

## 7.03 ESKETAMINE, Nasal spray solution 28 mg in 0.2 mL, Spravato<sup>®</sup>, Janssen-Cilag Pty Ltd.

### 1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 100 (Highly Specialised Drugs), Authority Required (telephone) listing of esketamine nasal spray for treatment resistant depression (TRD). Esketamine nasal spray is to be initiated in conjunction with a newly initiated oral antidepressant (OAD).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus a newly initiated OAD alone.

**Table 1: Key components of the clinical issue addressed in the resubmission**

Component	Description
<b>Population</b>	Adult patients with major depressive disorder, who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate to severe depressive episode.
<b>Intervention</b>	Esketamine hydrochloride is to be administered in conjunction with a newly initiated OAD. Induction phase (4 weeks): Esketamine is administered twice per week with the first dose of 56 mg and with subsequent doses of either 56 mg or 84 mg, depending on clinical response. A dose of 28 mg can be used in older adults (≥ 65 years). Evidence of therapeutic benefit should be evaluated at the end of induction phase (4 weeks) to determine need for continued treatment. Maintenance phase (week 5 onwards): Esketamine 56 mg or 84 mg administered once weekly or fortnightly. A dose of 28 mg can be used in older adults (≥ 65 years). After depressive symptoms improve, treatment should continue for at least 6 months, with patients monitored to determine continuing response. Esketamine is discontinued once a patient relapses or when a patient recovers.
<b>Comparator</b>	Initiation of a new OAD.
<b>Outcomes</b>	Change in depression severity (using the Montgomery-Asberg Depression Rating Scale (MADRS) total score), incidence of clinical response and remission, occupational, social and family functioning, quality of life, incidence of adverse events
<b>Clinical claim</b>	Esketamine nasal spray in combination with a newly initiated OAD is superior in terms of efficacy and inferior in terms of safety when compared to a newly initiated OAD alone

Source: Table 1-1, p.20 of the resubmission

Abbreviations: OAD, oral antidepressant

### 2 Background

#### **Registration status**

- 2.1 Esketamine nasal spray was registered on the Australian Register of Therapeutic Goods on 9 March 2021 for treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current moderate to

severe depressive episode), initiated in conjunction with a newly initiated oral antidepressant.

### ***Clinical consensus statement***

2.2 The resubmission included a consensus statement regarding the appropriate use of esketamine nasal spray for the treatment of TRD in clinical practice. The consensus group included senior psychiatrists and health professionals with treatment expertise working in the field of the mood disorders. The clinicians who were involved considered:

- The definition of a treatment resistant depression (TRD) patient as someone who has had an inadequate response to adequate trials of at least two prior antidepressant medications in the current episode and the prior exposure ranging from 2-5 prior treatments in the current episode is a reasonable representation of TRD in Australia. It was considered important to acknowledge that, consistent with RANZCP guidelines, appropriate psychosocial and psychotherapeutic interventions would have been trialled in addition to antidepressant therapy by the time the patient has reached this definitional point of TRD.
- The importance of rigorous clinical assessment to determine eligibility for treatment and that this process should include objective functional assessment (employment, education, social participation) by the clinician and subjective assessment by the patient and family, and that this assessment should be documented.
- There are currently data to support 6 months of treatment with esketamine but no long-term safety data beyond 12 months at this point in time. The group noted that close monitoring and regular open enquiry in relation to adverse events including post cessation should form part of good clinical care.
- That a patient should be treated for up to six months, when an assessment to determine continuing therapy should be conducted. In regard to assessing treatment response with esketamine, the group agreed that it would be the same as for other currently used antidepressants and that this would be consistent with the RANZCP treatment guidelines i.e., if after 6-8 weeks of antidepressant therapy at optimal dose there is no significant shift in symptoms/function, consider a change in treatment strategy.
- It may be challenging to switch to a new antidepressant at the same time as initiating esketamine, and agreed that mandating a switch to a new antidepressant will not always be in the best interest of the patient. The group agreed, consistent with the RANZCP guidelines, that when a patient has not responded adequately after 6-8 weeks at optimal dose, a change in treatment strategy should be considered. The group felt that the decision to keep a patient on the current antidepressant and commence esketamine would represent a change in treatment strategy and therefore advocate for the PBS listing to allow for this.
- The group considered the issues related to potential abuse or tolerance of esketamine. The trials did not report development of abuse or recreational use,

however given the known profile of the agent, there was agreement that this would need to be monitored and should form part of the ongoing monitoring for patients being treated with esketamine.

### **Department of Veterans Affairs experience with esketamine**

2.3 To inform its consideration of esketamine the PBAC requested advice from the Department of Veterans’ Affairs (DVA). A representative from the DVA provided advice to the PBAC about how esketamine and ketamine services are provided on an individual basis through the prior approvals process for a number of conditions including TRD, post-traumatic stress disorder and anxiety. The advice described that treatment selection via this approval pathway is led by clinicians, and the DVA’s primary roles are to confirm clinical criteria are satisfied and fund these services. While a specific instrument is not mandated, patients are monitored for clinical response. The advice also outlined there was no maximum limit to the duration of treatment approved under current processes, and noted that initial response is typically rapid, while the time interval between maintenance doses had tended to increase as patients continued treatment. The representative noted experience with longer term use of esketamine is currently limited. In addition, it was noted that DVA provides and funds services for all aspects of the treatment, including transportation and accommodation services for patients who need to travel and/or be accommodated while receiving treatment.

### **Previous PBAC consideration**

2.4 The matters of concern from the July 2021 PBAC meeting are summarised in the table below.

**Table 2: Summary of key matters of concern**

<b>Component</b>	<b>Matter of concern</b>	<b>How the resubmission addresses it</b>
Clinical positioning of esketamine	The PBAC considered the proposed placement of esketamine after failure of two antidepressants was too early in the treatment algorithm, given the availability of established alternatives such as combination OAD therapy, augmentation therapy, psychotherapy, ECT and other physical interventions. The PBAC noted that the management of depressive disorders such as TRD are complex and considered that as the place in therapy of esketamine nasal spray is unclear and emerging, the integration of esketamine alongside non-pharmacological treatment options in practice, such as ECT, is unclear (para 7.2, 7.11 esketamine Public Summary Document [PSD], July 2021 PBAC meeting).	The resubmission argued that the place in therapy as proposed in the original submission was appropriate. The primary evidence in support of this was a consensus statement obtained by the sponsor from practicing Australian psychiatrists (see Clinical Consensus Statement section above).

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Component	Matter of concern	How the resubmission addresses it
Appropriateness of initiating two antidepressant agents simultaneously	The PBAC noted the use of esketamine in combination with a newly initiated OAD was consistent with the clinical evidence and the TGA indication but considered the PBS restrictions should allow flexibility to enable the treatment needs of individual patients to be considered (para 7.5)	The resubmission noted that there was no definition supplied for 'newly' in the proposed restriction, which it argued was to provide a level of pragmatism for clinical practice.
Comparator	The PBAC noted the nominated comparator was a newly initiated OAD and considered that, while this may be an appropriate comparator for esketamine in the proposed clinical positioning, it was too early in the treatment algorithm. The PBAC noted there are a number of PBS and non-PBS alternative treatment options that may be appropriate comparators if esketamine was positioned later in the treatment algorithm (para 7.6).	The nominated comparator remained unchanged.
Clinical evidence	Uncertainty regarding the clinical significance of observed benefit in the clinical trials; the lack of long-term safety together with the potential for tolerance and dependence (para 7.1).	The clinical evidence is unchanged.
Economic analysis	The PBAC considered the proposed placement of esketamine in the July 2021 submission (after failure of two antidepressants) was too early in the treatment algorithm, and considered that the applicability of the model results if esketamine use was restricted to later in the treatment algorithm was unknown. (para 7.2, 7.11).	The resubmission argued that the clinical positioning of esketamine is appropriate and that the economic model therefore is applicable to the proposed use of esketamine in Australian clinical practice.
	The ESC advised a substantially revised economic model would be needed to assess the cost-effectiveness of esketamine. The ESC considered the following issues need to be addressed (para 6.61): <ul style="list-style-type: none"> <li>• model structure needs to account for the subsequent therapies (para 6.43).</li> </ul>	A number of changes were made to the economic model. <ul style="list-style-type: none"> <li>• a 'Recovery' health state has been included for the subsequent treatment pathway.</li> </ul>
	<ul style="list-style-type: none"> <li>• inclusion of clinical data from only one clinical trial for esketamine in the economic model</li> <li>• more conservative maintenance of treatment effect assumptions (para 6.43).</li> <li>• duration of treatment, treatment discontinuations and dose likely to be used in clinical practice (para 6.58 and 6.59).</li> </ul>	<ul style="list-style-type: none"> <li>• induction treatment transition probabilities are based on the TRANSFORM-2 (patients 18-64 years) and TRANSFORM-3 (patients ≥65 years) trials.</li> <li>• maintenance therapy transition probabilities for the placebo + OAD arm are derived from the STAR*D study, rather than SUSTAIN-1. However, the model assumes maintenance of treatment effect over the duration of the model for esketamine + OAD, including those who discontinue esketamine (but continue on OAD).</li> <li>• unchanged. The resubmission argued it was appropriate to apply treatment discontinuations as a reduction in drug costs; but no reduction in outcomes.</li> </ul>

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Component	Matter of concern	How the resubmission addresses it
	<ul style="list-style-type: none"> <li>• appropriate cost of administration (para 6.47).</li>   <li>• the applicability of the disease management costs (para 6.46).</li>   <li>• account for safety concerns (para 6.60).</li> </ul>	<ul style="list-style-type: none"> <li>• A higher cost of administration is used for esketamine (changed from MBS item 300 ≤15 minute psychiatrist consultation to MBS item 304 30-45 minute consultation). However, the resubmission maintains a cost of administration for placebo (MBS item 300).</li>   <li>• unchanged. The resubmission argued that Denee 2021 is applicable to the Australian population and an alternative source could not be identified.</li>   <li>• Disutilities due to adverse events are applied to the maintenance treatment phase as well as induction in the resubmission. However, the costs associated with adverse events have not been included.</li> </ul>
Financial estimates	The PBAC considered the financial estimates provided in the submission are based on esketamine being positioned too early in the treatment algorithm and any resubmission would require substantial revision to reflect use later in the treatment algorithm (para 7.12)	The resubmission argued that the clinical positioning of esketamine is appropriate and that the financial estimates therefore are applicable to the proposed use of esketamine in Australian clinical practice.

Source: Table 0-2, p.16 of the resubmission; constructed during the evaluation

Abbreviations: ECT, electroconvulsive therapy; OAD, oral antidepressant; MBS Medicare Benefits Schedule; TRD, treatment resistant depression.

### 3 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (effective) price for maximum quantity	dispensed for maximum quantity	Proprietary name and manufacturer
<b>Initial treatment/Induction (Treatment weeks 1-4)</b>						
ESKETAMINE Nasal spray device, 28 mg, 1	8	8	0	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)		Spravato®, Janssen-Cilag Pty Ltd
ESKETAMINE Nasal spray device, 28 mg, 2	8	16	0	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)		Spravato®, Janssen-Cilag Pty Ltd
ESKETAMINE Nasal spray device, 28 mg, 3	8	24	0	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)		Spravato®, Janssen-Cilag Pty Ltd
<b>Continuing treatment/Maintenance period (Treatment weeks 5 and onwards)</b>						
ESKETAMINE Nasal spray device, 28 mg, 1	4	4	2	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)		Spravato®, Janssen-Cilag Pty Ltd
ESKETAMINE Nasal spray device, 28 mg, 2	4	8	2	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)		Spravato®, Janssen-Cilag Pty Ltd
ESKETAMINE Nasal spray device, 28 mg, 3	4	12	2	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)		Spravato®, Janssen-Cilag Pty Ltd
<b>Category / Program:</b>	Section 100 – Highly Specialised Drugs Program					
<b>Prescriber type:</b>	Medical Practitioners					
<b>Severity:</b>	Moderate to severe					
<b>Condition:</b>	Major depressive disorder					
<b>PBS Indication:</b>	Treatment resistant depression					
<b>Treatment phase:</b>	Initial treatment/induction					
<b>Restriction:</b>	Authority Required – Telephone					
<b>Treatment criteria:</b>	Psychiatrist or under the supervision of a psychiatrist					
<b>Clinical criteria:</b>	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					
<b>Population criteria:</b>	Patients must be aged 18 years or older					
<b>Treatment phase:</b>	Continuing treatment					
<b>Restriction:</b>	Authority Required – Telephone					
<b>Treatment criteria:</b>	Psychiatrist or under the supervision of a psychiatrist					
<b>Clinical criteria:</b>	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND					

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	Patient must have responded adequately during the initial treatment phase AND Patient must not have relapsed while receiving treatment with this drug for this condition during subsequent treatment cycles.
<b>Population criteria:</b>	Patients must be aged 18 years or greater
<b>Treatment phase:</b>	Continuing treatment (Grandfathered)
<b>Restriction:</b>	Authority Required
<b>Treatment criteria:</b>	Psychiatrist or under the supervision of a psychiatrist
<b>Clinical criteria:</b>	Patient must have received treatment with this drug for this condition prior to PBS listing AND Patient must have responded adequately during the initial treatment phase AND Patient must not have relapsed while receiving treatment with this drug for this condition during subsequent treatment cycles
<b>Population criteria:</b>	Patient must be aged 18 years or greater
<b>Prescriber Instructions:</b>	Authority required (telephone and online) – General PBS administration Concept ID 25796. Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333. Dosing frequency and dosage should be individualised to the lowest frequency and dosage to maintain remission/response. The drug must be self-administered under the supervision of a healthcare professional. Patient must be monitored by a healthcare profession following administration in a healthcare facility.
<b>Administrative Advice:</b>	Care must be taken to comply with the provisions of the state/territory law for prescribing this drug Note: Special pricing arrangement applies Note: No increases in quantity or repeats will be authorised

- 3.1 The resubmission proposed an effective and published price for esketamine nasal spray with a special pricing arrangement. The proposed effective price in the resubmission was 10.8% lower than that proposed in the July 2021 submission.
- 3.2 The proposed restriction is consistent with the approved TGA indication of treatment for TRD (defined as prior failure of 2 antidepressants for that episode), initiated in combination with a new OAD.
- 3.3 The PBAC previously considered that substantial changes would be required to the proposed restriction for esketamine to reflect a more appropriate place in the treatment algorithm for TRD (paragraph 7.4, esketamine public summary document (PSD), July 2021 PBAC meeting). The ESC also previously considered that esketamine was positioned inappropriately early in the treatment algorithm (paragraph 2.5, esketamine PSD, July 2021 PBAC meeting). The place in therapy, and consequently the proposed restriction, remained largely unchanged from the original submission. The ESC noted the definition of a TRD patient in the consensus statement was ‘someone who has had an inadequate response to adequate trials of at least two prior anti-depressant medications in the current episode’. Based on the additional information and clinical views expressed in the resubmission, the ESC noted there may be some patients in whom esketamine may be an appropriate treatment option after only 2 anti-depressant mediations, for example patients with very poor initial response to oral antidepressants, however it was expected for most patients that additional

therapies should be trialled prior to esketamine. The ESC considered the role and appropriate use of esketamine in the treatment of TRD was complex and variable depending on many patient and health system factors. The ESC acknowledged the clinical consensus statement, however considered the appropriate use of esketamine remained unclear. The Pre-PBAC Response argued that in practice, the majority of patients accessing esketamine would have already trialled additional interventions beyond two prior OADs, and noted the results of a study of PBS data (Malhi et al 2022<sup>1</sup>), which found that GPs prescribe the majority of OADs in the second line (69.4%) and third line (58.3%) treatment setting, compared to psychiatrists prescribing only 7.7% as a second line treatment and 18.3% as a third line treatment. Therefore, the sponsor argued that in practice, given the request to restrict prescribing to psychiatrists (or in consultation with), most patients would have received additional lines of therapy beyond two prior OADs before accessing psychiatry services, and also argued the listing of esketamine would not substantially change clinical practice or how/when patients are referred to psychiatry services.

- 3.4 The proposed restriction states that “the drug must be self-administered under the supervision of a healthcare professional”, and that the “patient must be monitored by a healthcare professional following administration in a healthcare facility”. The resubmission stated access to esketamine nasal spray will be limited to sponsor-accredited treatment sites, which include appropriate facilities for patient administration and monitoring, access to emergency care and pharmacy. The pre-subcommittee response (PSCR) stated the accredited sites include metropolitan, regional and rural sites across all states and the number of sites is expected to increase to 1 by the end of 2022. The PSCR proposed the addition of a prescriber instructions stating “Esketamine can only be administered in a Janssen accredited treatment facility, which has appropriate facilities for patient administration and monitoring, access to emergency care and pharmacy” to address this issue.
- 3.5 Treatment with esketamine nasal spray is to be initiated in conjunction with a new OAD. The proposed restriction does not specify which oral agents should be initiated alongside esketamine nasal spray. Only four OADs were allowed in the induction clinical trials, two of which were selective serotonin reuptake inhibitors (SSRIs) and two of which were serotonin noradrenaline reuptake inhibitors (SNRIs). The PBAC noted the TGA indication does not limit to specific OADs but the dose and method of administration section of the product information states that in the clinical program patients were assigned SNRI or SSRI as the new OAD.
- 3.6 The PBAC previously noted the use of esketamine in combination with a newly initiated OAD was consistent with the clinical evidence and the TGA indication but considered the PBS restrictions should allow flexibility to enable the treatment needs

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<sup>1</sup> Malhi, G., Acar, M., Kouhkamari, M., Chien, T., Juneja, P., Siva, S., & Baune, B. (2022). Antidepressant prescribing patterns in Australia. *BJPsych Open*, 8(4), E120. doi:10.1192/bjo.2022.522. Accepted for publication at time referenced in Pre-PBAC Response.

of individual patients to be considered (para 7.5, esketamine PSD, July 2021 PBAC meeting). The resubmission stated the proposed restriction does not specify the exact timing of initiating a new OAD and that each could be initiated separately to assess tolerability while being unlikely to impact the efficacy of esketamine as observed in the clinical trials. The ESC considered flexibility as to the timing of the initiation of the new OAD was reasonable and noted the proposed restriction may require rewording to clarify the most appropriate approach to prescribing combination treatment for TRD. The ESC noted the clinical consensus statement stated a change in treatment strategy should be considered after 6 to 8 weeks and this was consistent the RANZCP guidelines. Further, the ESC considered the continuing and grandfather restrictions should specify that treatment must be in combination with an OAD.

