
    - There are no comparative clinical trials of rTMS versus esketamine (or ketamine).
    - The role of rTMS in clinical practice is less clear than for ECT and esketamine.
    - rTMS is often preferred to ECT in adolescents and young adults.
- In discussing the appropriate clinical positioning of esketamine, clinicians advised the MBS criteria for rTMS[3] (initial criteria provided below) was well described and largely consistent with the patient population who would be considered for treatment with esketamine in clinical practice.

> Professional attendance on a patient by a psychiatrist, who has undertaken training in Repetitive Transcranial Magnetic Stimulation (rTMS), for treatment mapping for rTMS, if the patient:
>
> (a) has not previously received any prior transcranial magnetic stimulation therapy in a public or private setting; and
>
> (b) is at least 18 years old; and
>
> (c) is diagnosed with a major depressive episode; and
>
> (d) has failed to receive satisfactory improvement for the major depressive episode despite the adequate trialling of at least 2 different classes of antidepressant medications, unless contraindicated, and all of the following apply:
>
> (i) the patient's adherence to antidepressant treatment has been formally assessed;
>
> (ii) the trialling of each antidepressant medication has been at the recommended therapeutic dose for a minimum of 3 weeks;
>
> (iii) where clinically appropriate, the treatment has been titrated to the maximum tolerated therapeutic dose; and
>
> (e) has undertaken psychological therapy, if clinically appropriate

[2] Rhee TG, Shim, SR, Forester BP et al. Efficacy and safety of ketamine vs electroconvulsive therapy among patients with major depressive episode. A Systematic review and meta-analysis. JAMA Psychiatry. 2022;79(12):1162-1172

[3] MBS Item codes: 14216, 14217, 14219 and 14220: http://www9.health.gov.au/mbs/search.cfm

- The stakeholders advised it would be appropriate and consistent with clinical practice to amend criteria (d) (ii) for esketamine to require trialling each antidepressant medication for a minimum of 4 to 6 weeks (rather than a minimum of 3 weeks).
- The stakeholders noted it would be difficult to further define the patient population that would be appropriate for esketamine as treatment needs to be tailored to each patients' clinical situation and medication history.
- The stakeholders noted the proposed PBS restriction criteria for initial treatment with esketamine in the July 2022 PSD:

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	Medical Practitioners
Severity:	Moderate to severe
Condition:	Major depressive disorder
PBS Indication:	Treatment resistant depression
Treatment phase:	Initial treatment/induction
Restriction:	Authority Required – Telephone
Treatment criteria:	Psychiatrist or under the supervision of a psychiatrist
Clinical criteria:	Patient must have received and not achieved an adequate response to at least two different antidepressant medications at adequate doses and duration to treat the current depressive episode. AND Treatment must be used in combination with a newly initiated oral antidepressant AND Patient must not receive more than 4 weeks of treatment under this restriction
Population criteria:	Patients must be aged 18 years or older

- The stakeholders strongly supported limiting initial prescribing to psychiatrists (rather than 'psychiatrists or under the supervision of a psychiatrist') given the treatment-resistant setting, specialised nature of the treatment, and concerns about serious adverse outcomes (including suicide attempts) where treatment has been given in Australia by general practitioners "under the supervision of a psychiatrist".
- The stakeholders noted the proposed clinical criteria "Treatment must be used in combination with a newly initiated oral antidepressant" was consistent with the clinical trial and the TGA approved indication; however, it was not consistent with clinical practice, would be difficult and complicated to adhere to and could result in unnecessary switching of treatments.
- The stakeholders advised it would be appropriate to add a caution note regarding the use of esketamine in people with a history of substance abuse and in people with psychosis.
- The stakeholders noted it was important for all patients to have a follow-up assessment one month after ceasing treatment to monitor for any post-withdrawal effects.

<u>Dose and treatment duration</u>

- The stakeholders noted the administration of esketamine was reasonably straightforward but emphasised the need for appropriate monitoring for adverse events and withdrawal effects.

- The stakeholders considered it was reasonable to limit esketamine to the dose (28 mg to 84 mg) and frequency (twice weekly in induction phase, once weekly or every two weeks in maintenance phase) outlined in the approved TGA Product Information document but to allow patient flexibility in terms of moving between lower and higher doses and less and more frequent dosing as clinically required. The stakeholders noted some patients on maintenance treatment may experience a relapse and require twice weekly treatment.
- The stakeholders considered that, after the initial 4 week induction phase, a decision regarding ongoing treatment should be made after 6 months of maintenance treatment. The stakeholders noted the appropriate duration of treatment with esketamine remains uncertain and there is limited data to support its long-term use. The stakeholders considered it would be appropriate to allow for a maximum treatment duration of 12 months per patient. The stakeholders considered that, based on their experience with esketamine and ketamine, the majority of patients would be treated for less than 12 months. However, there may be a small number of patients who require treatment beyond 12 months and for some patients, the anxiety experienced when approaching the 12 month limit may exacerbate their depression. The stakeholders considered there may need to be some flexibility regarding the maximum 12 month treatment duration.
- The stakeholders considered allowing retreatment with esketamine may be appropriate for some patients after a reasonable period of time off treatment.

<u>Likely extent of use</u>

- The stakeholders considered that, overall, with some refinement as discussed above (i.e., limit prescribing to psychiatrists, maximum 12 month treatment duration), the previous approach to estimating patient numbers (see Estimated PBS usage and Financial Implications in the July 2022 PSD) appeared reasonable.
- The stakeholders noted the incidence of depression in the community is increasing, particularly among younger people.
- The stakeholders considered the uptake of esketamine would be higher in patients who have failed more treatment options.
- The sponsor noted the delivery of esketamine is restricted to treatment centres that have been accredited as required by the conditions of the Risk Management Plan approved by the TGA.
- The stakeholders noted uptake of esketamine will be limited by access to psychiatrists and accredited treatment centres.
- The sponsor noted it had sourced additional data that would further inform the approach to estimating patient numbers.

Conclusion

The PBAC Chair thanked stakeholders for their time in attending the meeting and the advice provided.

The sponsor indicated its intention to use the advice provided to inform a future submission for listing esketamine on the PBS.