

**7.02 ESKETAMINE,
Nasal spray solution 28 mg in 0.2 mL,
Spravato[®],
Janssen-Cilag Pty Ltd.**

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 100 (Highly Specialised Drug Program) Authority Required (Telephone/Online) listing for the treatment of patients with treatment resistant depression (TRD). Esketamine nasal spray is to be initiated in conjunction with an 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
Population	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.
Intervention	Esketamine hydrochloride is to be administered in conjunction with a newly initiated oral antidepressant (OAD), <u>under the supervision of a healthcare professional</u> . 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. <u>The maximum treatment duration is 12 months per major depressive episode.</u>
Comparator	Initiation of a new oral antidepressant.
Outcomes	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.
Clinical claim	Esketamine nasal spray in combination with a newly initiated oral antidepressant is superior in terms of efficacy and inferior in terms of safety when compared to a newly initiated oral antidepressant alone.

Source: Table 11, p13 of the resubmission

Note: Changes from the July 2022 resubmission are underlined.

2 Background

Registration status

- 2.1 Esketamine nasal spray was registered on the Australian Register of Therapeutic Goods (ARTG) 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.

Stakeholder meeting

2.2 A stakeholder meeting was convened in February 2023 to discuss the PBS restriction, potential issues related to access, the likely extent of use, and what additional information might be required to support the PBS listing of esketamine (see Esketamine Stakeholder Meeting Outcome Statement, 1 February 2023¹). The attendees included members of the Pharmaceutical Benefits Advisory Committee (PBAC), clinicians with expertise in the management of treatment-resistant depression (TRD), representatives from health consumer organisations, the sponsor of esketamine and the Department of Health and Aged Care. The outcomes of this meeting included:

- The stakeholders noted that treatment choice (e.g., between esketamine, ketamine, repetitive transcranial magnetic stimulation [rTMS] or electroconvulsive therapy [ECT]) was needed and was dependant on a patient's age, treatment preferences, treatment history, severity of symptoms and location (i.e., metropolitan or rural/remote).
- The clinicians advised that the MBS criteria for rTMS was well described and largely consistent with the patient population who would be considered for treatment with esketamine in clinical practice, with an amendment to the criteria for esketamine to require trialling each antidepressant medication for a minimum of 4 to 6 weeks (rather than a minimum of 3 weeks).
- The stakeholders strongly supported limiting initial prescribing to psychiatrists given the treatment-resistant setting and specialised nature of the treatment.
- The stakeholders noted that although the proposed clinical criteria 'Treatment must be used in combination with a newly initiated oral antidepressant' was consistent with the clinical trial and the TGA approved indication, it was not consistent with clinical practice, would be difficult and complicated to adhere to, and could result in unnecessary switching of treatments.
- The stakeholders considered it was reasonable to limit esketamine to the dose and frequency outlined in the approved TGA Product Information document, but to allow patient flexibility in terms of moving between lower and higher doses and less and more frequent dosing as clinically required. The stakeholders noted some patients on maintenance treatment may experience a relapse and require twice weekly treatment.

¹ <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-stakeholder-meetings/Esketamine-Stakeholder-Meeting-Outcome-Statement.pdf>

- The stakeholders considered that, after the initial 4 week induction phase, a decision regarding ongoing treatment should be made after 6 months of maintenance treatment. The stakeholders noted the appropriate duration of treatment with esketamine remains uncertain and there is limited data to support its long-term use. The stakeholders considered it would be appropriate to allow for a maximum treatment duration of 12 months per patient. The stakeholders considered that, based on their experience with esketamine and ketamine, the majority of patients would be treated for less than 12 months. However, there may be a small number of patients who require treatment beyond 12 months and for some patients, the anxiety experienced when approaching the 12 month limit may exacerbate their depression. The stakeholders considered there may need to be some flexibility regarding the maximum 12 month treatment duration.
- The stakeholders considered allowing retreatment with esketamine may be appropriate for some patients after a reasonable period of time off treatment.
- The stakeholders considered that, overall, with some refinement as discussed above (i.e., limit prescribing to psychiatrists, maximum 12 month treatment duration), the previous approach to estimating patient numbers appeared reasonable. The stakeholders considered the uptake of esketamine would be higher in patients who have failed more treatment options.

Previous PBAC consideration

2.3 This is the third PBAC consideration of esketamine. Esketamine was previously considered for the treatment of patients with TRD at the July 2021 and July 2022 PBAC meetings.

2.4 The matters of concern from the July 2022 PBAC meeting are summarised in Table 2 below.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Restriction	Initial prescribing should be limited to psychiatrists (para 7.6, esketamine Public Summary Document [PSD], July 2022 PBAC meeting).	Prescribing was limited to psychiatrists (for both initial and continuing use).
	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 (para 3.13, esketamine PSD, July 2022 PBAC meeting).	rTMS criteria wording were used to inform the esketamine restriction.
Optimal treatment duration	The optimum duration of therapy is yet to be determined (para 6.42, esketamine PSD, July 2022 PBAC meeting).	Treatment with esketamine was limited to a maximum duration of 12 months per major depressive episode.
Appropriateness of initiating two antidepressant agents simultaneously	Include a clinical criterion that provides clarity on an appropriate interpretation of 'newly initiated' OAD (para 7.6, esketamine PSD, July 2022 PBAC meeting).	The wording 'newly initiated' was removed from the proposed restriction.