- 3.7 The restriction is based on a TRD definition of inadequate response to at least 2 antidepressants (inadequate response not defined). The definition of TRD in clinical practice may vary, and increasingly clinicians may be relying less upon pharmacological criteria to define TRD. The definition is also complicated by the lack of consensus in describing acute antidepressant responses, and what determines a treatment failure (i.e. inadequate dose or duration of pharmacotherapy, or nonadherence to treatment; para 3.7, esketamine PSD, July 2021 PBAC meeting).
- 3.8 The proposed restriction is generally consistent with the eligibility criteria of the key trials. However, the included trials excluded patients with comorbid conditions, particularly psychotic disorders, due to potential safety concerns. The PSCR proposed the addition of a note stating “Caution should be used in treating patients with a presence or history of psychosis, patients with personality disorder, a history of alcohol and substance abuse and those with suicidal ideation” to address this issue.
- 3.9 The proposed continuation rules are unchanged from the July 2021 submission. The PBAC previously considered that the proposed continuation rules were unclear, and interpretations may vary between clinicians (para 3.9, esketamine PSD, July 2021 PBAC meeting). The product information states that evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine the need for continued treatment, however the criteria for assessing therapeutic benefit are not stated. The proposed restriction for continuing treatment specifies that the patient must have ‘responded adequately’. In practice, this may vary between some reduction in symptoms, and achieving complete remission of depressive symptoms and may typically be evaluated over a longer timeframe than four weeks. In the resubmission’s consensus statement, it was noted that “quality of life and functional (social and economic) outcomes require assessment as well as symptomatic ones, including using instrumental assessment if indicated”.
- 3.10 The proposed restriction for continuing treatment specifies that the patient ‘must not relapse’. In practice, the definition of relapse may vary in terms of clinical symptoms and timeframes. The resubmission’s consensus statement made no statement regarding relapse. It is unclear whether the proposed restriction, and the definitions used in the clinical trials, align with the clinical definition of relapse. The current

Australian treatment guidelines suggest that symptoms of a depressive relapse include loss of interest, anhedonia, loss of self-worth or cognitive changes (Mahli et al., 2021).

- 3.11 The ESC previously noted that intravenously delivered ketamine is currently available in private treatment settings for a number of (off-label) psychiatric conditions including depression, post-traumatic stress disorder, obsessive-compulsive disorder and acute suicidal ideation and considered there was a high risk of use of esketamine in these conditions (para 3.12, esketamine PSD, July 2021 PBAC meeting). The ESC noted there was currently a randomised controlled trial underway (funded by the National Health and Medical Research Council) comparing subcutaneous ketamine and active treatment in patients with TRD (ANZCTR number: ACTRN12616001096448<sup>2</sup>). Patients (n=183) were randomised to ketamine via subcutaneous injection twice weekly or an active control with remission (the primary endpoint) assessed at 4 weeks. Patients could enter a 4 week open label extension after a one month break from treatment (i.e., at week 8). Key inclusion criteria included MDD for at least 3 months, an inadequate response to at least 2 adequate antidepressants courses and a MADRS score of at least 20.
- 3.12 The ESC considered psychological therapy should form an important part of the management of TRD and it may be reasonable to add a psychological therapy requirement to the restriction. The ESC considered it may be appropriate to limit initial prescribing to psychiatrists, rather than under the supervision of a psychiatrist although it was noted access to psychiatrists may be limited.
- 3.13 The PBAC noted the criteria for funding repetitive transcranial magnetic stimulation (rTMS) on the Medicare Benefits Schedule and considered aspects of the criteria may be appropriate for esketamine, including assessment of response to initial treatment using a validated major depressive disorder tool and the requirement to have undertaken psychological therapy (unless inappropriate).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Major depressive disorder (MDD) is a common, debilitating, and recurrent mental health disorder, characterised by persistent feelings of sadness and hopelessness, or loss of interest in activities once enjoyed, with additional psychophysiological changes including weight changes, fatigue, and decreased ability to concentrate, think, or make decisions. These core symptoms may vary from patient to patient; however, they are typically seen for much of the day, almost always every day for at least two weeks and are associated with relevant psychological distress and considerable impairment of psychosocial and work functioning.

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<sup>2</sup> <https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12616001096448>

- 4.2 The resubmission highlighted the impact of TRD and treatment cycles on functioning, including flat affect, lack of motivation, and failing to achieve a response to several treatments.
- 4.3 Although a number of pharmacological treatment options are currently available for MDD, up to one third of patients do not adequately respond to treatment, and up to 20% are considered non-responders, even if there is good compliance over a reasonable period of time with an adequate dosage (para 4.2, esketamine PSD, July 2021 PBAC meeting). This subpopulation is described as having treatment-resistant depression (TRD) and is the population for which PBS listing is sought for esketamine.
- 4.4 TRD most often refers to major depressive episodes that do not respond satisfactorily to at least two trials of antidepressant monotherapy, however the definition has not been standardised. The 2021 Australian guidelines for the treatment of mood disorders refer to the definition of TRD as the failure to achieve a suitable response to two or more adequate courses of pharmacotherapy as ‘a very modest and clinically meaningless threshold’ (Malhi et al., 2021).
- 4.5 Symptoms of TRD follow those of MDD in general, for example depressed mood, loss of interest or pleasure, sleep disturbance, fatigue, neurocognitive dysfunction and changes in appetite and weight. Compared to patients with non-TRD MDD, patients with TRD are thought to be at greater risk of relapse. Further, the probability of remission appears to decrease with successive treatment failures (Rush et al 2003, STAR\*D study).
- 4.6 Treatment options recommended in the 2020 RANZCP Guidelines for managing patients with TRD include optimising current antidepressant use (appropriate dose for an appropriate period of time), switching to a different antidepressant, combining two antidepressants, augmenting treatment by adding an antipsychotic or lithium to the existing antidepressant, and using non-pharmacologic physical therapies such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) (Mahli 2021). The treatment algorithm for MDD, and TRD in particular, is complex and broadly involves a combination of initial pharmacotherapy together with psychotherapy, followed by non-pharmacotherapies or physical therapies, including ECT, rTMS or vagus nerve stimulation (VNS).
- 4.7 There are no clear lines of therapy for TRD. The choice between switching therapy, augmenting therapy, psychotherapy or a physical therapy may be impacted by a number of factors, including availability and patient preference, because there is no compelling evidence that one is superior to the others for acute outcomes. Many patients switch antidepressants because this option is readily accessible.
- 4.8 Esketamine, the S-enantiomer of racemic ketamine, is an antidepressant with a novel mechanism of action. It is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Ketamine, administered by either intramuscular or intravenous route, is approved as an

anaesthetic drug by the TGA, but is not currently indicated for use in treating depression. Ketamine is not listed on the PBS for any indication.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 5 Comparator

- 5.1 The resubmission maintained that switching to a new antidepressant was the main comparator. The main arguments provided in support of this nomination were that switching to a new therapy is recommended in the RANZCP guidelines if a patient has not adequately responded to a therapy at optimal dose and duration, and that switching to a new OAD is the most commonly used treatment strategy in the requested PBS-eligible population according to utilisation data, therefore being the treatment most likely to be replaced by esketamine nasal spray in clinical practice. Switching to a new OAD is an appropriate comparator, however there are many other therapies used in the treatment of TRD that may also be considered appropriate comparators:
- Adding on another antidepressant (combination therapy);
  - Augmentation with lithium or an antipsychotic (e.g. olanzapine or aripiprazole);
  - Physical treatments like ECT or rTMS, which are less commonly used and typically reserved where pharmacological approaches have failed; and
  - Psychotherapy, such as cognitive-behavioural therapy.
- 5.2 The resubmission stated that according to the 10% PBS sample analysis provided with the resubmission, alternative treatment approaches such as antidepressant combination therapy or augmentation were used less commonly (35.3%) than switching to a new antidepressant (64.7%) in the psychiatry setting. This data, which is based on PBS prescriptions, does not capture use of other potential comparators such as ECT, rTMS, off-label, or psychological therapies. In the resubmission's consensus statement, it was noted that "it was considered important to acknowledge that, consistent with RANZCP guidelines, appropriate psychosocial and psychotherapeutic interventions would have been trialled in addition to antidepressant therapy by the time the patient has reached this definitional point (i.e. 2-5 pharmacological failures) of TRD".
- 5.3 The resubmission claimed that other HTA bodies, including CADTH, NICE, and ICER, examined indirect comparisons via a network analysis of esketamine to other pharmacological treatments and physical treatments (eg ECT) used in MDD. All the agencies considered that comparisons between agents outside of OADs were highly uncertain. Based on this, the resubmission argued that including other comparators would introduce highly uncertain comparisons, which would not be informative for decision making regarding cost-effectiveness. The resubmission stated that physical therapies, primarily ECT and rTMS, cannot be considered a comparator because according to the Australian mood guidelines, published by RANZCP, the MIDAS cycle (medication (M), followed by an Increase in Dose (ID), its Augmentation (A) and finally

a Switch (S) to another antidepressant), used to treat for response in MDD patients, should be repeated for as many antidepressants as possible (and at least 3) before considering a physical intervention (Malhi et al 2020).

- 5.4 The ESC noted the use of ketamine in the private treatment setting and the research into subcutaneous ketamine in TRD (see paragraph 3.11) and considered it may be informative to review any comparative evidence for ketamine and esketamine should it be available.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. Two clinicians presented on behalf of the group who prepared the clinical consensus statement provided with the resubmission. They reiterated that the management of TRD is not straightforward and a single sequence of treatments cannot be specified to cover all patients. Further, the clinicians noted the most extensive available evidence for esketamine was in the proposed clinical place, i.e. after failure of at least 2 prior OADs and also noted current clinical guidelines indicate lifestyle interventions and psychotherapy should also have been offered by this point where feasible. The clinicians considered that, in their view, the administration requirements of esketamine would make it unlikely it would enter the treatment algorithm as the third pharmacological treatment on every occasion, but considered that precluding the use of esketamine in this line of therapy would be inconsistent with the available evidence.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (22), health care professionals (10), health consumer organisations (2) and a medical provider organisation via the Consumer Comments facility on the PBS website. The comments from individuals described the feelings of fear, anxiety and hopelessness associated with severe and treatment-resistant depression and its broader impact on families, as well as the challenges of living with other mental health conditions (such as bipolar disorder and post-traumatic stress disorder (PTSD)); and how access to esketamine and ketamine treatment has been transformative by relieving the otherwise constant symptoms of depression. Patients described different ways in which esketamine and ketamine treatment improved their symptoms – some described the dissociative effects immediately post-administration as being released from negative thoughts, followed by improved emotional and functional capacity in following days; others described the benefits of esketamine and ketamine treatment as being realised the day after administration, when they experienced a marked reduction in anxiety, uplift in thoughts and feelings and improved ability to function.
- 6.3 The comments from clinicians involved in administering esketamine and ketamine

described the improvements observed in treated patients, as well as the challenges in providing physical interventions indicated in later-line use in TRD, such as rTMS. The comments from clinicians also highlighted that some patients experience unwanted effects which require management, and stressed the need for effective controls on esketamine and ketamine due to the risk of misuse and diversion. The clinician comments also highlighted the emerging evidence and ongoing clinical trials for racemic ketamine in TRD, and noted that racemic ketamine is likely to be substantially less costly than esketamine.

- 6.4 The comments from the Mental Illness Fellowship of Australia highlighted the rapid response observed with esketamine in clinical trials and described the administration requirements of esketamine, being in the presence of a health care professional, as beneficial, compared to current treatment options where compliance to therapy may be problematic. The comments from Lived Experience Australia included two patient stories, and discussed many of the themes shared by patients with TRD, including despair and hopelessness, as well as highlighting the difficulties patients with TRD face in maintaining employment, study, social relationships and the stigma of their condition. The comments also outlined that behavioural treatments such as cognitive behavioural therapy are often suggested, however significant issues accessing and affording psychiatric services make psychotherapy interventions infeasible for many patients. It was stated that it was important to have options like esketamine available early in a person's journey of seeking treatments to avoid prolonged treatment cycling and poor outcomes. The comments from the Solis Health and Samy Medical Group (a medical provider organisation) stated that restricting prescribing to psychiatrists would create issues due to accessibility and affordability.

### ***Clinical studies***

- 6.5 The resubmission was based on three short-term (induction), double blind, randomised controlled trials (RCTs) (TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3) and three long-term studies (SUSTAIN-1, SUSTAIN-2 and SUSTAIN-3), comparing esketamine nasal spray with a newly initiated OAD with intranasal placebo with a newly initiated OAD. All of these studies have previously been seen by the PBAC.
- 6.6 Details of the studies presented in the resubmission are provided in the table below.

**Table 3: Studies and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
TRANSFORM-2 (NCT02418585)	A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression (TRANSFORM-2)	Internal study report; 6 November 2017
	Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. (2019). Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study.	Am J Psychiatry; 176(6): 428-38.
	Hudgens S, Floden L, Blackowicz M, Jamieson C, Popova V, Fedgchin M, et al. (2021). Meaningful Change in Depression Symptoms Assessed with the Patient Health Questionnaire (PHQ-9) and Montgomery-Åsberg Depression Rating Scale (MADRS) Among Patients with Treatment Resistant Depression in Two, Randomized, Double-blind, Active-controlled Trials of Esketamine Nasal Spray Combined With a New Oral Antidepressant.	J Aff Dis; 281: 767-775
	Daly EJ, Turkoz I, Salvadore G, Fedgchin M, et al. (2021). The effect of esketamine in patients with treatment-resistant depression with and without comorbid anxiety symptoms or disorder.	Depress Anxiety; 38(11):1120-1130
	Saad Z, Hibar D, Fedgchin M, Popova V, Furey ML, Singh JB, et al. (2020). Effects of Mu-Opiate Receptor Gene Polymorphism rs1799971 (A118G) on the Antidepressant and Dissociation Responses in Esketamine Nasal Spray Clinical Trials.	Int J Neuropsychopharmacol; 23: 549-558.
	Citrome L, DiBernardo A, Singh J. (2020). Appraising Esketamine Nasal Spray for the Management of Treatment-Resistant Depression in Adults: number Needed to Treat, Number Needed to Harm, and Likelihood to be Helped/Harmed.	J Aff Dis; 271:228-238.
TRANSFORM-1 (NCT02417064)	A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression	Internal study report; 26 July 2018
	Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. (2019). Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1).	Int J Neuropsychopharmacol; 22: 616-630
	Citrome L, DiBernardo A, Singh J. (2020). Appraising esketamine nasal spray for the management of treatment-resistant depression in adults: Number needed to treat, number needed to harm, and likelihood to be helped or harmed.	J Aff Dis; 271 (228-238).
	Saad Z, Hibar D, Fedgchin M, Popova V, Furey ML, Singh JB, et al. (2020). Effects of Mu-Opiate Receptor Gene Polymorphism rs1799971 (A118G) on the Antidepressant and Dissociation Responses in Esketamine Nasal Spray Clinical Trials.	Int J Neuropsychopharmacol; 23: 549-558.
TRANSFORM-3 (NCT02422186)	Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects with Treatment-resistant Depression	Internal study report; 12 July 2018
	Citrome L, DiBernardo A, Singh J. (2020). Appraising esketamine nasal spray for the management of treatment-resistant depression in adults: Number needed to treat, number needed to harm, and likelihood to be helped or harmed.	J Aff Dis; 271 (228-238).
	Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, et al. (2020). Efficacy and Safety of Esketamine Nasal Spray Plus an Oral	Am J Geriatr Psychiatry; 28(2):121-141.

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	Antidepressant in Elderly Patients with Treatment-Resistant Depression-TRANSFORM-3.	
SUSTAIN-1 (NCT02493868)	A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression	Internal study report; 15 August 2018
	Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. (2019). Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial.	JAMA Psychiatry; 76(9):893-903
	Citrome L, DiBernardo A, Singh J. (2020). Appraising Esketamine Nasal Spray for the Management of Treatment-Resistant Depression in Adults: number Needed to Treat, Number Needed to Harm, and Likelihood to be Helped/Harmed.	J Aff Dis; 271:228-238.
SUSTAIN-2 (NCT02497287)	An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression	Internal study report; 14 August 2018
	Wajs E, Aluisio L, Holder R, Daly EJ, et al. (2020) Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: Assessment of long-term safety in a phase 3, open-label study (sustain-2).	J Clin Psychiatry; 81:3.
	Nijs M, Wajs E, Aluisio L, Turkoz I, et al. (2020) Managing esketamine treatment frequency toward successful outcomes: Analysis of phase 3 data.	Int J Neuropsychopharmacol; 23:7 (426-433).
SUSTAIN-3 (NCT02782104)	An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression	Internal study report; 21 May 2019

Source: Table 2-4, p.69 of the resubmission

6.7 The key features of the included studies are summarised in the table below.

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Esketamine nasal spray + OAD versus placebo + OAD</b>						
TRANSFORM-2	227	MC, DB, flexibly dosed (56 mg or 84 mg), active comparator RCT. Median duration of exposure was 25 days.	Low	Adults aged 18-64 years with single-episode or recurrent moderate to severe MDD, and non-response to prior treatment with 1-5 antidepressants in the current episode	Change from baseline in MADRS Proportion achieving response/ remission	Proportion achieving response/ remission
TRANSFORM-3	138	MC, DB, flexibly dosed (28 mg, 56 mg or 84 mg), active comparator RCT in older adults. Median duration of exposure was 25 days.	Low	Adults aged 65 years+ with single-episode or recurrent moderate to severe MDD, and non-response to prior treatment with 1-8 antidepressants in the current episode	Change from baseline in MADRS Proportion achieving response/ remission	Proportion achieving response/ remission
TRANSFORM-1	346	MC, DB, fixed dose (56 mg or 84 mg), active comparator RCT. Median duration of exposure was 25 days.	Low	Adults aged 18-64 years with single-episode or recurrent moderate to severe MDD, and non-response to prior treatment with 1-5 antidepressants in the current episode	Change from baseline in MADRS Proportion achieving response/ remission	Not used
SUSTAIN-1	452	MC, DB, flexibly dosed (56 mg or 84 mg), active comparator RCT relapse prevention study using a randomised withdrawal design.	Unclear	Adults aged 18-64 years with single-episode or recurrent moderate to severe MDD, and non-response to prior treatment with 1-5 antidepressants in the current episode	Proportion of relapses in stable remitters/ responders	Proportions of relapses in stable remitters/ responders, remission from response, recurrence from recovery
SUSTAIN-2	802	OL, MC, long-term safety study. The median duration of exposure was 22.9 weeks.	High	Adults aged 18 years+ with single-episode or recurrent moderate to severe MDD, and non-response to prior treatment with $\geq 2$ antidepressants in the current episode	Adverse events	Not used
SUSTAIN-3	1140	OL, MC, long-term safety study (ongoing). The median duration of exposure was 15.2 months.	High	Adult and elderly people with TRD, who previously participated in TRANSFORM-1, TRANSFORM-2, SUSTAIN-1, SUSTAIN-2, TRANSFORM-3 or TRD3006	Adverse events	Not used

Source: Table 2-5, p.78; Table 2-6, p.79; Table 2-7, p.85; Table 2-8, p.86 of the resubmission; Table 2.1, p.1; Table 2.2, p.3; Table 2.3, p.5, Attachment 2.5 of the resubmission

Abbreviations: DB, double blind; MADRS, Montgomery-Asberg Depression Rating Scale; MC, multi-centre; MDD, major depressive disorder; OAD, oral antidepressant; OL, open label; RCT, randomised controlled trial; TRD, treatment-resistant depression

6.8 The resubmission used the results from the TRANSFORM-2 and TRANSFORM-3 trials as the pivotal evidence of short-term response during treatment induction. These trials enrolled adult patients (age 18-64, and 65 years and over in TRANSFORM-2 and TRANSFORM-3 respectively), and evaluated flexibly-dosed esketamine, consistent

with the product information. Results of TRANSFORM-1 (adult patients 18-64 years; fixed esketamine dose regimens) were used as supportive evidence.

- 6.9 SUSTAIN-1 was conducted in response to an FDA request for a maintenance of effect study using a randomised withdrawal design, to assess whether intranasal esketamine delays relapse of depressive symptoms over time versus placebo, in subjects who had previously achieved stable remission or response on esketamine treatment. Only patients who achieved stable response or remission using esketamine nasal spray in combination with a newly initiated OAD during initiation and optimisation were eligible to be randomised in the double-blind maintenance phase to either continue with esketamine with an OAD, or discontinue esketamine and continue the OAD only. The PBAC previously noted that this type of design is at risk of overstating the efficacy of maintenance treatment, as the comparison group is at high risk of relapse, due to abruptly stopping treatment soon after improvement (para 6.8, esketamine PSD, July 2021 PBAC meeting). The trial is also at risk of functional unblinding, with patients assigned to placebo realising that they are no longer on esketamine after switching, given the immediate side effects associated with esketamine use. Such a withdrawal approach is also unlikely reflective of how esketamine cessation would be undertaken in practice. The PSCR maintained that the relapses observed in the placebo arm of SUSTAIN-1 are not attributable to the trial design or functional unblinding due to withdrawal or adverse effects. The PSCR stated the study design of the esketamine trials (including SUSTAIN-1) was agreed upon with both the FDA and CHMP (i.e., European regulator), and the trial results were accepted by both regulatory authorities as well as the TGA.
- 6.10 Maintaining blinding was a potential issue in all randomised esketamine nasal spray trials, as esketamine is known to cause transient dissociative effects in some individuals. This may also influence patient responses to outcome measurements.
- 6.11 Across all studies, patients were excluded who had: a current or prior DSM-5 diagnosis of a psychotic disorder; a history of suicidal behaviour in the past year; intent or suicidal ideation within 6 months before screening as clinically assessed by the investigator or based on the C-SSRS scale; a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria. Collectively, these features may limit generalisability to other populations. In particular, although patients with MDD with psychotic features would be eligible for treatment under the proposed restriction, due to their exclusion from the trials, the safety and effectiveness of treatment with esketamine nasal spray in this population is unknown.

### ***Comparative effectiveness***

- 6.12 Results were unchanged from the previous submission. The results of the primary efficacy endpoint for the TRANSFORM trials (change in MADRS total score from baseline to the end of the 4-week double-blind induction phase), are summarised in the table below.

**Table 5: Montgomery-Asberg Depression Rating Scale (MADRS) total score: change from baseline to Day 28 by MMRM or to Endpoint (DB) by ANCOVA LOCF; double-blind induction studies (Full analysis set)**

	Baseline		MMRM change from baseline to Day 28		ANCOVA change from baseline to Day 28	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>TRANSFORM-2 (flexible dosing, adult patients 18-64 years of age with TRD)</b>						
Esketamine+OAD	114	37.0 (5.69)	101	-21.4 (12.32)	112	-19.6 (13.58)
Placebo+OAD	109	37.3 (5.66)	100	-17.0 (13.88)	109	-16.3 (14.24)
Mean difference (95% CI)			-	<b>-4.0 (-7.3, -0.6)</b>	-	<b>-3.5 (-6.7, -0.3)</b>
<b>TRANSFORM-3 (flexible dosing, older patients ≥ 65 years of age with TRD)</b>						
Esketamine+OAD	72	35.5 (5.91)	63	-10.0 (12.74)	71	-9.3 (12.28)
Placebo+OAD	65	34.8 (6.44)	60	-6.3 (8.86)	64	-5.6 (9.11)
Mean difference (95% CI)			-	-3.6 (-7.2, 0.1)	-	-3.6 (-7.2, 0.0)
<b>TRANSFORM-1 (fixed dosing, adult patients 18-64 years of age with TRD)</b>						
Esketamine 56 mg + OAD	115	37.4 (4.76)	111	-19.0 (13.86)	115	-18.3 (14.21)
Esketamine 84 mg + OAD	114	37.8 (5.58)	98	-18.8 (14.12)	113	-17.4 (14.25)
Placebo + OAD	113	37.5 (6.16)	108	-14.8 (15.07)	113	-14.3 (15.00)
Mean difference, ESK 56 mg vs placebo (95% CI)			-	-4.1 (-7.7, -0.5)	-	-4.1 (-7.5, -0.6)
Mean difference, ESK 84 mg vs placebo (95% CI)			-	-3.2 (-6.9, 0.5)	-	-2.0 (-5.5, 1.4)

Source: Table 2-13, p.114 of the resubmission; Table 2.50, Attachment 2.6 of the resubmission

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DB = double-blind; ESK, esketamine; MMRM, Mixed-Effect Model for Repeated Measures; OAD, oral antidepressant; SD, standard deviation; TRD, treatment-resistant depression

Notes: Tests for treatment effects based on mixed model for repeated measures (MMRM) with change from baseline as the response variable applied the fixed effect model terms for treatment (intranasal esketamine + OAD, OAD + intranasal placebo), day, country, class of OAD (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favours esketamine

Tests for treatment effect based on analysis of covariance (ANCOVA) model with change from baseline as the response variable applied factors for treatment (intranasal esketamine + OAD, OAD + intranasal placebo), country, and class of OAD (SNRI or SSRI), and baseline value as a covariate. A negative difference favours esketamine

For TRANSFORM-2, the difference from placebo is the least-squares mean difference between esketamine + OAD and OAD + placebo

For TRANSFORM-3, difference from placebo is the median unbiased estimate, which is a weighted combination of the least squares means of the difference from placebo

For both TRANSFORM-1 and TRANSFORM-3 95% CI value is the 2-sided flexible CI for the difference from placebo

For both TRANSFORM-1 and TRANSFORM-3, the p-values are based on the weighted combination test statistic

In TRANSFORM-1, the comparison for 56 mg was considered statistically significant only if the analysis was significant for 84 mg. As tests showed that the 84 mg dose treatment arm was not statistically significantly different from placebo, 56 mg was not formally evaluated

MADRS Total score ranges from 0 to 60; a higher score indicates a more severe condition and negative change in score indicates improvement

6.13 Of the three short-term induction trials, only TRANSFORM-2 showed a statistically significant treatment effect with esketamine nasal spray compared with placebo. The PBAC previously considered the observed difference in the esketamine + OAD arm compared to a new OAD alone of 4 points on the MADRS scale was of uncertain clinical significance (para 7.8, esketamine PSD, July 2021 PBAC meeting). The confidence intervals are wide, and the lower bound falls below the nominated minimum clinically important difference (MCID), suggesting that treatment effects are variable, and the between-group difference falls below published MCIDs. This suggests that a significant proportion of patients do not derive any additional benefit from treatment with esketamine. Although the absolute mean change from baseline in MADRS score seen with esketamine in TRANSFORM-2 is -21.4 points, which is substantially above the MCID indicated by Leucht 2017 (7-9 point change) and therefore is highly clinically meaningful for patients, around 80% of this change (-19.6) was achieved in the placebo arm, suggesting most of this change was due to the switch to a novel antidepressant plus additional contact with health professionals due to trial

enrolment. The evaluation stated the mean difference between treatment arms is small and unlikely to be noticeable by patients on average.

- 6.14 The proportion of responders and remitters at day 28 of the TRANSFORM-2 and TRANSFORM-3 trials are summarised in the table below. A subject was defined as a responder at a given time point if the percent improvement (decrease) in MADRS total score from baseline was  $\geq 50\%$ . Subjects who had a MADRS total score of  $\leq 12$  were considered remitters. This was not a standard definition of remission; other trials have used a more stringent cut-off of  $< 10$  or  $< 7$  to define remission, however the potential impact of this on the trial results is unclear. These outcomes were used to inform the transition probabilities in the economic model.

**Table 6: Proportion of responders and remitters at day 28 based on MADRS total score, TRANSFORM-2 and TRANSFORM-3 (full analysis set)**

	Esketamine + OAD	Placebo + OAD
<b>Response (<math>\geq 50\%</math> improvement MADRS score)</b>		
<b>TRANSFORM-2</b>		
Observed cases, n/N (%)	70/101 (69.3)	52/100 (52.0)
LOCF, n/N (%)	71/112 (63.4)	54/109 (49.5)
<b>TRANSFORM-3</b>		
Observed cases, n/N (%)	17/63 (27.0)	8/60 (13.3)
End point (DB), n/N (%)	17/71 (23.9)	8/64 (12.5)
<b>Remission (MADRS total score <math>\leq 12</math>)</b>		
<b>TRANSFORM-2</b>		
Observed cases, n/N (%)	53/101 (52.5)	31/100 (31.0)
LOCF, n/N (%)	54/112 (48.2)	33/109 (30.3)
<b>TRANSFORM-3</b>		
Observed cases, n/N (%)	11/63 (17.5)	4/60 (6.7)
End point (DB), n/N (%)	11/71 (15.5)	4/64 (6.3)

Source: Table 2-17, p.123; Table 2-18, p.125; Table 2-19, p.126; Table 2-20, p.127 of the resubmission

- 6.15 In TRANSFORM-2 the number needed to treat for response at day 28 based on MADRS total score was 5.8, and for remission was 4.7. In TRANSFORM-3 the number needed to treat for response at day 28 was 7.3, and for remission was 9.3. Overall, the population aged 65 years and over enrolled in TRANSFORM-3 achieved lower remission and response rates on average in both esketamine treatment and placebo arms, compared with the population enrolled in TRANSFORM-2.
- 6.16 The PSCR argued that given the difficulties in treating patients with TRD that a holistic consideration of the evidence was required, beyond just the results in terms of MADRS outcomes. The PSCR argued the Clinical Global Impression of Severity (CGI-S) scale, which takes into account all available information including patient history, psychosocial circumstances, symptoms, behaviour and the impact of symptoms on ability to function was frequently used in the clinical setting to assess disease severity, on a scale of 0 to 7. The PSCR noted the median CGI-S scores of esketamine and placebo groups at baseline was 5.0, indicating markedly ill patients, with a median improvement from baseline to endpoint of the double-blind induction phase of -2.0 in the esketamine arm, which the sponsor argued was indicative that patients went from being markedly ill to mildly ill. Additionally, the PSCR noted esketamine also resulted

in improvements in both the patient health questionnaire 9 (PHQ-9) and Sheehan Stability Scale (SDS) total score, which indicated esketamine was more effective than placebo in reducing depressive symptoms, reducing functional impairment and disruption of work/school, social and family/home responsibilities. The ESC noted the results of the secondary outcomes reported in the PSCR were favourable to esketamine and considered the evidence presently likely supported that esketamine is effective (at least, for some patients) for the treatment of TRD in the short-term induction phase.

6.17 The results for the EQ-5D-5L health status index in the TRANSFORM trials are summarised in the table below.

Table 7: EQ-5D health status index in the TRANSFORM trials

	Esketamine + OAD		Placebo + OAD	
	N	Mean (SD)	N	Mean (SD)
<b>TRANSFORM-2</b>				
Baseline	114	0.530 (0.208)	109	0.501 (0.214)
End point (day 28)	111	0.815 (0.177)	105	0.737 (0.230)
<b>TRANSFORM-3</b>				
Baseline	72	0.581 (0.226)	65	0.635 (0.228)
End point (day 28)	70	0.653 (0.255)	64	0.657 (0.211)
<b>TRANSFORM-1</b>				
Baseline (56 mg)	115	0.531 (0.220)	113	0.521 (0.216)
Baseline (84 mg)	114	0.502 (0.208)		
End point (56 mg)	113	0.755 (0.216)	113	0.703 (0.217)
End point (84 mg)	112	0.741 (0.203)		

Source: TEFEQ5D01A, p.4465 TRANSFORM-1 CSR; TEFEQ5D01A, p.2853 TRANSFORM-2 CSR; TEFEQ5D01A, p.1930 TRANSFORM-3 CSR

Abbreviations: OAD, oral antidepressant; SD, standard deviation

Note: Health Status Index ranges from -0.148 to 0.949 and is anchored at 0 (health state valued equal to dead) and 1 (full health)

6.18 Participants in the placebo and esketamine treatment arms of the TRANSFORM trials experienced improvements in quality of life as measured by the EQ-5D-5L health status index between baseline and end of study, with a trend favouring treatment with intranasal esketamine. There were some differences in mean scores at baseline between treatment groups, particularly in TRANSFORM-3.

6.19 In the SUSTAIN-1 trial, the primary efficacy endpoint was the time from randomisation (in the maintenance phase) to the first relapse in patients who previously achieved stable remission with esketamine nasal spray by the end of the optimisation phase. Time to relapse in the stable remitters and stable responders sets are summarised in the table below.

**Table 8: Time to relapse<sup>a</sup> in the SUSTAIN-1 trial (stable remitters and responders)**

	<b>Esketamine + OAD</b>	<b>Placebo + OAD</b>	<b>Mean difference</b>	<b>Hazard ratio (95% CI)<sup>b</sup></b>
<b>Stable Remitters</b>	<b>N=90</b>	<b>N=86</b>	-	-
Number of relapses, n (%)	24 (26.7)	39 (45.3)	18.6	<b>0.49 (0.29, 0.84)</b>
Median time to relapse, days (95% CI)	NE	273.0 (97.0, NE)	NE	
<b>Stable Responders</b>	<b>N=62</b>	<b>N=59</b>	-	-
Number of relapses, n (%)	16 (25.8)	34 (57.6)	31.8	<b>0.30 (0.16, 0.55)</b>
Median time to relapse, days (95% CI)	635.0 (264.0, 635.0)	88.0 (46.0, 196.0)	547	

Source: Table 2-25, p.136; Table 2-26, p.139 of the resubmission

Abbreviations: CI, confidence interval; NE, not estimable; OAD, oral antidepressant

<sup>a</sup> Based on Kaplan-Meier product limit estimates

<sup>b</sup> Hazard ratio and CI are weighted estimates based on Wassmer (2006) and calculated using R

6.20 Treatment with esketamine nasal spray significantly delayed relapse in stable remitters and stable responders compared with intranasal placebo.