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Component	Matter of concern	How the resubmission addresses it
Clinical criteria	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 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 (para 7.5, esketamine PSD, July 2022 PBAC meeting).	Additional detail was included based on the rTMS criteria; however the clinical criterion still positions esketamine after only 2 prior OADs
Clinical evidence	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 (para 7.8, esketamine PSD, July 2022 PBAC meeting).	The clinical evidence is unchanged.
Economic analysis	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 (paragraph 6.62, esketamine PSD, July 2022 PBAC meeting).	The model was amended so that patients in the esketamine + OAD arm who discontinue esketamine receive the transition risks of the placebo + OAD treatment group. Time horizon is unchanged. The use of the STAR*D study data to inform transition probabilities of subsequent treatment is unchanged.
	The PBAC considered that a key uncertainty is the duration of treatment (para 7.14, esketamine PSD, July 2022 PBAC meeting).	The revised economic model includes a maximum esketamine treatment duration of 1 year.
	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 6.62, esketamine PSD, July 2022 PBAC meeting).	Patients in the esketamine + OAD treatment arm who discontinue esketamine receive the transition risks of the placebo + OAD treatment group. In the placebo + OAD treatment group, risks are unchanged when they are off treatment.
	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 (para 6.62, esketamine PSD, July 2022 PBAC meeting).	The model includes increased monitoring costs in the esketamine + OAD treatment arm, and removed monitoring costs from the placebo + OAD treatment arm.

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Component	Matter of concern	How the resubmission addresses it
	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, and 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 (para 6.62, esketamine PSD, July 2022 PBAC meeting).	Use of Denee (2021) to inform healthcare resource use is unchanged.
	The ESC noted there were significant safety and adverse event concerns and considered these were not adequately modelled in the submission (para 6.62, esketamine PSD, July 2022 PBAC meeting).	The model included costs associated with blood pressure and bladder related adverse events.
Financial estimates	PBAC considered the utilisation and financial estimates in the resubmission were highly uncertain and likely substantially overestimated (para 7.12, esketamine PSD, July 2022 PBAC meeting).	Eligible patient numbers were informed by a DUSC analysis of the 100% PBS sample (previously utilised a 10% PBS sample). Retreatment with esketamine in subsequent MDD episodes was included in the financial implications from Year 3 onwards.
Risk sharing arrangement	The PBAC agreed with the ESC that a █████% rebate was inadequate to manage the range of risks to the Commonwealth (para 7.14, esketamine PSD, July 2022 PBAC meeting).	The rebate for utilisation over caps was increased from █████% to █████%.

Source: Table 0-1, p13 of the resubmission; constructed during the evaluation.

Abbreviations: ECT, electroconvulsive therapy; OAD, oral antidepressant; MBS Medicare Benefits Schedule; TRD, treatment resistant depression; PSD = Public Summary Document

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Published (effective) dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESKETAMINE					
Initial treatment/induction (Treatment weeks 1-4)					
Nasal spray device 28 mg, 1	Public Hospital: \$1 (\$) Private Hospital/Community access: \$1 (\$)	8	8	0	Spravato
Nasal spray device 28 mg, 2	Public Hospital: \$1 (\$) Private Hospital/Community access: \$1 (\$)	8	16	0	Spravato
Nasal spray device 28 mg, 3	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)	8	24	0	Spravato
Continuing treatment (weeks 5-52)					
Nasal spray device 28 mg, 1	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)	4	4	2	Spravato

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Nasal spray device 28 mg, 2	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)	4	8	2	Spravato
Nasal spray device 28 mg, 3	Public Hospital: \$1 (\$) Private Hospital/Community Access: \$1 (\$)	4	12	2	Spravato
Category / Program: Section 100 – Highly Specialised Drugs Program					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
Severity: Moderate to severe					
Condition: Major depressive disorder					
Indication: Treatment resistant depression					
Treatment Phase: Initial treatment/induction (weeks 1-4)					
Clinical criteria:					
Patient is at least 18 years old					
AND					
Clinical criteria:					
Is diagnosed with a major depressive episode					
AND					
Clinical criteria:					
Has failed to achieve satisfactory improvement for the major depressive episode despite the adequate trialling of at least 2 different classes of antidepressant medications and all of the following apply:					
i. the patient's adherence to antidepressant treatment has been formally assessed; AND					
ii. the trialling of each antidepressant medication has been at the recommended therapeutic dose for a minimum of 4-6 weeks; AND					
iii. where clinically appropriate, the treatment has been titrated to the maximum tolerated therapeutic dose;					
AND					
Clinical criteria:					
Has undertaken psychological therapy, if clinically appropriate					
AND					
Clinical criteria:					
Treatment must be in combination with an oral anti-depressant.					
AND					
Clinical criteria:					
Patient must not receive more than 4 weeks of treatment under this restriction.					
Treatment criteria:					
Psychiatrist					
Population criteria:					
Patient must be aged 18 years or older					
Treatment Phase: Continuing treatment from week 5 until relapse or week 52					
Clinical criteria:					
Patient must have previously received four weeks of PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria:					
Patient must have been assessed to have responded adequately (with consideration to function and quality of life) during the initial four week treatment phase					
AND					
Clinical criteria:					
Patients must continue to demonstrate a response to treatment with this drug for this condition during the maintenance treatment period. Patients should discontinue treatment with esketamine if no longer responding					
AND					

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Clinical criteria:
The treatment duration with esketamine does not extend beyond 12 cumulative months from the first administered dose
AND
Clinical criteria:
Treatment must be in combination with an oral antidepressant.
Treatment criteria:
Psychiatrist
Population criteria:
Patient must be aged 18 years or older
Treatment Phase: Grandfathering treatment- transitioning from non-PBS to PBS-subsidised supply
Clinical criteria:
Patient must have received non PBS subsidised treatment with this drug for this condition prior to PBS listing
AND
Clinical criteria:
Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug
AND
Clinical criteria:
Patient must have been assessed to have responded adequately (with consideration to function and quality of life) during the initial four week treatment phase
AND
Clinical criteria:
Patients must continue to demonstrate a response to treatment with this drug for this condition during the maintenance treatment period. Patients should discontinue treatment with esketamine if no longer responding
AND
Clinical criteria:
The treatment duration with esketamine does not extend beyond 12 cumulative months from the first administered dose
AND
Clinical criteria:
Treatment must be in combination with an oral antidepressant.
Treatment criteria:
Psychiatrist
Population criteria:
Patient must be aged 18 years or older
Prescribing Instructions:
Esketamine should be used with caution in patients with psychosis or a history of psychosis. Careful consideration is advised prior to treatment of individuals with a history of substance use disorder, including alcohol. Monitoring for signs of abuse or dependence is recommended. 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. Post cessation monitoring is recommended.
Administrative Advice: Care must be taken to comply with the provisions of the state/territory law for prescribing this drug. Note: No increases in quantity or repeats will be authorised Note: Special pricing arrangement applies