6.21 The FDA review committee noted that there was a faster rate of relapse observed in SUSTAIN-1 compared to other maintenance of effect studies of MDD (FDA, 2019). This could reflect functional unblinding, with patients randomised to placebo realising that they are no longer on esketamine after switching, given the immediate side effects associated with esketamine use. The abrupt withdrawal of esketamine nasal spray so soon after achieving remission may not reflect use in clinical practice, and there is a risk that this overstates the relapse rate in the placebo treatment arm. The product information states that after depressive symptoms improve, treatment should continue for at least 6 months. Clinical guidelines recommend that for all antidepressant therapy, “it is generally recommended that patients should stop their antidepressant medication after they have been in remission for around 9 months to a year (Malhi et al., 2015). After ceasing medication, many patients will remain depression-free, but some may have a depressive relapse and up to 40% may experience discontinuation or withdrawal symptoms. Because of this, it has been recommended that antidepressants should be withdrawn gradually, with doses tapered down over an extended period of time”. The clinical trials did not provide information on how and when to cease treatment with esketamine nasal spray to avoid relapse.

6.22 Remission and response from baseline (maintenance) to endpoint in the SUSTAIN-1 trial is summarised in the table below.

**Table 9: Remission and response based on Montgomery-Asberg Depression Rating Scale (MADRS) total score over time; Maintenance phase (Study SUSTAIN-1: Full (Stable Remitters and Responders) Analysis Set)**

MADRS total score	Stable remitters		Stable responders	
	Esk + OAD (N = 90)	Pbo + OAD (N = 86)	Esk + OAD (N = 62)	Pbo + OAD (N = 59)
<b>Remission</b>				
Baseline				
≤12	90 (100.0)	85 (98.8)	37 (59.7)	38 (64.4)
>12	0	1 (1.2)	25 (40.3)	21 (35.6)
Endpoint				
≤12	58 (65.2)	36 (41.9)	29 (46.8)	15 (25.4)
>12	31 (34.8)	50 (58.1)	33 (53.2)	44 (74.6)
<b>Response</b>				
Baseline				
≥ 50% improvement	90 (100.0)	86 (100.0)	62 (100.0)	59 (100.0)
< 50% improvement	0	0	0	0
Endpoint				
≥ 50% improvement	67 (75.3)	48 (55.8)	41 (66.1)	20 (33.9)
< 50% improvement	22 (24.7)	38 (44.2)	21 (33.9)	39 (66.1)

Source: Table 2-28, p.143; Table 2-29, p.144 of the resubmission

Abbreviations: Esk, esketamine; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant; Pbo, placebo

- 6.23 Remission was achieved or maintained by a higher percentage of subjects in the esketamine nasal spray treatment groups. Remission during the maintenance phase among stable remitters decreased less over time in the esketamine nasal spray group compared with the intranasal placebo group (33.6% versus 57.9%), which indicates fewer patients lose remission over the trial period. Similarly, in stable responders, remission was achieved or maintained by a higher percentage of subjects in the esketamine nasal spray treatment groups compared with patients in the intranasal placebo treatment groups. The reduction over time was smaller in the esketamine nasal spray group, indicating fewer patients lost remission over the trial time period when treated with esketamine nasal spray and an OAD versus continuing on an OAD alone.
- 6.24 Response was also maintained or lost at a slower rate by a higher percentage of subjects in the esketamine nasal spray treatment groups. Response during the maintenance phase among stable remitters decreased from 100% of patients in both the esketamine nasal spray treatment group and intranasal placebo group at baseline to 75.3% and 55.8%, respectively, at endpoint. This suggests that fewer patients lost response over the trial period with esketamine nasal spray. Similarly, subjects with response in stable responders decreased from 100% in the esketamine nasal spray treatment group and 100% in the intranasal placebo group at baseline to 66.1% and 33.9% of subjects, respectively, at endpoint. Fewer patients lost response over the trial time period when treated with esketamine nasal spray.
- 6.25 Esketamine nasal spray can have dissociative and sedative effects that are difficult to mimic with placebo. To examine the possibility that subjects who were randomised to intranasal placebo and experienced a relapse event were aware of the change in study drug, a post-hoc evaluation of Clinician Administered Dissociative States Scale (CADSS)

and Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) total scores over time was included in the resubmission. Results for the CADSS during the maintenance phase of SUSTAIN-1 suggested some effect in the esketamine treatment arm at around 40 minutes post dose, which did not remit over time. This suggests that if this was a noticeable effect patients may have been aware of treatment assignment. The MOAA/S was used to measure treatment-emergent sedation. In the intranasal esketamine plus OAD group, moderate or greater sedation as assessed using the MOAA/S (score  $\leq 3$ ) was observed in a small percentage of subjects during the open-label induction phase (45 [10.3%] of patients), the optimisation phase (16 [3.5%] of patients) and the maintenance phase (8 [5.3%] of patients), with none of the subjects in the OAD plus intranasal placebo group showing moderate or greater sedation. Collectively, these results suggest that there may have been noticeable differences between treatment arms in the SUSTAIN-1 trial; the risk of bias of these differences is unclear.

### Comparative harms

6.26 A summary of treatment-emergent adverse events from the TRANSFORM trials is presented in the table below.

**Table 10: Incidence of adverse events in the double-blind induction phase of the TRANSFORM trials (safety analysis set)**

	TRANSFORM-2		TRANSFORM-3		TRANSFORM-1		
	ESK + OAD N = 115	PBO + OAD N = 109	ESK + OAD N = 72	PBO + OAD N = 65	ESK 56 mg + OAD N = 115	ESK 84 mg + OAD N = 116	PBO + OAD N = 113
TEAE	98 (85.2)	90 (78.3)	51 (70.8)	39 (60.0)	100 (87.0)	103 (88.8)	77 (68.1)
TEAE possibly related to intranasal drug <sup>a</sup>	90 (78.3)	39 (35.8)	42 (58.3)	22 (33.8)	89 (77.4)	92 (79.3)	54 (47.8)
TEAE possibly related to OAD <sup>a</sup>	39 (33.9)	26 (23.9)	13 (18.1)	11 (16.9)	44 (38.3)	43 (37.1)	34 (30.1)
TEAE leading to death	1 (0.9)	0	0	0	0	0	0
1 or more serious TEAE	1 (0.9)	1 (0.9)	3 (4.2)	2 (3.1)	2 (1.7)	0	0
TEAE possibly related to intranasal drug withdrawn <sup>b</sup>	8 (7.0)	1 (0.9)	4 (5.6)	2 (3.1)	1 (0.9)	7 (6.0)	2 (1.8)
TEAE possibly related to OAD withdrawn <sup>b</sup>	4 (3.5)	0	1 (1.4)	1 (1.5)	0	1 (0.9)	2 (1.8)

Source: Table 2.5-18, p.167 and Table 2.5-19, p168 of the July 2021 submission

Abbreviations: ESK, esketamine nasal spray; OAD, oral antidepressant; PBO, placebo nasal spray; TEAE, treatment-emergent adverse event

<sup>a</sup> Study drug relationship of possible, probable, and very likely are included in this category

<sup>b</sup> An adverse event that started in the double-blind induction phase and resulted in discontinuation in the follow-up phase is counted as treatment-emergent in the double-blind induction phase

6.27 The overall incidence of adverse events was higher in the esketamine treatment arms compared with the placebo treatment arms across all three trials. There was also a higher incidence of adverse events considered to be related to the intranasal study drug in the esketamine treatment arms.

6.28 Across the TRANSFORM trials, the most common treatment-emergent adverse events in the esketamine nasal spray treatment group included dissociation, nausea, vertigo,

dysgeusia, dizziness, headache, somnolence, vision blurred, paraesthesia, anxiety, hypoaesthesia oral, hypoaesthesia, increased blood pressure, and fatigue. In TRANSFORM-3, which enrolled older adults aged 65 years and over, urinary tract infections were also more commonly reported in the esketamine nasal spray treatment group. Across trials, in the placebo treatment group, the most commonly reported treatment emergent adverse events included headache, dysgeusia, somnolence, and nausea.

- 6.29 A summary of treatment-emergent adverse events by phase, for the induction, optimisation, and maintenance phases of the SUSTAIN-1 trial is included in the table below.

**Table 11: Overall summary of treatment-emergent adverse events; induction phase, optimisation phase and maintenance phase of SUSTAIN-1 (Safety analysis set)**

	Induction phase	Optimisation phase	Maintenance phase	
	ESK + OAD N = 437	ESK + OAD N = 455	ESK + OAD N = 152	PBO + OAD N = 145
Total number with a TEAE	336 (76.9)	335 (73.6)	125 (82.2)	66 (45.5)
TEAE possibly related to intranasal drug <sup>a</sup>	301 (68.9)	281 (61.8)	106 (69.7)	37 (25.5)
TEAE possibly related to OAD <sup>a</sup>	71 (16.2)	61 (13.4)	13 (8.6)	9 (6.2)
TEAE leading to death	0	0	0	0
1 or more serious TEAE	13 (3.0)	11 (2.4)	4 (2.6)	1 (0.7)
TEAE possibly related to intranasal drug withdrawn <sup>b</sup>	22 (5.0)	5 (1.1)	4 (2.6)	3 (2.1)
TEAE possibly related to OAD withdrawn <sup>b</sup>	8 (1.8)	2 (0.4)	3 (2.0)	0

Source: Table 2.5-23, p.173 and Table 2.5-24, p.173 of the July 2021 submission

Abbreviations: ESK, esketamine nasal spray; OAD, oral antidepressant; PBO, intranasal placebo

<sup>a</sup> Study drug relationship of possible, probable, and very likely are included in this category

<sup>b</sup> An adverse event that started in the double-blind induction phase and resulted in discontinuation in the follow-up phase is counted as treatment-emergent in the double-blind induction phase

\* Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Adverse events are coded using MedDRA version 20.0.

- 6.30 The types and incidences of most common treatment-emergent adverse events were generally consistent across the 4-week induction phases of the short-term studies and the induction phase of SUSTAIN-1. In the double-blind maintenance phase treatment-emergent adverse events were reported at a higher rate in the esketamine nasal spray versus the intranasal placebo group.
- 6.31 The most common treatment-emergent adverse events in SUSTAIN-1 included dysgeusia, vertigo, dissociation, somnolence, dizziness, headache, nausea, vision blurred, and hypoaesthesia oral and were consistent with the types of adverse events observed in the induction phase. In the double blinded maintenance phase, these events occurred at a higher incidence in the esketamine nasal spray treatment arm compared with the intranasal placebo treatment arm. This suggests that the adverse events associated with esketamine nasal spray, which may affect tolerability, continue to be experienced in the maintenance phases of treatment.
- 6.32 The ESC previously noted that ‘adverse events continued to be experienced at a greater incidence in the esketamine treatment group compared with the placebo

treatment group in the SUSTAIN-1 trial, suggesting that adverse events may continue throughout maintenance treatment’ (para 6.33, esketamine PSD, July 2021 PBAC meeting). The resubmission stated that although esketamine nasal spray has a distinct side effect profile and patients treated with esketamine nasal spray are likely to experience these upon dosing into the maintenance phase, the majority of esketamine side effects are transient, self-limiting, and mostly mild or moderate in severity. At present, longer-term (>12 months) safety of use of esketamine nasal spray is unknown. The longer term, repeated use of esketamine may potentially lead to adverse effects that are seen with longer-term, repeated use of ketamine, including abuse and addiction, neurotoxicity, bladder toxicity, and hepatotoxicity.

- 6.33 A number of adverse events were of clinical interest during the esketamine nasal spray clinical development program: adverse events potentially suggestive of abuse, increased blood pressure, increased heart rate, transient dizziness or vertigo, impaired cognition, cystitis, anxiety, and treatment-emergent suicidality.
- 6.34 Across all studies, adverse events of drug abuse, drug abuser, drug dependence, drug detoxification, drug rehabilitation, drug tolerance, drug tolerance increased, or drug use disorder were not identified. There were no reports from the investigational sites of any subjects requesting an increase either in the dose of esketamine nasal spray or in the frequency of treatment sessions (as a potential early indicator of drug-seeking behaviour). It may be difficult to observe these outcomes in a tightly regulated trial setting; it is unclear whether potential abuse or misuse may occur in clinical practice and this is likely to be dependent upon the model used for administration. Increased blood pressure or increased heart rate, dizziness/vertigo, and anxiety in all studies were primarily mild or moderate in severity. Suicidality-related adverse events were reported as severe in only a small number of subjects, and most were considered either not related or doubtfully related to esketamine nasal spray treatment in the opinion of the investigator and therefore likely associated with the underlying disease. There were very low reported cases of cystitis (9 subjects in SUSTAIN-1, 5 subjects in SUSTAIN-2 and 8 subjects in SUSTAIN-3) and impaired cognition (1 subject in SUSTAIN-3) in the esketamine nasal spray studies. Adverse events such as impaired cognition may not be observable over short-term trial durations.
- 6.35 The Pre-PBAC Response acknowledged the absence of trial-based safety data beyond 12 months, however noted the most recent Periodic Benefit Risk Evaluation Report (PBER) from October 2021, included information from the ongoing open-label extension safety trial of SUSTAIN-2, which found no new safety concerns with continued intermittent esketamine dosing of up to 56 months.

### ***Benefits/harms***

- 6.36 The benefits and harms are unchanged from the July 2021 submission, except for the addition of the TRANSFORM-3 trial results.
- 6.37 On the basis of the direct evidence presented in the submission (4 weeks of double-blind induction treatment in TRANSFORM-2), for every 100 patients aged 18-64 years

with treatment-resistant depression treated with esketamine nasal spray plus an OAD in comparison to intranasal placebo plus an OAD:

- Approximately 17 additional patients would have a response, defined as a  $\geq 50\%$  reduction in symptoms of depression as measured on the MADRS.
- Approximately 22 additional patients would experience remission, defined as a MADRS score  $\leq 12$ .
- Approximately 16 additional patients would experience dizziness.
- Approximately 22 additional patients would experience dissociation.
- Approximately 23 additional patients would experience vertigo.
- Approximately 10 additional patients would have an increase in blood pressure.

6.38 On the basis of the direct evidence presented in the submission (4 weeks of double-blind induction treatment in TRANSFORM-3), for every 100 patients aged 65 years and over with treatment-resistant depression treated with esketamine nasal spray plus an OAD in comparison to intranasal placebo plus an OAD:

- Approximately 14 additional patients would have a response, defined as a  $\geq 50\%$  reduction in symptoms of depression as measured on the MADRS.
- Approximately 11 additional patients would experience remission, defined as a MADRS score  $\leq 12$ .
- Approximately 13 additional patients would experience dizziness.
- Approximately 11 additional patients would experience dissociation.
- Approximately 8 additional patients would experience vertigo.
- Approximately 8 additional patients would have an increase in blood pressure.

6.39 On the basis of the direct evidence presented in the submission (double-blind maintenance treatment in SUSTAIN-1), for every 100 patients with treatment-resistant depression who achieved remission or response and continued treatment with esketamine nasal spray plus an OAD compared to those who achieved remission or response who then discontinued treatment with esketamine nasal spray, instead receiving an intranasal placebo plus an OAD in the maintenance phase:

- In those who achieved remission, approximately 19 fewer patients would experience relapse to depression.
- In those who achieved response, approximately 32 fewer patients would experience relapse to depression.
- Approximately 16 additional patients would experience dizziness.
- Approximately 23 additional patients would experience dissociation.
- Approximately 20 additional patients would experience vertigo.
- Approximately 3 additional patients would have an increase in blood pressure.

### **Clinical claim**

6.40 The PBAC previously considered that the claim of superior comparative effectiveness of esketamine plus a new OAD to a new OAD alone may be reasonable, however the magnitude and clinical importance of the observed benefits was uncertain (para 6.34, esketamine PSD, July 2021). The PBAC considered that the claim of inferior safety of

esketamine + new OAD to a new OAD alone was reasonable (para 6.34, esketamine PSD, July 2021).

- 6.41 The resubmission described esketamine nasal spray in combination with a new OAD for the treatment of TRD as superior in terms of effectiveness, and inferior in terms of safety, compared with a newly initiated OAD alone.
- 6.42 The evaluation stated there were a number of important potential issues:
- The clinical importance of the treatment benefit was uncertain. Of the three included randomised induction trials, only TRANSFORM-2 was able to demonstrate statistical superiority of esketamine over placebo, while the other two trials showed similar mean differences in change scores without statistical significance.
  - Clinically important reductions in MADRS total scores were observed in both the esketamine (21.4 points) and placebo (17.0 points) arms in the TRANSFORM-2 trial, however the incremental difference between treatment groups may not be clinically important. The PSCR argued that given the difficulties in treating patients with TRD, a holistic consideration of the evidence was required, beyond just the results in terms of MADRS outcomes. The PSCR argued the Clinical Global Impression of Severity (CGI-S) scale, and other secondary measures consistently supported the claim of superior comparative effectiveness of esketamine over placebo in the induction phase (see paragraph 6.15 for more information). The ESC noted the results of the secondary outcomes favoured esketamine and considered the evidence presented supported the clinical importance of the benefits of treatment with esketamine.
  - Long-term data about the maintenance of treatment effect is currently unavailable. The SUSTAIN-1 trial suggested that participants who discontinue esketamine after improvement are more likely to relapse in comparison with those who do not discontinue esketamine. However, PBAC considered that this type of withdrawal trial design tends to overemphasise the efficacy of maintenance treatment, as the comparison group is at extremely high risk of relapse considering that treatment is abruptly stopped soon after improvement (para 6.32, esketamine PSD, July 2021 PBAC meeting).
  - The optimum duration of therapy is yet to be determined. Current guidelines suggest at least 6 months, and ideally more than one year of maintenance treatment with pharmacotherapies for people with major depression, with longer treatment durations suggested for patients with recurrent episodes (Malhi et al., 2021). Patients in the intranasal placebo arm of the SUSTAIN-1 trial, who discontinued treatment after 12 or 16 weeks of treatment, experienced more relapse episodes than those continuing treatment. As the durability of benefit has not been established, it is unclear for how long esketamine should be prescribed to prevent relapse.
  - More people in the esketamine treatment arms withdrew from treatment compared with the placebo treatment arms in the included trials. In addition, the

proposed supervised administration and monitoring may comprise a significant burden to patients. These results suggest that the overall tolerability and acceptability of esketamine may be low for some patients.

- 6.43 The PBAC considered that while there remained uncertainty regarding the primary outcome results from the clinical trials, when taking into account the totality of the available evidence, the claim of superior comparative effectiveness was likely to be reasonable, however the magnitude of benefit remained uncertain.
- 6.44 The PBAC reaffirmed its view previously expressed at its July 2021 meeting that the claim of inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.45 The resubmission presented a stepped economic evaluation of esketamine nasal spray plus a newly initiated OAD versus a newly initiated OAD alone in patients with moderate to severe TRD. The economic analysis was based on evidence from the TRANSFORM-2, TRANSFORM-3 and SUSTAIN-1 trials, as well as additional modelled variables. The economic evaluation was presented as a cost-utility analysis.
- 6.46 Key changes to the economic model compared to the July 2021 submission included:
- The addition of a recovery health state in the subsequent treatment pathway in response to PBAC concerns that the exclusion of a recovery state in subsequent treatment was inappropriate and did not reflect clinical practice (para 6.43, esketamine PSD, July 2021 PBAC meeting).
  - The inclusion of data from TRANSFORM-3 (in adults  $\geq 65$  years) with TRANSFORM-2 data to inform induction transition probabilities and health state utilities in response to PBAC concerns that the model did not utilise all available clinical data (para 6.37, 6.61, 7.7, esketamine PSD, July 2021 PBAC meeting).
  - Maintenance transition probabilities for the placebo arm informed by the STAR\*D study (previously based on the SUSTAIN-1 trial) in response to PBAC concerns that the abrupt withdrawal trial design of the SUSTAIN-1 trial likely overstates the relapse rate in the placebo arm (para 6.20, esketamine PSD, July 2021 PBAC meeting).
  - Including disutilities due to adverse events in the maintenance phase of treatment (previously only applied in the first/induction cycle) in response to ESC concerns that the model should capture the significant safety concerns associated with the use of esketamine (para 6.60, esketamine PSD, July 2021 PBAC meeting).
  - A lower price of esketamine.
  - A higher cost of administration for esketamine, in response to PBAC concerns that the cost of administration was a significant underestimate (para 6.47, esketamine PSD, July 2021 PBAC meeting).
- 6.47 The table below compares the key components of the economic evaluations in the July 2021 submission and current resubmission.

**Table 12: Summary of model structure, key inputs and rationale**

Component	July 2021 submission	Resubmission
Type of analysis	Cost-effectiveness analysis and cost-utility analysis	Unchanged.
Treatments	Esketamine nasal spray with a newly initiated OAD; intranasal placebo with a newly initiated OAD; subsequent therapy (based on OADs)	Unchanged.
Outcomes	Quality-adjusted life-years MDE-free life years Proportions of patients with remission and response	Unchanged.
Time horizon	5 years	Unchanged.
Method used to generate results	Markov cohort analysis with multiple lines of treatment.	Unchanged.
Health states	Major Depressive Episode (MDE) Response Remission Recovery Death	The Recovery health state was added to the subsequent treatment pathway.
Cycle length	Four weeks.	Unchanged.
Transition probabilities	<p>Transitions from MDE to response or remission based on patients who achieved remission or response at the end of the induction phase in TRANSFORM-2.</p> <p>Transitions from response to remission, remission to recovery, remission to MDE, and response to MDE are informed by the proportions of patients achieving these outcomes in the maintenance phase of SUSTAIN-1.</p> <p>Transition probabilities for MDE to response or remission, and for response or remission to MDE in patients who failed initial treatment in the model are based on data from patients in their fourth line of treatment in the STAR*D study.</p> <p>Esketamine treatment discontinuation for any cause is applied in the continuation, maintenance, and recovery phases (week 5 onwards), based on an exponential distribution fit to all-cause discontinuations in SUSTAIN-1.</p> <p>Age-specific all-cause mortality was modelled based on Australian Bureau of Statistics life tables for males and females (2017-2019). No additional mortality risk associated with TRD was assumed.</p>	<p>Transitions from MDE to response or remission based on patients who achieved remission or response in TRANSFORM-2 and TRANSFORM-3, weighted by the proportion of the Australian general population aged &lt;65 and ≥65 years.</p> <p>Transitions in the esketamine plus OAD arm unchanged; transitions for remission and response to MDE in the placebo plus OAD arm based on the average of third- and fourth-line treatment outcomes from the STAR*D study.</p> <p>Unchanged.</p> <p>Unchanged.</p> <p>The same approach was used; using updated ABS life tables (2018-2020).</p>
Utilities	<p>Patient-level EQ-5D-5L data from baseline and day 28 of the TRANSFORM-2 trial were transformed into health state utilities using the Canadian value set.</p> <p>Adverse event disutilities derived from a number of published sources, weighted by the incidence of adverse events in the TRANSFORM-2 trial; applied to the induction (first) cycle only.</p>	<p>Patient-level EQ-5D-5L data from baseline and day 28 of the TRANSFORM-2 and TRANSFORM-3 trials were transformed into health state utilities using the UK value set; weighted by the proportion of the Australian population aged &lt;65 and ≥65 years.</p> <p>Disutilities unchanged; but applied during induction and maintenance treatment.</p>

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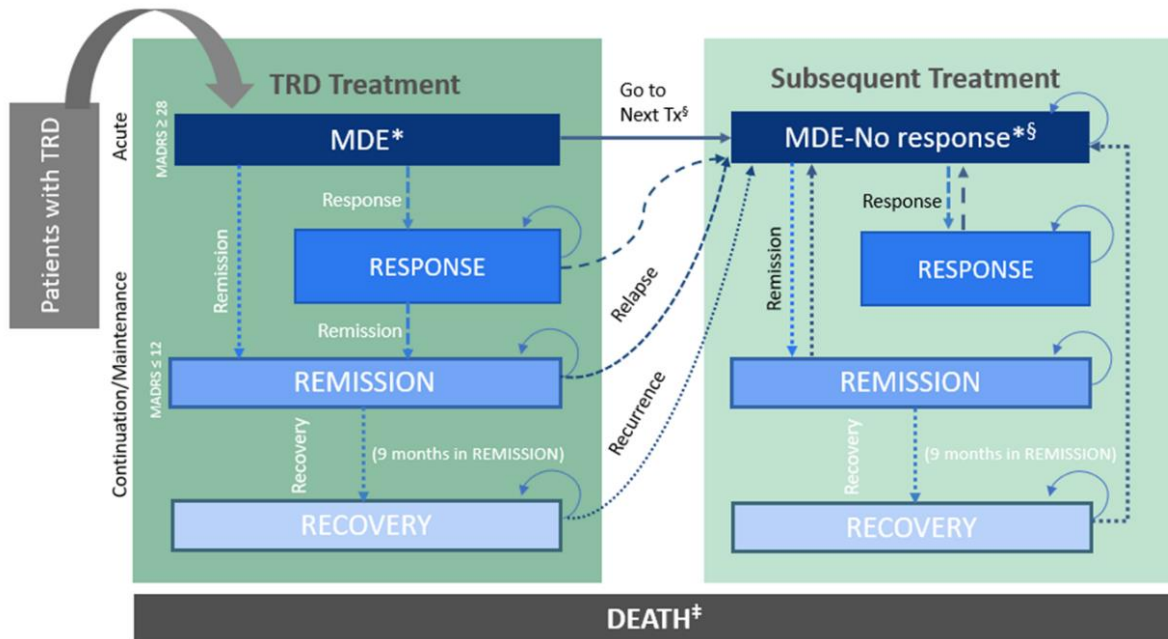
Component	July 2021 submission	Resubmission
Costs	Esketamine drug costs based on the proposed effective DPMQ, with a weighted public/private split (20/80). Mean dose and frequency of administration during induction and maintenance periods were based on data from the TRANSFORM-2 and SUSTAIN-1 trials.	Esketamine drug cost based on revised effective DPMQ, with a weighted public/private split (20/80). Mean dose and frequency of administration based on TRANSFORM-2 and TRANSFORM-3 trials, weighted by the proportion of patients aged <65 and ≥65 years for the induction period; and SUSTAIN-1 trial for maintenance periods.
	OAD drug costs based on March 2021 PBS schedule, dosage based on product information documents, weighted by utilisation from PBS item reports (February 2020 to January 2021).	OAD drug costs based on January 2022 PBS schedule, dosage based on product information documents, weighted by utilisation from PBS item reports (December 2020 to December 2021).
	Administration costs based on July 2020 MBS item 300 for esketamine and placebo (psychiatrist consultation ≤15 minutes); frequency of administration for both arms based on the esketamine arm of TRANSFORM-2 for the induction period; and SUSTAIN-1 trial for maintenance periods.	Administration costs based on November 2021 MBS item 304 for esketamine (psychiatrist consultation 30-45 minutes) and item 300 for placebo (psychiatrist consultation ≤15 minutes); frequency of administration for both arms based on the esketamine arm of TRANSFORM-2 and TRANSFORM-3 trials, weighted by the proportion of patients aged <65 and ≥65 years for the induction period; and SUSTAIN-1 trial for maintenance periods.
	Disease management resource use (GP visits, specialist visits, community health centre visits, hospitalisations, emergency department visits) by health state based on a UK study by Deneo et al. (2021). Hospitalisation costs were estimated based on AR-DRG items for major affective disorder; emergency department costs were based on URG items for psychiatric illness (NHCDC round 22, 2017-2018). GP and specialist visit costs based on July 2020 MBS (item 3: level A GP consultation; item 300: psychiatrist consultation ≤15 minutes).	Disease management resource use unchanged. Hospitalisation and emergency department costs updated to NHCDC round 23, 2018-2019. GP and specialist visit costs based on November 2021 MBS (item 23: level B GP consultation; average of items 300, 302, 304, 306, 308: psychiatrist consultations ≤15 to >75 minutes; weighted by MBS item reports January 2021 to December 2021).
Software package	Microsoft Excel.	Unchanged.

Source: Table 3-2, pp156-158 of the resubmission.

Abbreviations: MDE, major depressive episode

6.48 The figure below illustrates the structure of the economic model in the resubmission, reflecting the addition of the recovery state in the subsequent treatment pathway.

Figure 1: Model structure



\* Age- and sex-adjusted background mortality. Increased mortality due to suicide may be assigned.

\*Treatment-dependent AEs rated may be assigned.

§Includes patients who had no response or stop responding to the initial treatment selected in the model.

Source: Figure 3-1, p173 of the resubmission

Abbreviations: AEs, adverse events; MADRS, Montgomery-Asberg Depression Rating Scale; MDE, major depressive event; TRD, treatment resistant depression; Tx, treatment

6.49 Key drivers of the model are summarised in the table below.

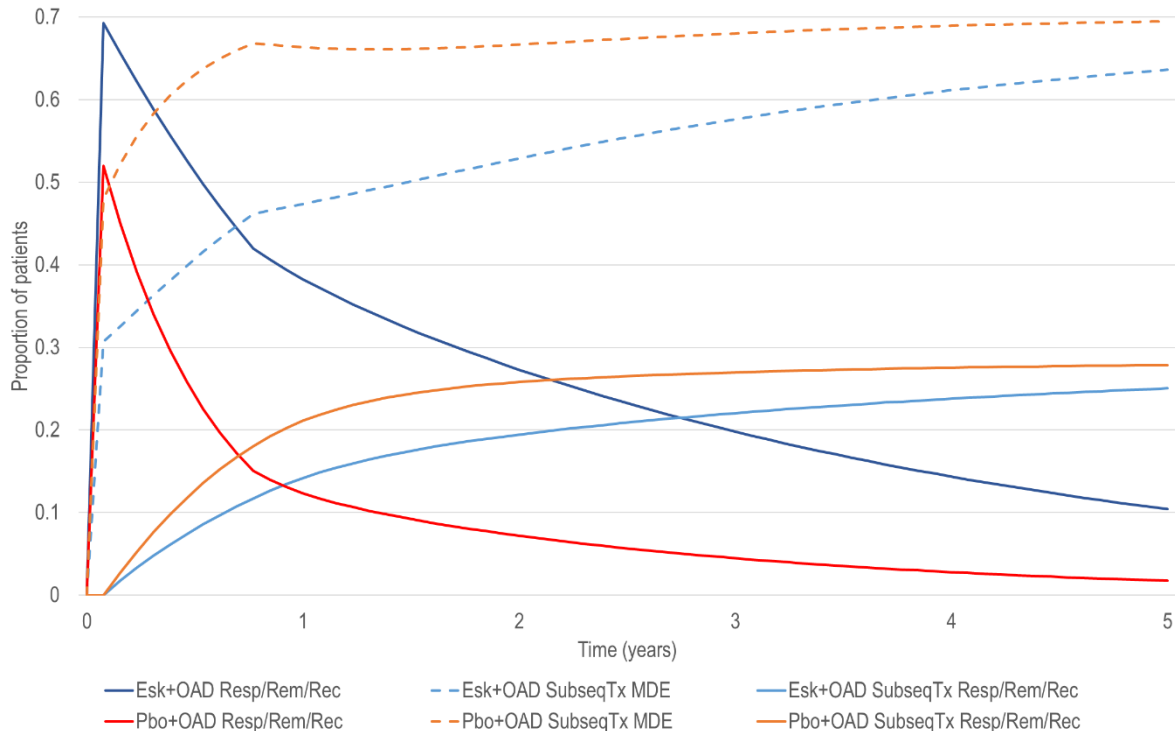
**Table 13: Key drivers of the model**

Description	Method/Value	Impact
Transition probabilities in the maintenance phase	The application of transition probabilities for the esketamine arm derived from the SUSTAIN-1 trial was unchanged. For maintenance transitions in the placebo arm for loss of response and relapse from remission (the STAR*D study) in response to concerns that the withdrawal trial design was not reflective of clinical practice. The STAR*D study was conducted between 2001 and 2006 and some of the included treatments are not commonly used in Australia for the treatment of depression. The ESC previously considered that the STAR*D study may not reflect contemporary treatment practises for TRD and the appropriateness of using it to inform transition probabilities was uncertain (para 6.39, esketamine PSD, July 2021 PBAC meeting).	High, favours esketamine
Costs of administration and monitoring	The revised model included a higher cost for administration and monitoring of esketamine based on a longer psychiatrist consultation (30-45 minutes versus 15 minutes in the previous submission). However, it is unclear whether this is an appropriate proxy for post-administration monitoring, which the resubmission claimed would last 1-2 hours with supervision predominantly by nurses. Additionally, the model included administration costs for the placebo plus OAD arm, which the ESC previously considered to be inappropriate as they would not be incurred in clinical practice for a patient treated with a newly initiated OAD (para 6.57, esketamine PSD, July 2021 PBAC meeting).	Moderate, favours esketamine
Treatment discontinuations	Treatment discontinuations are only applied as a reduction in drug costs in all health states from week 5 onwards. The ESC previously considered that the application of treatment persistence as a reduction to drug costs only beyond the observed trial period is inappropriate, as treatment persistence would also impact the effectiveness and safety of the treatment (i.e. non-persistent patients will reduce drug costs but also receive reduced benefits/harms of treatment) (para 6.59, esketamine PSD, July 2021 PBAC meeting).	High, favours esketamine
Healthcare resource use and costs	The model generates a large number of hospitalisations over the time horizon, based on resource use estimates from a UK retrospective chart review (Denee 2021). It is unclear whether the reductions in hospitalisations generated in the model will be realised in practice. The ESC previously noted that Denee 2021 may have limited applicability to the Australian context (para 6.46, esketamine PSD, July 2021 PBAC meeting).	Moderate, favours esketamine

Source: Constructed during the evaluation

6.50 The model trace is summarised in the figure below. To simplify the model trace the response, remission and recovery health states were combined and death (with no difference between treatment arms) was excluded.