3.1 The resubmission proposed an effective and published price for esketamine nasal spray with a special pricing arrangement. The published price remained unchanged from the previous resubmission. The proposed effective price in the resubmission was \square % lower than that proposed in the July 2022 resubmission.

- 3.2 The proposed restriction has incorporated elements of the rTMS criteria, including more specific criteria defining adequate trialling of at least 2 antidepressant medications, from 2 different classes, and incorporating a history of psychological therapy. The evaluation considered these changes to the restriction may be more appropriate for defining the place in therapy for esketamine nasal spray more holistically in the framework of available, efficacious therapies, and in terms of defining treatment failure more rigorously. Psychological therapies are an adjunctive therapy, and form a relevant part of the treatment pathway in the management of all forms of depression.
- 3.3 Treatment with esketamine is limited to a maximum duration of 12 months per episode. Capping treatment at a maximum of 12 months may be an appropriate pragmatic approach to limiting ongoing or indefinite treatment, for which there is little available clinical evidence. Although there is no specific guidance on treatment duration with esketamine nasal spray, current guidelines for antidepressant therapies in general recommend continuing treatment for at least 6 months after depressive symptoms improve. However, whilst a 12-month maximum treatment duration may be sufficient for many patients, it is still unclear whether patients continuing to benefit will relapse once treatment with esketamine nasal spray is ceased.
- 3.4 The Pre-Sub-Committee Response (PSCR) reiterated there is no clinical data or real world evidence that addresses the optimal duration of treatment, and argued that while the evaluation considered the appropriateness of restricting to a maximum of 12 months therapy per episode to be unclear, stated it was important to note that in making such a proposal, the sponsor consulted widely and the clinicians at the stakeholder meeting expressed a view it was appropriate to allow for a maximum treatment duration of 12 months per patient per episode.
- 3.5 The ESC noted the input from the stakeholder meeting that while the majority of patients would likely be treated with esketamine for less than 12 months, there may need to be some flexibility regarding the maximum 12 month treatment duration. The ESC noted the proposed restriction limits use to a 12 month treatment duration and it was unclear how use beyond 12 months would be implemented in clinical practice. The Pre-PBAC Response argued the advice from an advisory board in January 2023 was that a 12 month treatment duration provides patients and psychiatrists with an understanding of the maximum time they can be on treatment, which was considered desirable from both a treating clinician and patient perspective. The Response further argued that based on current experience, most patients would be treated for less than 12 months, and that the OAD (taken in combination with esketamine) would continue to provide some efficacy beyond this time.
- 3.6 The sponsor did not make proposals on a number of components of the listings of esketamine, however stated they would require further consideration. These issues included:

- Whether re-treatment or additional treatment cycles should be allowed, and if so;
 - Whether a patient must have previously responded to esketamine to be eligible for re-treatment or additional treatment cycles; and
 - Whether the initial requirement for treatment with two prior OADs must be met again to be eligible for re-treatment or additional treatment cycles.
- 3.7 The evaluation considered that retreatment may be appropriate, particularly if patients have responded to treatment in a previous major depressive episode. The ESC noted that, as the economic model only included one treatment course over the 5 year time horizon, the cost effectiveness of retreatment had not been considered. The ESC noted the financial estimates assume 40% of patients would receive retreatment for a subsequent episode of MDD.
- 3.8 The proposed restriction aimed to increase the flexibility with which the co-administered oral antidepressant can be prescribed by wording the clinical criterion to read ‘treatment must be used in combination with an oral antidepressant’, deleting the requirement for it to be ‘newly initiated’.
- 3.9 The proposed restriction included a caution in prescriber notes regarding populations who were excluded from the trials, including personality disorders, alcohol and substance use disorders, and those with suicidal ideation.
- 3.10 The proposed restriction did not require that a disease specific scale or instrument be used to assess either baseline severity of disease or treatment response, but has been updated since the July 2022 resubmission to specify that to qualify for continuing therapy, a ‘patient must have been assessed to have responded adequately (with consideration to function and quality of life) during the initial four week treatment phase’.
- 3.11 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.

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.

- 4.2 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 4.3, esketamine PSD, July 2022 PBAC meeting). This subpopulation is described as having treatment-resistant depression (TRD) and is the population for which PBS listing is sought for esketamine.
- 4.3 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).
- 4.4 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).
- 4.5 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).
- 4.6 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.
- 4.7 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 approved or indicated for use in treating depression. Ketamine is not listed on the PBS for any indication.

- 4.8 The ESC considered the use of ketamine to treat TRD in the private setting was now established in Australia (albeit off-label) and the ESC noted a growing body of evidence supporting its use. The PBAC noted a number of publications had recently become available, including Nikolin 2023², Anand 2023³, Nikayin 2022⁴, Ekstrand 2022⁵ and Rhee et al 2022⁶, that provided additional support for the use of esketamine and ketamine.
- 4.9 The proposed clinical management algorithm positions esketamine nasal spray, initiated with a new antidepressant, for use in patients with TRD who have previously failed treatment with two prior oral antidepressants in the same depressive episode. Esketamine nasal spray is included alongside other management options like switching antidepressant therapy, combination antidepressant therapy, and augmentation. If patients achieve an adequate response to esketamine nasal spray, patients will continue maintenance therapy until they achieve recovery (where they may or may not stop treatment), experience relapse or recurrence of symptoms, or reach a 12-month duration of treatment. The effect of stopping treatment with esketamine in responders, and therefore the optimum treatment duration, is unknown. 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. 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). As the durability of benefit has not been established, it is unclear for how long esketamine should be prescribed to prevent relapse.
- 4.10 The PBAC previously 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 (para 7.5, esketamine PSD, July 2022 PBAC meeting). 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,

² Nikolin S, Rodgers A, Schwaab A, et al. Ketamine for the treatment of major depression: a systematic review and meta-analysis. *eClinicalMedicine* 2023;62: 102127

³ Anand A, Mathew SJ, Sanacora G, Murrrough JW, Goes FS, Altinay M, Aloysi AS, Asghar-Ali AA, Barnett BS, Chang LC, Collins KA. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. *New England Journal of Medicine*. 2023 May 24

⁴ Nikayin S, Rhee TG, Cunningham ME, de Fontnouvelle CA, Ostroff RB, Sanacora G, Wilkinson ST. Evaluation of the trajectory of depression severity with ketamine and esketamine treatment in a clinical setting. *JAMA psychiatry*. 2022 Jul 1;79(7):736-8.

⁵ Ekstrand J, Fattah C, Persson M, et al. Racemic ketamine as an alternative to electroconvulsive therapy for unipolar depression: a randomized, open-label, non-inferiority trial (KetECT). *Int J Neuropsychopharmacol* 2022; 25: 339-49

⁶ Rhee TG, Shim SR, Forester BP, et al. Efficacy and safety of ketamine vs electro-convulsive therapy among patients with major depressive episode: a systematic review and meta-analysis. *JAMA Psychiatry* 2022; 79: 1162-72.

augmentation with lithium or other agents and physical treatments such as ECT and rTMS) have been trialled or at least considered (para 7.5, esketamine PSD, July 2022 PBAC meeting). 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 (para 7.5, esketamine PSD, July 2022 PBAC meeting).

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 the ESC noted 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.
- Psychotherapy, such as cognitive-behavioural therapy.
- Ketamine (given intravenously or as a subcutaneous injection).

5.2 At the July 2022 meeting, the PBAC reaffirmed its previously expressed view the nominated comparator of a newly initiated OAD alone was reasonable (para 7.7, esketamine PSD, July 2022 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (58), health care professionals (20) and organisations (1) via the Consumer Comments facility on the PBS website. The comments from individuals came from patients who have used

either esketamine or ketamine, individuals who are seeking access to these therapies, and their family and friends. The PBAC noted the advice from patients who had used esketamine or ketamine and their family and friends described the treatments as life-changing and describing better daily functioning and enjoyment in life, improved relationships, restored optimism and hope, and reduced suicidal ideation. The PBAC also noted the advice from patients seeking to access esketamine or ketamine about the hope that these treatments could improve their lives and reduce or eliminate the symptoms of TRD, as well as outlined the challenges and practical issues with other later-line therapies such as ECT. Comments described the prohibitive cost of esketamine treatment and the difficulties accessing clinics for regular treatment. Comments noted a preference for a nasal spray over injections. Some individuals who have used this medicine commented that it is important administration is in a setting that allows for adverse events and potential addiction to be monitored.

- 6.3 The PBAC also noted the advice from health professionals who described the rapid response to treatment with esketamine, with some clinicians anecdotally reporting a substantial proportion of patients achieving remission (about a quarter) and about half achieving a significant clinical improvement; however also noted other clinicians reported limited success, highlighting that not all patients will benefit from treatment with esketamine or ketamine. Comments described esketamine as more accessible than other available options but noted the cost of treatment was prohibitive. The PBAC noted a number of comments emphasised the importance of administration in a controlled setting due to the adverse events (dissociation, in particular) which can be uncomfortable for some patients.
- 6.4 The PBAC noted the advice received from the Royal Australian and New Zealand College of Psychiatrists (RANZCP) advising that a priority for the College is ensuring patients have access to evidence based treatments, with affordability being a component of access. The College also stated that esketamine is a form of ketamine and noted the College has published a clinical memorandum on the use of ketamine in psychiatric practice.

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 versus 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 Table 3 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	Internal study report; 6 November 2017

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Trial ID	Protocol title/ Publication title	Publication citation
	Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression (TRANSFORM-2)	
	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 Antidepressant in Elderly Patients with Treatment-Resistant Depression-TRANSFORM-3.	Am J Geriatr Psychiatry; 28(2):121-141.
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

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Trial ID	Protocol title/ Publication title	Publication citation
	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 July 2022 resubmission

6.7 The key features of the included studies are summarised in Table 4 below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
TRANSFORM-2	227	Multi-centre, double-blinded, 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	Multi-centre, double-blinded, 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	Multi-centre, double-blinded, 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	Multi-centre, double-blinded, 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	Open-label, multi-centre, 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 ≥ 2 antidepressants in the current episode	Adverse events	Not used
SUSTAIN-3	1140	Open-label, multi-centre, 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 July 2022 resubmission; Table 2.1, p.1; Table 2.2, p.3; Table 2.3, p.5, Attachment 2.5 of the July 2022 resubmission
 Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant; 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 included 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 6.9, esketamine PSD, July 2022 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.
- 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 July 2021 and July 2022 submissions. 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 Table 5 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)
TRANSFORM-2 (flexible dosing, adult patients 18-64 years of age with TRD)						
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)			-	-4.0 (-7.3, -0.6)	-	-3.5 (-6.7, -0.3)
TRANSFORM-3 (flexible dosing, older patients ≥ 65 years of age with TRD)						
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)
TRANSFORM-1 (fixed dosing, adult patients 18-64 years of age with TRD)						
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 July 2022 resubmission; Table 2.50, Attachment 2.6 of the July 2022 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 6.13, esketamine PSD, July 2022 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.