Figure 2: Model trace



Source: Constructed during the evaluation using 'Attachment 3.2 Esketamine TRD CE model' Excel spreadsheet provided with the resubmission

Abbreviations: Esk, esketamine; MDE, major depressive disorder; OAD, oral antidepressant; Pbo, placebo; Rec, recovery; Rem, remission; Resp, response; SubseqTx, subsequent treatment

- 6.51 As in the July 2021 submission, the current model is driven by a smaller proportion of patients in the MDE health state, and a greater proportion of patients in the recovery health state in the esketamine plus OAD arm compared to the OAD alone arm. Compared with the July 2021 model, the current model trace indicates a smaller initial treatment effect for esketamine plus OAD, consistent with the inclusion of the TRANSFORM-3 study, although the benefit of esketamine treatment is maintained over the duration of the model. The current model also generates smaller proportions of patients with MDE and higher proportions in response/remission/recovery on subsequent treatment compared to the July 2021 model, due to the inclusion of a recovery health state for subsequent treatment.
- 6.52 The table below summarises the incremental costs for health care resource items used in the economic evaluation.

**Table 14: Disaggregated summary of cost impacts (discounted) in the economic evaluation**

Cost description	Esketamine + OAD	OAD	Increment
<b>Treatment costs</b>	<b>\$</b>	<b>\$982</b>	<b>\$</b>
- esketamine	\$	\$0	\$
- OAD	\$	\$112	\$
- subsequent therapies	\$	\$870	-\$
<b>Administration/monitoring</b>	<b>\$</b>	<b>\$904</b>	<b>\$</b>
<b>Adverse events</b>	<b>\$</b>	<b>\$0</b>	<b>\$</b>
<b>Disease management costs</b>	<b>\$</b>	<b>\$93,192</b>	<b>-\$</b>
- primary care visits	\$	\$629	-\$
- specialist visits	\$	\$2,635	-\$
- ED visits	\$	\$3,918	-\$
- hospitalisations	\$	\$86,110	-\$
<b>TOTAL</b>	<b>\$</b>	<b>\$95,078</b>	<b>\$</b>

Source: Table 3-34, p220 of the resubmission; and 'Attachment 3.2 Esketamine TRD CE model' Excel spreadsheet provided with the resubmission

- 6.53 The difference in costs between treatment arms was driven by esketamine drug and administration costs, which were substantially offset by reduced disease management costs (primarily costs of hospitalisations). The model generated 50.3 hospital days in the esketamine arm and 58.9 hospital days in the placebo arm, a difference of 8.5 hospital days (at a cost per day of \$1,647.70) over the 5-year model duration. It is unclear whether such a significant reduction in hospitalisation will occur in practice. The source data for resource use by health state was based on a retrospective chart review study conducted in the UK (Denee et al., 2021), which the ESC previously considered may have limited applicability to the Australian context (para 6.46, esketamine PSD, July 2021 PBAC meeting).
- 6.54 The submission presented a simplified stepped economic evaluation. The results of an expanded stepped economic evaluation, conducted during the evaluation, are summarised below.

**Table 15: Results of the stepped economic evaluation**

Step and component	Esketamine+OAD	OAD	Increment
<b>Step 1:</b> Trial-based four-week induction phase (proportions of patients with response and in remission from TRANSFORM-2 and -3 weighted by the proportion of the Australian population aged <65 and ≥65 years; esketamine and OAD drug costs; administration costs applied to both arms).			
Costs	\$	\$356	\$
Proportion of responders (Day 28)	62.5%	45.8%	16.7%
Proportion in remission (Day 28)	46.9%	27.1%	19.8%
<b>Incremental cost/additional responder</b>			<b>\$</b>
<b>Incremental cost/additional patient in remission</b>			<b>\$</b>
<b>Step 2a:</b> Modelled induction and maintenance phases over 52 weeks (modelled time spent in response, remission and recovery states based on TRANSFORM-2 and -3, SUSTAIN-1 and STAR*D data; esketamine and OAD drug costs; administration costs applied to both arms <sup>1,2</sup>			
Costs	\$	\$974	\$
Years in response, remission, recovery	0.4356	0.2313	0.2043
<b>Incremental cost/MDE-free life year gained</b>			<b>\$<sup>4</sup></b>
<b>Step 2b:</b> As for Step 2b, with treatment discontinuation			
Costs	\$	\$949	\$
Years in response, remission, recovery	0.4356	0.2313	0.2043
<b>Incremental cost/MDE-free life year gained</b>			<b>\$<sup>4</sup></b>
<b>Step 2c:</b> As for Step 2c, with subsequent treatment costs and consequences included (based on STAR*D study)			
Costs <sup>3</sup>	\$	\$949	\$
Years in response, remission, recovery	0.5137	0.3444	0.1693
<b>Incremental cost/MDE-free life year gained</b>			<b>\$<sup>5</sup></b>
<b>Step 2d:</b> as for Step 2d, with health care resource use included (primary care, specialist and ED visits and hospitalisation days)			
Costs	\$	\$23,366	\$
Years in response, remission, recovery	0.5137	0.3444	0.1693
<b>Incremental cost/MDE-free life year gained</b>			<b>\$<sup>4</sup></b>
<b>Step 3a:</b> as for Step 2d, with utilities derived from TRANSFORM-2 and -3 applied to time in health states			
Costs	\$	\$23,366	\$
QALYs	0.6437	0.5714	0.0723
<b>Incremental cost/extra QALY gained</b>			<b>\$<sup>6</sup></b>
<b>Step 3b:</b> as for Step 3a, with disutilities associated with adverse events included			
Costs	\$	\$23,366	\$
QALYs	0.6413	0.5708	0.0706
<b>Incremental cost/extra QALY gained</b>			<b>\$<sup>6</sup></b>
<b>Step 3c:</b> as for Step 3b, with half-cycle correction applied			
Costs	\$	\$22,945	\$
QALYs	0.6495	0.5764	0.0731
<b>Incremental cost/extra QALY gained</b>			<b>\$<sup>6</sup></b>
<b>Step 4a:</b> as for Step 3c, extrapolated from 52 weeks to 5 years			
Costs	\$	\$106,990	\$
QALYs	3.1301	2.9256	0.2046
<b>Incremental cost/extra QALY gained</b>			<b>\$<sup>7</sup></b>
<b>Step 4b:</b> As for Step 4a, with costs and outcomes discounted at 5%			
Costs	\$	\$95,078	\$
QALYs	2.7779	2,5905	0.1874
<b>Incremental cost/extra QALY gained (base case)</b>			<b>\$<sup>7</sup></b>

Source: Table 3-33, p219 of the submission and 'Attachment 3.2 - Esketamine TRD CE model' spreadsheet provided with the resubmission. Abbreviations: MDE, major depressive episode; OAD, oral antidepressant

<sup>1</sup> In Step 1, the proportion of responders and proportion in remission are not mutually exclusive, however in Step 2a, the proportion of responders has been adjusted to remove the proportion in remission to make the model health states mutually exclusive.

<sup>2</sup> Modelled drug and administration costs assuming patients with non-response, relapse or remission receive OAD only.

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<sup>3</sup> Costs are the same as for Step 2b, as the cost of subsequent therapy is assumed to be the same as the cost for OAD.

The redacted values correspond to the following ranges:

<sup>4</sup> \$55,000 to < \$75,000

<sup>5</sup> \$75,000 to < \$95,000

<sup>6</sup> \$115,000 to < \$135,000

<sup>7</sup> \$45,000 to < \$55,000

6.55 Incorporating the costs and consequences of maintenance treatment, including health care resource use, applying health state utilities and extrapolation of the model to five years had the largest impacts on the stepped economic evaluation.

6.56 Based on the economic model, treatment with esketamine nasal spray plus a newly initiated OAD versus treatment with a newly initiated OAD in patients with TRD is associated with an incremental cost per QALY gained of \$45,000 to < \$55,000. This compares to an incremental cost per QALY gained of \$25,000 to < \$35,000 in the July 2021 submission. The main changes contributing to the higher ICER in the resubmission’s model despite the lower price are the higher cost of administration for esketamine, using estimates of loss of response/remission for the placebo plus OAD arm from STAR\*D rather than SUSTAIN-1, and the inclusion of a recovery health state in the subsequent therapy pathway.

6.57 On average, for every patient treated with esketamine plus OAD compared with OAD alone and followed up for 5 years, the (undiscounted) economic model estimates that there would be:

- Esketamine drug and administration costs of \$<sup>7</sup>; based on an average duration of treatment of 0.95 years (11.4 months).
- An additional 0.48 years (5.8 months) free from major depressive disorder, which would save \$14,932 in disease management costs, and be associated with improved quality of life.

6.58 An alternative analysis presented in the resubmission including indirect costs to patients due to loss in productivity associated with TRD resulted in a cost per QALY gained of \$25,000 to < \$35,000. The Pre-PBAC Response stated indirect cost benefits due to reduction in depression symptoms has been demonstrated consistently in the published literature, and should be considered in any assessment of the value of esketamine.

6.59 The results of key sensitivity analyses are summarised below.

**Table 16: Results of sensitivity analyses**

	Incremental cost	Incremental QALYs	ICER	% change in ICER
<b>Base case</b>	\$ <sup>4</sup>	0.1874	\$ <sup>1</sup>	-
<b>Discount rate (base case: 5%)</b>				
0%	\$ <sup>4</sup>	0.2046	\$ <sup>1</sup>	-7.6%
3.5%	\$ <sup>4</sup>	0.1922	\$ <sup>1</sup>	-2.3%
<b>Time horizon (base case: 5 years)</b>				
1 year	\$ <sup>4</sup>	0.0712	\$ <sup>2</sup>	148.0%
3 years	\$ <sup>4</sup>	0.1519	\$ <sup>3</sup>	30.0%
10 years	\$ <sup>4</sup>	0.2133	\$ <sup>4</sup>	-22.0%

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	Incremental cost	Incremental QALYs	ICER	% change in ICER
<b>Probability of remission in induction phase (base case: remission 46.9% ESK+OAD vs 27.1% OAD from TRANSFORM-2 and -3 weighted average)</b>				
Increase ESK+OAD probability of remission by 20%	\$	0.2344	\$ <sup>4</sup>	-24.4%
Decrease ESK+OAD probability of remission by 20%	\$	0.1404	\$ <sup>3</sup>	40.8%
<b>Maintenance transition probabilities (base case values for ESK+OAD and OAD arms derived from SUSTAIN-1)</b>				
OAD transitions same as for ESK+OAD	\$	0.0832	\$ <sup>5</sup>	299.6%
Increase probabilities to MDE by 20%; decrease response to remission probability by 20%: ESK+OAD arm	\$	0.1406	\$ <sup>3</sup>	49.9%
Decrease probabilities to MDE by 20%; increase response to remission probability by 20%: ESK+OAD arm	\$	0.2454	\$ <sup>6</sup>	-36.3%
<b>Recurrence of MDE from recovery (base case: 2.427% ESK+OAD; 3.558% OAD)</b>				
Same probability of recovery to MDE in each arm, based on OAD: 3.558%	\$	0.1438	\$ <sup>3</sup>	51.3%
Same probability of recovery to MDE in each arm, based on esketamine: 2.427%	\$	0.1695	\$ <sup>3</sup>	25.6%
<b>Subsequent treatment remission and response (base case: remission 4.5%/cycle; response 1.1%/cycle; assuming response estimates in STAR*D study double-count remission estimates and are based on a 12-week duration)</b>				
Response 5.8%/cycle (no double-counting assumed)	\$	0.1726	\$ <sup>3</sup>	25.1%
STAR*D probabilities adjusted to 4-weekly estimates based on time to response (8.3 weeks)/remission (7.4 weeks)	\$	0.1557	\$ <sup>3</sup>	49.0%
<b>Subsequent treatment loss of response, relapse from remission and recurrence from recovery (base case: recovery to MDE 3.6% per cycle; remission to MDE 12.8%/cycle; response to MDE 22.8%/cycle)</b>				
Increase probabilities by 20%	\$	0.2004	\$ <sup>4</sup>	-16.0%
Decrease probabilities by 20%	\$	0.1715	\$ <sup>3</sup>	23.0%
<b>Esketamine utilisation and costs (base case: based on utilisation in the TRANSFORM-2, TRANSFORM-3 and SUSTAIN-1 trials, see Table 17)</b>				
Use of 56 mg dose only	\$	0.1874	\$ <sup>6</sup>	-44.3%
Use of 84 mg dose only	\$	0.1874	\$ <sup>3</sup>	34.5%
All patients receive once weekly dosing during maintenance weeks 9+	\$	0.1874	\$ <sup>7</sup>	83.5%
All patients receive once fortnightly dosing during maintenance weeks 9+	\$	0.1874	\$ <sup>8</sup>	-50.5%
<b>Cost of administration and monitoring (base case MBS item 304 (psychiatrist 30-45 min) \$140.55 for esketamine; MBS item 300 (psychiatrist &lt;15 min) \$45.75 for placebo)</b>				
MBS item 304 applied to esketamine arm; no costs for placebo arm	\$	0.1874	\$ <sup>1</sup>	9.7%
MBS item 306 (45-75 min) \$194.00 applied to esketamine arm only	\$	0.1874	\$ <sup>3</sup>	30.7%
MBS item 308 (>75 min) \$225.10 applied to esketamine arm only	\$	0.1874	\$ <sup>3</sup>	42.9%
<b>Treatment discontinuation (probability of discontinuing esketamine 1.7% per cycle; affects drug and administration costs only)</b>				
No treatment discontinuation	\$	0.1874	\$ <sup>7</sup>	73.1%
Treatment discontinuations only applied for the duration of the SUSTAIN-1 maintenance period (weeks 5-40)	\$	0.1874	\$ <sup>3</sup>	43.6%
<b>Health care resource use (base case: estimates of primary care, specialist, and ED visits and hospitalisation days by health state based on Denee 2021)</b>				
Hospitalisation days per 28 days increased by 20%	\$	0.1874	\$ <sup>4</sup>	-27.7%
Hospitalisation days per 28 days decreased by 20%	\$	0.1874	\$ <sup>3</sup>	27.7%

	Incremental cost	Incremental QALYs	ICER	% change in ICER
<b>Health state utility values (base case derived from weighted average of TRANSFORM-2 and -3 trial data using UK value set: MDE 0.4316; response 0.7664; remission 0.8606; recovery 0.8606)</b>				
Health state utilities from TRANSFORM-2 using Canadian value set	\$█	0.1666	\$█ <sup>3</sup>	12.5%
Utility values from Yrondi 2021 (0.41; 0.63; 0.80; 0.90)	\$█	0.2111	\$█ <sup>4</sup>	-11.2%
Utility values from NICE committee papers (0.417; 0.764; 0.866; 0.866)	\$█	0.1963	\$█ <sup>1</sup>	-4.6%
Utility values used in Ross (2019) based on Sapin (2004) (0.58; 0.72; 0.85; 0.85)	\$█	0.1172	\$█ <sup>7</sup>	59.8%

Source: Table 3-37, pp225-226 and Figure 3-9, p226 of the resubmission and 'Attachment 3.2 - Esketamine TRD CE model' spreadsheet provided with the resubmission.

The redacted values correspond to the following ranges:

<sup>1</sup> \$45,000 to < \$55,000

<sup>2</sup> \$115,000 to < \$135,000

<sup>3</sup> \$55,000 to < \$75,000

<sup>4</sup> \$35,000 to < \$45,000

<sup>5</sup> \$155,000 to < \$255,000

<sup>6</sup> \$25,000 to < \$35,000

<sup>7</sup> \$75,000 to < \$95,000

<sup>8</sup> \$15,000 to < \$25,000

- 6.60 The results were most sensitive to the probability of achieving remission at treatment induction, transition probabilities in the maintenance period, the effectiveness of the subsequent treatment mix, the probability of recurrence from the recovery state, the esketamine dosing schedule in the maintenance period, the costs of administration and monitoring, treatment discontinuations and hospitalisation days.
- 6.61 The PSCR noted the evaluation highlighted the assumption of constant maintenance treatment transitions for esketamine over the 5-year model duration due to the short duration of the trial (stated to be 10 – 17 weeks), however clarified the time to relapse data was drawn from the SUSTAIN-1 trial at the 12-month time point that informed the transitions for relapse in the esketamine arm. The PSCR also stated the trial data used to inform these transition probabilities for esketamine through to 33-37 weeks, and the observed pattern of relapse risk from SUSTAIN-1 supported the use of the constant recurrence rate, given there was a plateau in risk after 24 weeks that reflects recovery. The PSCR stated that 80% and 90% patients in the esketamine arm are estimated in the model as treatment failures by the end of 3 and 5 years, respectively,) and move to the subsequent treatment. Hence, the benefits of esketamine are applied for a relatively short period within the model horizon which limits the extent of uncertainty in the model. The ESC noted there was a very small number of patients at risk at 12 months in the KM curves provided in the PSCR.
- 6.62 The ESC expressed concerns with the following inputs to the economic model, which remained key drivers that favoured esketamine:
- The ESC reiterated its view that the model should incorporate more conservative maintenance of treatment assumptions. The ESC considered extrapolating data from the SUSTAIN-1 trial to a five year time horizon may not be appropriate and

also expressed concern that the use of the STAR\*D study to inform some of the transition probabilities may not reflect current practice, given the age of the study.