6.14 The proportion of responders and remitters at day 28 of the TRANSFORM-2 and TRANSFORM-3 trials are summarised in Table 6 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 ≥50%. Subjects who had a MADRS total score of ≤12 were considered remitters. 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
Response ($\geq 50\%$ improvement MADRS score)		
TRANSFORM-2		
Observed cases, n/N (%)	70/101 (69.3)	52/100 (52.0)
LOCF, n/N (%)	71/112 (63.4)	54/109 (49.5)
TRANSFORM-3		
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)
Remission (MADRS total score ≤ 12)		
TRANSFORM-2		
Observed cases, n/N (%)	53/101 (52.5)	31/100 (31.0)
LOCF, n/N (%)	54/112 (48.2)	33/109 (30.3)
TRANSFORM-3		
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 July 2022 resubmission.

6.15 In TRANSFORM-2 the number needed to treat for response at day 28 based on MADRS total score was 6, and for remission was 5. In TRANSFORM-3 the number needed to treat for response at day 28 was 7, and for remission was 9. 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 results for the EQ-5D-5L health status index in the TRANSFORM trials are summarised in Table 7 below.

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

	Esketamine + OAD		Placebo + OAD	
	N	Mean (SD)	N	Mean (SD)
TRANSFORM-2				
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)
TRANSFORM-3				
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)
TRANSFORM-1				
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).

6.17 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.

- 6.18 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 Table 8 below.

Table 8: Time to relapse^a in the SUSTAIN-1 trial (stable remitters and responders)

	Esketamine + OAD	Placebo + OAD	Mean difference	Hazard ratio (95% CI)^b
Stable Remitters	N=90	N=86	-	-
Number of relapses, n (%)	24 (26.7)	39 (45.3)	18.6	0.49 (0.29, 0.84)
Median time to relapse, days (95% CI)	NE	273.0 (97.0, NE)	NE	
Stable Responders	N=62	N=59	-	-
Number of relapses, n (%)	16 (25.8)	34 (57.6)	31.8	0.30 (0.16, 0.55)
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 July 2022 resubmission

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

^aBased on Kaplan-Meier product limit estimates

^bHazard ratio and CI are weighted estimates based on Wassmer (2006) and calculated using R

- 6.19 Treatment with esketamine nasal spray significantly delayed relapse in stable remitters and stable responders compared with intranasal placebo.
- 6.20 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. 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. The relapse rate from SUSTAIN-1 informs the relapse rate of the esketamine treatment arm in the economic model. This may be underestimated because of selection bias due to the inclusion of people with stable response and stable remission only, and the potential for unblinding as people randomised to placebo may notice the absence of psychoactive effects, possibly biasing the results in favour of esketamine.
- 6.21 Remission and response from baseline (maintenance) to endpoint in the SUSTAIN-1 trial is summarised in Table 9 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)
Remission				
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)
Response				
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 July 2022 resubmission

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

- 6.22 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.
- 6.23 Response was also maintained or lost at a slower rate by a higher percentage of subjects in the esketamine nasal spray treatment groups.
- 6.24 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 ≤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.

- 6.25 The benefits and safety of longer-term esketamine treatment, and the optimum duration of treatment, are not known, due to the relatively short duration of treatment in the included clinical trials. Although the results of SUSTAIN-1 suggested that among patients who were successfully treated with esketamine plus an antidepressant, maintenance treatment with the combination was more efficacious than antidepressant monotherapy, this study cannot inform treatment decisions around duration due to limitations of the study design.
- 6.26 The resubmission noted that the duration of treatment in Australian clinical practice, and when it would be appropriate to reduce or discontinue treatment remain uncertain. The sponsor proposed a maximum 12-month duration of treatment per episode, which is a pragmatic decision rather than one based on clinical evidence.

Comparative harms

- 6.27 A summary of treatment-emergent adverse events from the TRANSFORM trials is presented in Table 10 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 ^a	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 ^a	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 ^b	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 ^b	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

^a Study drug relationship of possible, probable, and very likely are included in this category

^b 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

- 6.28 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.

- 6.29 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.
- 6.30 A summary of treatment-emergent adverse events by phase, for the induction, optimisation, and maintenance phases of the SUSTAIN-1 trial is included in Table 11 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 ^a	301 (68.9)	281 (61.8)	106 (69.7)	37 (25.5)
TEAE possibly related to OAD ^a	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 ^b	22 (5.0)	5 (1.1)	4 (2.6)	3 (2.1)
TEAE possibly related to OAD withdrawn ^b	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

^a Study drug relationship of possible, probable, and very likely are included in this category

^b 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.

- 6.31 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.
- 6.32 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.
- 6.33 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 6.32, esketamine PSD, July 2022 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 (UpToDate, 2022).

- 6.34 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.
- 6.35 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 few 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.

Benefits/harms

- 6.36 The benefits and harms are unchanged from the July 2022 resubmission.
- 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 more 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 ≤ 12 .
 - Approximately 16 patients would experience dizziness.
 - Approximately 22 patients would experience dissociation.
 - Approximately 23 patients would experience vertigo.
 - Approximately 10 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 more 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 ≤ 12 .
 - Approximately 13 patients would experience dizziness.
 - Approximately 11 patients would experience dissociation.
 - Approximately 8 patients would experience vertigo.
 - Approximately 8 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 patients would experience dizziness.
 - Approximately 23 patients would experience dissociation.
 - Approximately 20 patients would experience vertigo.
 - Approximately 3 patients would have an increase in blood pressure.

Clinical claim

- 6.40 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.