- The proposed costs of administration remained highly uncertain, particularly in the absence of an MBS item or alternative method to estimate the cost of administration and monitoring in practice.
- The model included administration costs for the placebo plus OAD arm. The ESC reiterated its previously-expressed view that this approach was inappropriate as they would not be incurred in clinical practice for a patient treated with a newly initiated OAD (para 6.57, esketamine PSD, July 2021 PBAC meeting).
- The ESC noted treatment discontinuations were applied in the model as a reduction in drug costs only in all health states from week 5 onwards, and reiterated its previously-expressed view this was likely to be inappropriate beyond the trial duration, as treatment persistence would also impact the effectiveness and safety of the treatment (i.e. non-persistent patients will reduce drug costs but also receive reduced benefits/harms of treatment) (para 6.59, esketamine PSD, July 2021 PBAC meeting).
- The ESC noted that for esketamine to be cost-effective it needs to be accepted that its use will result in substantial savings associated with the treatment of TRD, including reduced hospitalisations. The ESC noted that the cost of esketamine plus administration is approximately \$1 per patient and it is modelled that there will be a reduction in hospitalisation costs of approximately \$14,000. The ESC recalled it has previously noted that the source of healthcare resource use in the model (Denee 2021, a UK study), may have limited applicability to the Australian context (paragraph 6.46, esketamine PSD, July 2021 PBAC meeting).
- The ESC also noted there were significant safety and adverse event concerns and considered these were not adequately modelled in the submission.

6.63 The Pre-PBAC Response commented on the concerns raised by the ESC with regards to the economic model as follows:

- Although no Australian data was used or available to inform hospitalisation costs, the modelled savings may be considered conservative;
- Although the STAR\*D study used to inform utility values is not new, large-scale clinical trials in psychiatry are rare and it represented the best available data to inform the economic evaluation.
- In the model patients can discontinue esketamine due to relapse, recovery or for other reasons (e.g. safety). The PSCR stated that patients who do not relapse will have a treatment duration below the time to relapse curve, and thus on average these patients accrue benefits for being relapse-free after stopping therapy. The PSCR argued it was therefore appropriate to model treatment discontinuation as no longer incurring costs, with loss of benefits occurring once a patient experiences relapse.

6.64 The ESC noted the final appraisal document (dated May 2022) published by NICE<sup>3</sup> stated that “the limitations in the clinical evidence and economic model mean it is not possible to determine a reliable cost-effectiveness estimate” for esketamine in the treatment of TRD.

### Drug cost/patient/treatment phase

Table 17: Drug costs per patient for esketamine

Value	Esketamine trials <sup>1</sup>	Economic model	Financial estimates
<b>ESKETAMINE DRUG COSTS</b>			
<b>Acute treatment phase (Weeks 1-4)</b>			
Mean dose	TRANSFORM-2: 70.8 mg (2.530×28 mg devices) TRANSFORM-3: 59.8 (2.136×28 mg devices)	69.1 mg <sup>2</sup> (2.467×28 mg devices)	70.8 mg <sup>3</sup> (2.530×28 mg devices)
Unit cost (DPMQ) per 28 mg device	-	\$ <sup>4</sup>	\$ <sup>5</sup>
Average doses per week	TRANSFORM-2: 1.851 TRANSFORM-3: 1.844	1.850 <sup>2</sup>	-
Adherence	Not reported	Not explicitly modelled	92.5%
Cost/patient/4-week period	-	\$	\$
Persistence	TRANSFORM-2: 84.5% TRANSFORM-3: 86.1%	100%	100%
<b>Maintenance phase (Week 5+)</b>			
Mean dose	Weeks 5 - 40: 72.9 mg (2.605×28 mg devices) <sup>5</sup> Week 41+: 72.0 mg (2.571×28 mg devices) <sup>5</sup>	Weeks 5 - 40: 72.9 mg (2.605×28 mg devices) Week 41+: 72.0 mg (2.571×28 mg devices)	Week 5+: 72.9 mg (2.605×28 mg devices)
Unit cost per 28 mg device	-	\$ <sup>7</sup>	\$ <sup>8</sup>
Average doses per week	Weeks 5 - 8: 0.992 <sup>6</sup> Weeks 9 - 40: 0.711 <sup>6</sup> Week 41+: 0.675 <sup>6</sup>	Weeks 5 - 8: 0.992 Weeks 9 - 40: 0.711 Week 41+: 0.675	-
Adherence	Not reported	Not explicitly modelled	Weeks 5 - 52: 73.83% Weeks 53+: 67.46%
Cost/patient/4-week period	-	Weeks 5 - 8: \$ Weeks 9 - 40: \$ Week 41+: \$	Weeks 5 - 52: \$ Weeks 53+: \$
Persistence <sup>9</sup>	91.4%	Y1: 33.04% Y2: 18.85% Y3: 10.94% Y4: 6.35% Y5: 3.69%	Y1: 48.40% Y2: 24.53% Y3: 14.17% Y4: 8.22% Y5: 4.78% Y6: 2.77%
<b>OAD costs</b>			
Cost/patient/4-week period	-	\$17.16 <sup>10</sup>	Not included
Adherence	Varies by treatment	100%	Not included
Persistence	TRANSFORM-2: 89.2% TRANSFORM-3: 90.9%	100%	Not included

Source: Table 3-19, p199; Section 4.2.1, p. 234 of the resubmission. 'Drug costs' and 'Drug cost – details' worksheets of 'Attachment 3.2 - Esketamine TRD CE model'; 'Compliance and persistence', 'Scripts – proposed' and 'Impact – proposed (eff)' worksheets of the 'Utilisation cost model – esketamine TRD' Excel workbook, Attachment 4.1 of the resubmission.

<sup>3</sup> <https://www.nice.org.uk/guidance/gid-ta10371/documents/html-content-4>

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Abbreviations: DPMQ, dispensed price for maximum quantity.

<sup>1</sup> TRANSFORM-2 and TRANSFORM-3 for acute treatment phase and SUSTAIN-1 for maintenance phase.

<sup>2</sup> Based on a weighted average of TRANSFORM-2 and -3 data, based on the proportion of the Australian population aged <65 (84%) and ≥65 (16%) years.

<sup>3</sup> Based on TRANSFORM-2 data

<sup>4</sup> Based on a weighted Public/Private (20%/80%) hospital split; public DPMQ of \$█; private DPMQ of \$█ for 28 mg dose (8 x 28 mg units).

<sup>5</sup> Based on a weighted Public/Private (20%/80%) hospital DPMQ of \$█ for 56 mg dose (16 x 28 mg units) and \$█ for 84 mg dose (24 x 28 mg units), assuming a 47%/53% split between 56 mg and 84 mg doses.

<sup>6</sup> The source data could not be verified during the evaluation.

<sup>7</sup> Based on a weighted Public/Private (20%/80%) hospital split; public DPMQ of \$█; private DPMQ of \$█ for 28 mg dose (4 x 28 mg units).

<sup>8</sup> Based on a weighted Public/Private (20%/80%) hospital split DPMQ of \$█ for 56 mg dose (8 x 28 mg units) and \$█ for 84 mg dose (12 x 28 mg units), assuming a 39%/61% split between 56 mg and 84 mg doses.

<sup>9</sup> Economic model persistence based on the proportion of patients remaining on esketamine at the end of each treatment year; financial estimates persistence based on average annual persistence.

<sup>10</sup> Average cost of PBS-listed antidepressants weighted by market share according to PBS data from December 2020 to December 2021.

### Estimated PBS usage & financial implications

6.65 The resubmission was not considered by DUSC. The resubmission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of esketamine for TRD, whereas the July 2021 submission used an epidemiological approach. There was also a decrease in the proposed effective price, the cost associated with post-administration monitoring were removed, and patients currently being treated with esketamine were added to the prevalent patient pool.

Table 18: Key inputs for the financial estimates

Data	Value applied and source	Comment
Number of patients meeting criteria for TRD	PBS 10% sample analysis. From November 2019 to October 2020, 28,820 patients who had inadequate responses to two or more antidepressants in the current MDD episode started a new treatment (switching to a new antidepressant, adding on an augmentation agent or another antidepressant) were identified across all prescriber settings	It is unclear whether the method used to conduct the 10% Medicare PBS sample analysis captured all relevant patients with TRD and those with TRD initiating a new treatment. The availability of a new treatment may result in an increase in patients initiating a new therapy.
Average annual rate of growth in the MDD population	Based on the average annual rate of growth of Australians reporting 'depression or feelings of depression' in the Australian National Health Survey between 2014-2015 and 2017-2018 (from 8.9% to 10.4%). The resubmission therefore estimated an average annual growth of 5.3% for 2014/2015 to 2017/18.	The applicability of the Australian National Health Survey results (which were based on self-reported depression or feelings of depression rather than a clinical diagnosis of depression) to the prevalence of MDD and TRD was unclear and not adequately justified in the resubmission.
Prescription setting	PBS 10% sample analysis. Of 28,820 patients who initiated a new treatment from November 2019 to October 2020, 6,340 patients (22.0%) started the new treatment in the psychiatry setting and the remaining 78.0% started the new treatment in the non-psychiatry setting. An increase of 3% per year was applied to incorporate the expected increase in the number of patients referred to the psychiatry setting over time with the listing of esketamine nasal spray.	The rate of new referrals may be substantially higher given that esketamine is a novel treatment for a disorder that is resistant to standard therapies. However, the number of treated patients is likely to be constrained by the availability of psychiatrists to provide treatment, given the logistical issues associated with delivery of esketamine, the need for post-administration monitoring, and the ability to comply with Schedule 8 medicine handling requirements.

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Data	Value applied and source	Comment
Grandfathered patients	Estimated number of patients enrolled in the sponsor's early access program and self-funded (N=300), with time to treatment discontinuation extrapolation in the July 2021 economic model applied to estimate numbers in subsequent years.	The resubmission did not adequately justify the addition of the grandfathered patients to the estimated population. It is possible that these patients would already be accounted for in the resubmission's estimates of eligible patients. Further, the total number of patients who are self-funded and may be eligible for PBS treatment is unclear and may be greater than that estimated by the sponsor.
Uptake rate (psychiatry setting)	30% in year 1 to 50% in year 6 in the psychiatry setting; 2% in year 1 to 7% in year 6 in the GP setting. Sponsor assumption based on expert opinion. Uptake rate in GP setting includes those referred to the care of a psychiatrist.	The uptake of esketamine is considered highly uncertain, particularly in the GP setting where the majority of MDD is managed. Esketamine represents a novel treatment for a disorder that is resistant to standard therapies. However, uptake is likely to be constrained by the ability of treatment sites comply with esketamine delivery, handling and monitoring requirements. The PBAC noted uptake in the GP setting should be removed from the financial estimates, given the recommendation to limit initiation to psychiatrists.
Uptake rate (GP setting)		
Dose distribution between 56 mg and 84 mg dose	Initial: 56 mg - 47.0%; 84 mg - 53.0%. Continuing: 56 mg - 39.5%; 84 mg - 60.5%. Distribution derived from the mean daily dose of esketamine in the TRANSFORM-2 trial four-week initial treatment period (70.7 mg, equating to 2.5298 esketamine devices), and the average number of esketamine devices used per session in the SUSTAIN-1 maintenance phase (2.605). Assumed that patients received either 2 x 28 mg devices for a 56 mg dose or 3 x 28 mg devices for an 84 mg dose.	The submission did not account for use of a 28 mg dose among elderly patients. The dose distribution among the PBS population may differ from the distribution in the clinical trial setting. The recommended dose for patients aged ≥65 years is 28 mg, however, patients ≥65 years were excluded from the trials informing dose distribution. The PBAC considered assumptions regarding dose frequency were also important, particularly given the tendency to extend treatment interval (refer para 2.3).
Persistence	48.4% in year 1 to 58.05% in year 6. Derived from the proportion of patients remaining on treatment each year in the July 2021 economic model.	Differences between the clinical trial setting and Australian clinical practice may result in differences in persistence. The proposed restriction does not preclude repeat courses of esketamine, which were not accounted for in the financial estimates.
Adherence	92.5% for initial treatment, 73.8% for continuing treatment in the initiation year, and 67.5% in subsequent years. Derived from TRANSFORM-2 (initial treatment) and SUSTAIN-1 (maintenance) trial data.	Differences between the clinical trial setting and Australian clinical practice may result in differences in adherence. Difficulty in accessing supervised administration, the burden of twice weekly, weekly, or fortnightly appointments for administration, and the inability to drive for the rest of the day following treatment, may impact adherence.

Source: Section 4.2, p.234-237; Section 4.3, p.237-243 of the resubmission; Utilisation cost model – esketamine TRD' Excel workbook  
Abbreviations: AEMP, approved ex-manufacturer price; GP, general practitioner; MDD, major depressive disorder; TRD, treatment-resistant depression; Yr, Year.

6.66 The estimated net cost of listing esketamine on the PBS/RPBS for TRD is summarised in the table below.

Table 19: Estimation of use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients with TRD <sup>1</sup>	4	4	4	4	4	13
Proportion treated in psychiatry setting (22%)	5	5	5	5	5	5
Uptake rate in psychiatry setting	30.0%	40.0%	48.0%	49.0%	50.0%	50.0%
Treated patients in psychiatry setting	6	6	6	6	6	6
Proportion treated in GP setting (78%)	7	7	7	7	4	4
Uptake rate in GP setting	2.0%	5.0%	6.5%	7.0%	7.0%	7.0%
Treated patients in GP setting	8	6	6	6	6	6
<b>Initiating scripts</b>						
Initiating patients	6	6	5	5	5	5
Initiating scripts <sup>2</sup>						
- 56 mg	6	6	6	6	6	6
- 84 mg	6	6	6	6	6	6
<b>Continuing scripts- initiation year</b>						
Continuing patients (48.4%) <sup>3</sup>	6	6	6	6	6	6
Continuing scripts <sup>2</sup>						
- 56 mg	6	5	5	9	9	9
- 84 mg	5	9	9	9	9	9
<b>Continuing scripts- subsequent years</b>						
Total continuing patients in subsequent years	8	6	6	6	6	6
Continuing scripts <sup>2</sup>						
- 56 mg	8	6	6	5	5	9
- 84 mg	8	6	5	9	9	9
<b>Grandfathered patients</b>						
Grandfathered patients	8	8	8	8	8	8
Grandfather scripts <sup>2</sup>						
- 56 mg	6	6	8	8	8	8
- 84 mg	6	6	8	8	8	8
<b>Net cost to PBS/RPBS</b>						
Total scripts	9	7	13	16	16	17
Total cost to PBS/RPBS	\$ 10	\$ 12	\$ 14	\$ 15	\$ 15	\$ 15
Patient copayments	-\$ 11	-\$ 11	-\$ 11	-\$ 11	-\$ 11	-\$ 11
<b>Net cost to PBS/RPBS</b>	<b>\$ 10</b>	<b>\$ 12</b>	<b>\$ 14</b>	<b>\$ 15</b>	<b>\$ 15</b>	<b>\$ 15</b>
<b>Net cost to PBS/RPBS (July 2021 submission)</b>						
Initiating patients	6	6	5	5	5	5
Continuing patients- initiation year	6	6	6	6	6	6
Continuing patients- subsequent years	8	6	6	6	6	6
Total scripts	9	7	13	16	17	17
Total PBS/RPBS cost	\$ 10	\$ 12	\$ 15	\$ 15	\$ 15	\$ 15
Patient copayments	\$ 11	\$ 11	\$ 11	\$ 11	\$ 11	\$ 11
<b>Net PBS/RPBS cost</b>	<b>\$ 10</b>	<b>\$ 12</b>	<b>\$ 15</b>	<b>\$ 15</b>	<b>\$ 15</b>	<b>\$ 15</b>

Source: Table 4-2, p.240; Table 4-4, p.242; Table 4-5, p.243; Table 4-6, p.244 of the resubmission

<sup>1</sup> Based on the 10% PBS sample estimated to have TRD, with 5.3% growth rate applied per annum based on the National Mental Health Survey data

<sup>2</sup> Includes adherence of 92.5% for initiating patients, 73.8% for patients continuing in initiation year, and 67.5% in subsequent years.

<sup>3</sup> Average proportion of initiated patients receiving continuing treatment, derived based on the treatment persistence in the July 2021 economic model (derived from the TRANSFORM-2 and SUSTAIN-1 trial data).

The redacted values correspond to the following ranges:

<sup>4</sup> 30,000 to < 40,000

<sup>5</sup> 5,000 to < 10,000

<sup>6</sup> 500 to < 5,000

<sup>7</sup> 20,000 to < 30,000

<sup>8</sup> < 500

<sup>9</sup> 10,000 to < 20,000

<sup>10</sup> \$30 million to < \$40 million

<sup>11</sup> \$0 to < \$10 million

<sup>12</sup> \$60 million to < \$70 million

<sup>13</sup> 40,000 to < 50,000

<sup>14</sup> \$90 million to < \$100 million

<sup>15</sup> \$100 million to < \$200 million

<sup>16</sup> 50,000 to < 60,000

<sup>17</sup> 60,000 to < 70,000

6.67 The estimated net cost to the PBS/RPBS based on the proposed effective price was \$30 million to < \$40 million in Year 1 of listing, increasing to \$100 million to < \$200 million in Year 6, an estimated net cost of \$500 million to < \$600 million over the first six years of listing. In the July 2021 submission, the estimated net cost to the PBS/RPBS based on the proposed effective price was \$600 million to < \$700 million over the first six years of listing.