- 6.41 The PBAC previously 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 (para 6.43, esketamine PSD, July 2022 PBAC meeting). The PBAC reaffirmed its view previously expressed at its July 2021 meeting that the claim of inferior comparative safety was reasonable (para 6.44, esketamine PSD, July 2022 PBAC meeting).
- 6.42 There are several outstanding issues which should be considered:
- There are clinical questions which cannot be addressed with the available clinical data. This includes how to cease or taper treatment in responders, and whether retreatment with esketamine should be allowed in subsequent episodes of MDD.
 - The proposed limited duration of treatment per episode (a maximum of 12 months) reduces some financial and economic uncertainty, however, there remains significant clinical uncertainty around the duration of treatment. Although the sponsor provided a summary of non-randomised studies to support the evidence for the efficacy of esketamine, these had substantial limitations and did not provide data that could inform the duration of treatment, or how best to cease treatment in responders. The ESC agreed with the evaluation that the lack of data on how best to cease treatment in responders and the potential for some patients to benefit from longer durations of treatment was a relevant clinical concern.
 - The magnitude of the clinical benefit, and the subgroups most likely to respond to treatment, are uncertain. Only one of the included short-term induction trials showed a statistically significant difference in the primary outcome. Although an additional short-term induction trial has been published since the July 2022 resubmission (Chen et al. [2023]; published to support the registration of esketamine nasal spray in China), this also failed to demonstrate statistical significance for the primary outcome, change from baseline in MADRS total score at day 28.
 - There is limited long-term evidence for safety. Esketamine is associated with some potentially serious adverse events. In SUSTAIN-2, 6.9% of people had serious adverse events including depression, suicidal ideation, suicide attempt, anxiety and gastroenteritis.
- 6.43 The PBAC noted no new clinical data was provided in the current resubmission, and reaffirmed its view (expressed at its July 2022 meeting) that while there remained uncertainty regarding the primary outcome results from the clinical trials, based on 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 previous views expressed at its July 2021 and July 2022 meetings 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 2022 resubmission included:
- A maximum esketamine treatment duration of 1 year (13 model cycles), after which all patients on esketamine are off treatment.
 - Applying separate transition risks for patients on and off treatment, that is, patients in the esketamine + OAD arm who discontinue esketamine receive the transition risks of the placebo + OAD group, whilst the placebo + OAD group risks are unchanged when they are off treatment.
 - Using an MBS item code corresponding to the highest psychiatrist consultation fee (>75 mins; MBS item code 308) as a proxy for the administration and monitoring cost of esketamine nasal spray, and removal of the administration and monitoring cost in the placebo arm.
 - The addition of adverse event costs for hypertension and bladder-related adverse events.
 - Applying the adverse event cost and disutility of esketamine to patients on treatment, while the adverse event cost and disutility of placebo arm were applied once patients transition to off treatment.
 - Changing the proportion of the population aged 65 years and over, based on the age distribution of the national population estimated by the Australian Bureau of Statistics (ABS), and updated ABS life tables for background mortality.
 - Revising the effective AEMP of esketamine nasal spray (from \$| to \$| per 28 mg device).
 - Updating DPMQs for costs of oral antidepressants, and MBS and AR-DRG costs for disease management costs.
- 6.47 Table 12 summarises the key components of the economic evaluation.