6.68 The ESC considered there were a number of potential issues associated with the estimation of use and financial impact of PBS listing esketamine:

- The estimated eligible patient population is entirely based on a pharmacological definition of TRD based on 2 prior treatment failures. This may either underestimate (by neglecting to include people with TRD who may have switched to other therapy types such as physical therapies or psychotherapy), or overestimate (by identifying patients earlier than they will be treated in clinical practice, and including patients with mild major depressive episodes who would not be eligible under the proposed restriction) the eligible population.
- The financial impacts incorporated adherence, persistence and dose distribution estimates derived from the TRANSFORM-2 and SUSTAIN-1 clinical trials, and the DUSC previously considered the applicability of the trial-based estimates to Australian clinical practice is unclear. The DUSC noted the submission did not account for patients receiving the 28 mg dose of esketamine (para 6.66, esketamine PSD, July 2021 PBAC meeting). These estimates were not revised in the resubmission.
- A proportion of patients included in the model remain on treatment for 6 years; given that most treatment guidelines which include treatment with esketamine nasal spray recommend it for short term use only, it may not be appropriate for patients to be maintained on treatment for multiple years.
- The DUSC previously noted that difficulty in accessing supervised administration, the burden of twice weekly, weekly, or fortnightly appointments for administration, and the inability to drive for the rest of the day following treatment, may impact compliance (para 6.66, esketamine PSD, July 2021 PBAC meeting). This was not addressed in the resubmission.

- The DUSC previously noted that there is a significant risk of use outside the proposed restriction in patients with: depression that is not treatment resistant, post-traumatic stress disorder (PTSD), anxiety, chronic pain, insomnia, fibromyalgia, suicidality and other conditions with ketamine currently used in many of these additional indications. The DUSC considered there is the potential for a large cohort of patients currently being treated with ketamine infusions to move to esketamine nasal spray (para 6.66, esketamine PSD, July 2021 PBAC meeting).

### **Quality Use of Medicines**

- 6.69 The resubmission stated that a controlled access program has been created in which the supply of esketamine will be restricted to sponsor-accredited esketamine treatment sites where a health care professional is trained to administer esketamine and monitor patients in accordance with the product information. The submission stated that the program has been developed to mitigate the potential risk of drug abuse, misuse and diversion.
- 6.70 The PSCR acknowledged there may be out of pocket costs to patients, mainly relating to the absence of a Medicare Benefits Schedule (MBS) item for monitoring requirements, however reiterated it had previously been advised the MBS was not an appropriate funding mechanism for the monitoring of adverse events. The PSCR also noted the sponsor was amenable to further discussions with the Department to discuss the appropriateness of an MBS item for the administration and monitoring of esketamine treatment.
- 6.71 The ESC was concerned the proposed model of care for the administration and monitoring of esketamine would lead to substantial socio-economic and geographical equity of access issues. The ESC noted no information was available to estimate what the expected out of pocket costs may be. The ESC also considered that the risk of substantial out of pocket costs to patients was of concern and should be addressed to achieve equitable access to esketamine treatment in TRD. The Pre-PBAC Response acknowledged there was a cost associated with health care professional monitoring of patients following administration of esketamine and that no funding mechanism currently existed to cover these costs, meaning they would often be passed on to patients, some of whom will not be able to afford esketamine treatment as a result. The sponsor advised they were amenable to further discussions on the management and funding of out of pocket costs for patient monitoring. In terms of geographical access issues, the sponsor argued that the number of accredited treatment sites was increasing, with 1 sites expected by the end of 2022, with planned sites across metropolitan, regional and rural areas in both the public and private sectors. The sponsor argued that issues with access to treatment were more likely to be caused by the shortage of psychiatrists and difficulties accessing psychiatric services in Australia.

- 6.72 The PBAC noted that of the 30 sites currently accredited, 3 were in the public treatment setting, 7 were in regional areas (5 in NSW and 2 in Queensland) and 3 were in rural areas (1 in NSW and 2 in South Australia).
- 6.73 The PBAC noted that, as outlined in the TGA Risk Management Plan Australian Specific Annex, treatment centres will be identified and established based on:
- Prescribers must be licensed to prescribe S8 Controlled Drug in accordance with their state or territory requirements.
  - Treatment centres will not be able to order esketamine unless the primary healthcare professionals (responsible or lead psychiatrist, responsible or lead nurse and lead/dispensing pharmacist) at the centre have been trained by the Sponsor and passed a knowledge test.
  - Treatment centres will need to have access to appropriate storage (such as a lockable safe) for storage of esketamine prior to patient treatment and any other measures required by their state or territory requirements for storage of S8 controlled drugs.
  - Treatment centres will need to have a suitable patient area for monitoring the patient pre and post treatment.
  - Treatment centres will need to have an arrangement with a supplying pharmacy to provide esketamine directly to the treatment room so that the patient is unable to obtain esketamine themselves from the pharmacy nor take it away from the treatment centre.
  - Disposal of esketamine will follow normal pharmacy practice to dispose of S8 Controlled Drugs as per their state or territory requirements.
- 6.74 The resubmission noted that the PBAC requested additional guidance for a number of quality use of medicines issues, and provided additional quality use of medicines activities in order to address these. The commissioned quality use of medicines strategy included recommendations for mechanisms such as enhanced consent for patients, care coordination, ongoing monitoring of risks, and clinician education around safety and place in therapy. The consultant recommended educational resources already developed by the sponsor be enhanced by including a clinical consensus statement or guideline for prescribers and a guide for clinician-led enhanced consent process. These guidelines should include (but are not limited to):
- Place of esketamine in therapy with respect to physical therapies;
  - Choice and timing of third line antidepressant;
  - Contraindications and drug interactions;
  - Best tool(s) to assess eligibility and effectiveness of esketamine;
  - Management of acute and delayed adverse events and
  - Criteria for cessation of therapy.
- 6.75 The PBAC noted any educational resources (as outlined in the paragraph above) would need to be consistent with the restriction criteria.

## Financial Management – Risk Sharing Arrangements

6.76 The resubmission noted potential uncertainty in the utilisation of esketamine, including the number of patients eligible for treatment, and the number of treated patients. The resubmission proposed a risk-sharing arrangement consisting of annual subsidisation caps set at the estimated annual Commonwealth Payment (net cost) of esketamine nasal spray at the requested effective prices. In addition, the resubmission proposed a reimbursement of  $\frac{1}{2}$ % for any potential use above specified subsidisation caps. The proposed subsidisation caps were set according to the estimated financial impacts over the first five years of listing. The ESC noted the significant uncertainties associated with the financial estimates and considered a  $\frac{1}{2}$ % rebate was inadequate to manage the risk to the Commonwealth.

6.77 The table below presents the subsidisation caps proposed in the resubmission.

**Table 20: Proposed risk-sharing arrangement subsidisation caps**

	Year 1	Year 2	Year 3	Year 4	Year 5
Value of subsidisation caps	\$ <sup>1</sup>	\$ <sup>2</sup>	\$ <sup>3</sup>	\$ <sup>4</sup>	\$ <sup>4</sup>
Proposed rebate for spend above cap	$\frac{1}{2}$ %	$\frac{1}{2}$ %	$\frac{1}{2}$ %	$\frac{1}{2}$ %	$\frac{1}{2}$ %
July 2021 subsidisation caps	\$ <sup>1</sup>	\$ <sup>2</sup>	\$ <sup>4</sup>	\$ <sup>4</sup>	\$ <sup>4</sup>

Source: Table 4-13, p.250 of the submission; Table 4-14, p.273 of the July 2021 submission

The redacted values correspond to the following ranges:

<sup>1</sup> \$30 million to < \$40 million

<sup>2</sup> \$60 million to < \$70 million

<sup>3</sup> \$90 million to < \$100 million

<sup>4</sup> \$100 million to < \$200 million

For more detail on PBAC's view, see section 7 PBAC outcome.

## 7 PBAC Outcome

7.1 The PBAC did not recommend the PBS listing of esketamine for the treatment of treatment-resistant depression (TRD), in patients who have not responded adequately to at least two prior oral antidepressants (OADs). The Committee considered there was a moderate to high clinical need for alternative treatment options for TRD, however considered a number of issues remained unresolved in the resubmission. This included the wording of the restriction, when it would be appropriate to reduce or discontinue treatment, structure and inputs to the economic model and substantially overestimated financial impact.

7.2 The PBAC noted and welcomed the input from individuals, clinicians and organisations, which highlighted the severe impact of TRD on daily life. The PBAC also noted the experience of individuals and clinicians with using and providing esketamine and ketamine, who described the treatments as being able to restore hope to patients, when other options had failed.

7.3 The PBAC also noted and welcomed the input from clinicians through the clinical consensus statement provided alongside the resubmission. The Committee noted the statement supported the listing of esketamine for TRD and considered exposure to 2-

5 prior treatments in the current episode a reasonable representation of TRD in Australia. The clinical consensus statement recommended the duration of therapy with esketamine should be up to 6 months, followed by an assessment of the need to continue therapy and advocated for flexibility with the requirement to initiate a new OAD. While the advice in the clinical consensus statement was somewhat inconsistent with clinical advice previously received (paragraph 2.5, esketamine PSD, July 2021), the PBAC recognised that the management of TRD is complex and variable depending on many patient and health system factors.

- 7.4 The PBAC noted the information provided by the Department of Veterans Affairs' (DVA) (paragraph 2.3) regarding the use of esketamine and ketamine to treat TRD (and other conditions including PTSD and anxiety) in clinical practice and considered the advice was informative. The PBAC considered some additional information should be sought from the DVA, as outlined in para 7.11.
- 7.5 The PBAC acknowledged that esketamine may be an appropriate treatment option after an inadequate response to only two prior OADs for a subset of patients, such as those with severe symptoms, imminent risk of self-harm or no response to prior treatment. However, the PBAC considered that for most patients, esketamine should be initiated after additional treatment options that have longer-term safety and effectiveness data and are more established in clinical practice (for example, combination therapy, augmentation with lithium or other agents and physical treatments such as ECT and rTMS) have been trialled or at least considered. The PBAC noted this was consistent with the consensus statement which considered patients appropriate for esketamine would have received prior treatment with two to five OADs. The PBAC considered that, given the severity of TRD and to ensure esketamine is used in appropriate patients, the decision to initiate esketamine should be limited to psychiatrists.
- 7.6 The PBAC advised the restriction criteria for esketamine would require a number of amendments, including the following:
- Initial prescribing should be limited to psychiatrists rather than 'psychiatrists or under the supervision of a psychiatrist' (as discussed in the para above).
  - Amend the 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' to better describe the intended patient population (as discussed in the para above).
  - Include a clinical criteria that provides clarity on an appropriate interpretation of 'newly initiated' OAD (as discussed in para 3.6).
  - Provide for assessment by a psychiatrist after 6 months of treatment to determine the benefit of ongoing treatment (as discussed in para 7.3).
  - Amend the continuing and grandfather restrictions to specify that treatment with esketamine must be in combination with an OAD (as discussed in para 3.6).

- 7.7 The PBAC reaffirmed its previously expressed view the nominated comparator of a newly initiated OAD alone was reasonable (para 7.6, esketamine PSD, July 2021).
- 7.8 The PBAC noted no new clinical evidence was provided in the resubmission, and the clinical claim remained primarily based upon the results of TRANSFORM-2 for induction therapy and SUSTAIN-1 for maintenance therapy. The PBAC reiterated its previously-expressed view that the TRANSFORM-1 and TRANSFORM-3 induction trials also provided relevant information, despite being limited to a fixed dose regimen (TRANSFORM-1) or only including patients aged 65 years or over (TRANSFORM-3). The PBAC noted that of the three short-term induction trials, only TRANSFORM-2 showed a statistically significant treatment effect with esketamine nasal spray compared with placebo. The PBAC also acknowledged the arguments included in the PSCR regarding the difficulties in assessing the effectiveness of treatments for TRD and the need to consider a range of outcomes. Overall the PBAC considered that, consistent with its view in July 2021, the claim of superior comparative effectiveness may be reasonable, although the magnitude and clinical importance of the observed benefits was uncertain. The PBAC considered esketamine likely provided at least a moderate benefit for some patients, however considered that for a proportion of patients there may be no clinical benefit from treatment with esketamine, with added toxicity.
- 7.9 The PBAC reaffirmed its previously expressed view that the claim esketamine is of inferior comparative safety to a new OAD alone was reasonable (para 7.10, esketamine PSD, July 2021 PBAC meeting). The Committee remained concerned there was limited long-term safety data for esketamine, including data assessing the potential for developing dependence, especially in the context that some patients may use esketamine continuously or for long periods.
- 7.10 The PBAC noted a number of key changes were made to the economic model based on the previous consideration by the ESC (as outlined in paragraph 6.46) but a number of issues remained outstanding (as outlined in paragraph 6.62). The PBAC noted the base case economic model in the resubmission resulted in an ICER of \$45,000 to < \$55,000 per QALY gained. The PBAC noted the results were sensitive to a number of inputs and assumptions, including the probability of achieving remission at treatment induction, transition probabilities in the maintenance period, the effectiveness of the subsequent treatment mix, the probability of recurrence from the recovery state, the esketamine dosing schedule in the maintenance period, the costs of administration and monitoring, treatment discontinuations and hospitalisation days. The PBAC noted one way sensitivity analyses resulted in a very wide range of ICERs (see Table 16) and considered the cost effectiveness of esketamine remained highly uncertain.
- 7.11 The PBAC noted the cost of administration of esketamine remained highly uncertain, particularly in the absence of an MBS item or alternative method to estimate the cost of administration and monitoring in practice. The PBAC also noted the model included administration costs for the placebo plus OAD arm which was not appropriate. The PBAC noted that removing administration costs from the placebo treatment arm increased the ICER from of \$45,000 to < \$55,000 per QALY gained to between of

\$45,000 to < \$55,000 and of \$55,000 to < \$75,000 per QALY gained, depending on the MBS item code used. The PBAC noted the MBS item code (which was for professional attendance by a psychiatrist) may not capture all costs associated with the administration and monitoring of esketamine and out of pocket costs may be incurred by patients. The PBAC noted DVA may be able to provide information regarding the costs associated with the administration and monitoring of esketamine to inform this input.

- 7.12 The PBAC noted the net cost to the PBS/ RPBS of listing esketamine was estimated to be \$500 million to < \$600 million over the first six years of listing. The PBAC noted the key inputs used to estimate the net cost to the PBS/ RPBS as outlined in Table 18 and discussed in paragraph 6.68 and considered the utilisation and financial estimates in the resubmission were highly uncertain and likely substantially overestimated.
- 7.13 The PBAC noted the resubmission estimated 500 to < 5,000 patients would initiate treatment with esketamine in year 1, increasing to 500 to < 5,000 in year 2 and 5,000 to < 10,000 in year 6. The PBAC noted this included patients initiating treatment in the GP setting (< 500 in year 2, increasing to 500 to < 5,000 in year 6) and considered this was not appropriate, given the recommendation to limit initiation to psychiatrists (as discussed in para 7.5). The PBAC noted a number of aspects of treatment, including access to psychiatrists, access to accredited treatment centres, patient reluctance given the monitoring requirements and nature of the treatment and out of pocket costs, may limit the uptake of esketamine. Additionally, the PBAC noted the estimated eligible patient population was based on the minimum prior exposure (i.e., at least two prior OADs) rather than the expected prior exposure (i.e., two to five prior OADs) which would overestimate the eligible population. The PBAC considered the estimated number of patients likely to initiate treatment with esketamine was not well justified and likely to be substantially overestimated.
- 7.14 The PBAC noted the resubmission proposed a risk share arrangement with a [REDACTED] % rebate of any expenditure over the caps. The PBAC considered a risk share arrangement was appropriate due to the uncertainty regarding patient numbers, dose, dosing interval and duration of treatment and the high risk of use in other mental health conditions, such as bipolar disorder, anxiety and PTSD. However, the PBAC agreed with the ESC that a [REDACTED] % rebate was inadequate to manage the range of risks to the Commonwealth and a [REDACTED] % reimbursement over risk-sharing subsidisation caps would provide greater certainty around the substantially high proposed cost to government.
- 7.15 The PBAC noted that the TGA Risk Management Plan stated that the sponsor is proposing to implement a Controlled Access Program to mitigate the risk of drug abuse, misuse and diversion. The PBAC further noted the PSCR proposed the addition of a prescriber instruction to the restriction stating “Esketamine can only be administered in a Janssen accredited treatment facility, which has appropriate facilities for patient administration and monitoring, access to emergency care and pharmacy”. Although the PSCR stated the accredited sites include metropolitan,

regional and rural sites and the number of sites is expected to increase to | by the end of 2022, the PBAC considered the impact of the program on access to esketamine remained unclear.

- 7.16 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.
- 7.17 The PBAC considered a resubmission for esketamine addressing outstanding issues may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.18 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

Janssen are disappointed that the PBAC did not recommend esketamine but welcome the PBAC's consideration that there is a need for treatment options for treatment resistant depression, their understanding of the severe impact of treatment resistant depression on daily life and their acceptance of the clinically meaningful benefits of esketamine. Janssen agree with the PBAC that a Stakeholder meeting would be useful to help discuss some of the remaining issues and help move towards reimbursement of this important treatment for patients. Janssen looks forward to working with the PBAC to bring SPRAVATO® (esketamine hydrochloride) to Australian patients in a timely way.