Table 12: Key components of the economic evaluation

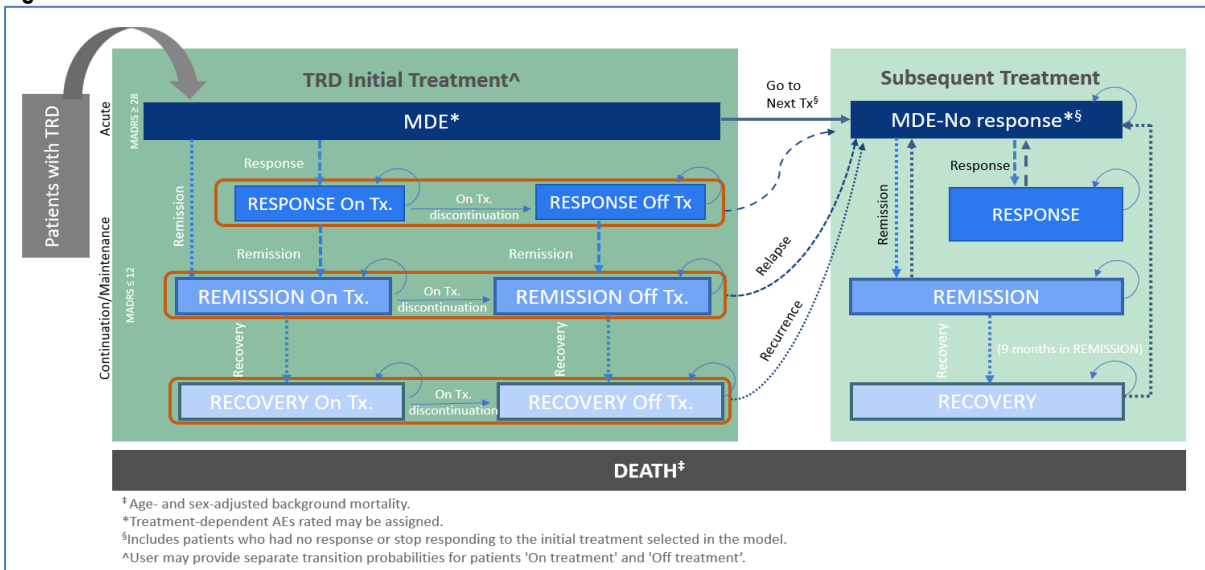
Component	Description
Treatments	Esketamine + OAD versus placebo + OAD.
Time horizon	5 years in model base case versus four weeks in the short-term induction trials (TRANSFORM trials), and a median exposure to intranasal esketamine of 17.7 weeks among patients who achieved stable remission, and 19.4 weeks among patients who achieved stable response in the esketamine treatment arm, and a median exposure to placebo of 10.2 weeks among patients who achieved stable remission and 10.1 weeks among those who achieved stable response in the SUSTAIN-1 trial.
Outcomes	Quality-adjusted life-years MDE-free life years Proportions of patients with remission and response
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Method used to generate results	Markov state transition model with multiple lines of treatment.
Health states	Major depressive episode, Response, Remission, Recovery, Death
Cycle length	Four weeks.
Transition probabilities	Initial Treatment: Transition probabilities based on data from TRANSFORM-2 and TRANSFORM-3, weighted by the proportion of the Australian population aged <65 and ≥65 years. Maintenance setting: Transition probabilities based on data from SUSTAIN-1 for the esketamine arm; and the average of third- and fourth-line treatment outcomes from the STAR*D study for the placebo arm. Maximum treatment duration with esketamine limited to 12 months; patient who discontinue for any reason during the maintenance phase return to the transition probabilities of the placebo arm (OAD only). Subsequent Treatment: Response, remission, loss of response and relapse rates were based on the fourth-line treatment outcomes from the STAR*D study.
Utility values	Patient-level EQ-5D scores from the TRANSFORM -1 and -2 trials were mapped to a UK value set for patients at baseline (MDE: 0.4326) and in response (0.7666) or remission (0.8604), weighted by the proportion of the population aged below 65 years, and 65 years and above. Recovery was assumed to be equal to remission. Disutility for adverse events based on published sources, weighted by average duration in TRANSFORM-2.
Costs	Drug costs associated with esketamine were based on the proposed DPMQ, and frequency and dose based on usage in the key clinical trials (TRANSFORM- 1 and -2, and SUSTAIN-1). Drug costs for OADs (both in combination with esketamine/placebo, and for subsequent treatment) were based on market shares of oral antidepressants based on number of scripts (Services Australia Item Reports between November 2021 and November 2022) and published DPMQs from the February 2023 PBS Schedule. Esketamine administration and monitoring costs were based on MBS item 308 (psychiatrist consultation of more than 75 minutes duration). Disease management costs were based on MBS fees for GP and specialist visits, the Australian Emergency care Classification (AECC) for emergency department visits, and the Australian Refined Diagnosis Related Groups (AR-DRG) for costs of hospitalisations associated with major depressive disorder. Adverse event costs were applied to both the esketamine + OAD and the placebo + OAD arms, based on the incidence of increased blood pressure, bladder pain/discomfort, and urinary tract infection in the TRANSFORM-2 trial, and costs of GP visits and the DPMQ of antihypertensives and antibiotics.
Software package	Microsoft Excel.

Source: Table 3-2, pp156-158 of the resubmission; compiled during the evaluation using 'Attachment 3.3 – Esketamine TRD CE model' spreadsheet.

Abbreviations: MDE, major depressive episode; OAD, oral anti-depressant

6.48 Figure 1 illustrates the structure of the economic model in the resubmission, reflecting the addition of the on and off treatment transitions for initial treatment.

Figure 1: Model structure



Source: Figure 3-1, p82 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 Table 13 below.

Table 13: Key drivers of the model

Description	Method/Value	Impact
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). Esketamine drug and administration costs are largely offset by the cost of hospitalisations avoided, and it is unclear whether the reductions in hospitalisations generated in the model will be realised in practice. The ESC previously 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 (para 6.62, esketamine PSD, July 2022 PBAC meeting). The ESC previously noted that Denee 2021 may have limited applicability to the Australian context (para 6.62, esketamine PSD, July 2022 PBAC meeting).	High, favours esketamine.
Transition probabilities in the maintenance phase	The ESC reiterated its view that the model should incorporate more conservative maintenance of treatment assumptions (para 6.62, esketamine PSD, July 2022 PBAC meeting). Although the revised model limits esketamine duration to a maximum duration of one year, and patients who discontinue esketamine treatment receive the transition risks of the placebo + OAD group, benefits associated with esketamine treatment are maintained over the 5-year model duration. There are only limited data to inform the long-term use and outcomes associated with esketamine nasal spray treatment.	Moderate, favours esketamine.
Costs of administration and monitoring	The revised model included a higher cost for administration and monitoring of esketamine (\$228.70) based on a longer psychiatrist consultation (>75 minutes versus 30-45 minutes in the previous resubmission). However, it is unclear whether this is an appropriate proxy for post-administration monitoring, which the resubmission claimed would last approximately 2 hours with supervision predominantly by nurses. The revised model also appropriately removed administration costs for the placebo plus OAD arm.	Moderate, favours esketamine.
Circumstances of use	Frequency of administration and dose in the maintenance phases can vary, and in the model was based on use in the included clinical trials. More or less frequent use	Moderate, unclear direction.

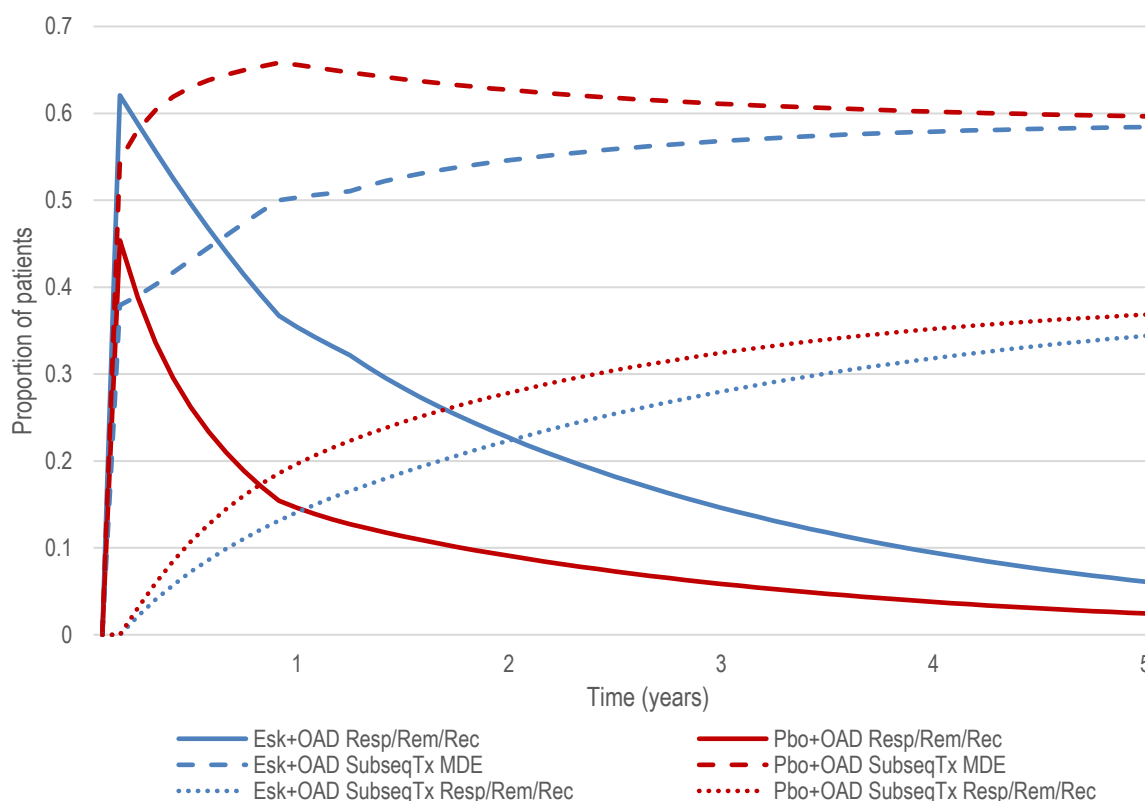
	than was observed in the trials will impact the cost-effectiveness of esketamine. It is unlikely that usage in the clinical trials will be replicated in clinical practice.	
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Source: Constructed during the evaluation

6.50 The PSQR argued the frequency of administration and dose in the maintenance phase were derived from the clinical trials and were appropriate. The PSQR further noted sensitivity analysis of these variables in the evaluation indicated the ICER remained below \$25,000 to < \$35,000 per QALY except in two scenarios (use of 84 mg only and all patients receiving weekly dosing), and argued these scenarios were highly unlikely to occur in practice.

6.51 The model trace is summarised in Figure 2. 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: Markov trace



Source: Constructed during the evaluation using 'Attachment 3.3 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

6.52 As in the July 2022 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 2022 model, the current model trace indicates a slightly smaller initial treatment effect by the end of the time horizon for the esketamine plus

OAD treatment group, and a greater proportion of patients with MDE on subsequent treatment, both consistent with the 12-month maximum duration of treatment in the current resubmission.

6.53 Table 14 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 + oral antidepressant (\$)	Oral antidepressant	Increment (\$)
Treatment costs	\$	\$981	\$
- esketamine	\$	\$0	\$
- oral antidepressant	\$224	\$111	\$113
- subsequent therapies	\$757	\$870	-\$113
Administration/monitoring	\$	\$0	\$
Adverse events	\$21	\$1	\$20
Disease management costs	\$88,480	\$99,346	-\$10,865
- primary care visits	\$507	\$538	-\$31
- specialist visits	\$2,565	\$2,665	-\$100
- ED visits	\$3,972	\$4,500	-\$527
- hospitalisations	\$81,437	\$91,643	-\$10,206
TOTAL	\$	\$100,328	\$

Source: Table 326, p113 of the resubmission; and 'Attachment 3.3 Esketamine TRD CE model' Excel spreadsheet provided with the resubmission

6.54 The difference in costs between treatment arms was driven by esketamine drug and administration costs, which were partially offset by reduced disease management costs (primarily costs of hospitalisations). The ESC noted the administration costs (\$) accounted for 35% of the esketamine drug and administration cost (\$). It is unclear whether such a significant reduction in hospitalisations will occur in practice with esketamine treatment. 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 was based on a relatively small and heterogeneous sample, who may have had severe disease courses and/or higher than average visits to clinicians. The heterogeneity was reflected in the wide distribution of results. It is likely that there is large variation in costs of TRD in practice, which makes it difficult to estimate an accurate cost in the model. The ESC previously considered that Denee et al. (2021) may have limited applicability to the Australian context (para 6.53, esketamine PSD, July 2022 PBAC meeting).

6.55 The PSCR argued these assumptions, based on the Denee 2021 study, represent the best available data as it provides information for the specific model health states, has been validated by four Australian expert clinicians who advised the results were generalisable to the Australian setting, and the sponsor's advisory board felt the predicted reduction of 8.5 hospital days over 5 years estimated in the July 2022 model was reasonable for the TRD setting. The PSCR further argued that studies of treatments in MDD/TRD presented in the previous two submissions were supportive of hospital reductions in responders/remitters, and given the current submission had reduced the number of hospitalisations avoided (to 5.8 hospitals days), and sensitivity

analyses for hospitalisation offsets demonstrated the ICER remained below \$45,000 to < \$55,000 per QALY when increased or decreased by 20%. On that basis, the PSCR concluded the uncertainty in terms of hospitalisation cost offsets had been adequately addressed. The ESC noted no additional data had been provided to support the appropriateness of the hospitalisation estimates to the Australian population, and that offsets for a reduction in hospitalisations remained a key driver of the cost-effectiveness.

- 6.56 The Pre-PBAC Response argued the sensitivity analyses (see Table 16 below) demonstrate the ICER range of \$5,000 to < \$15,000 - \$35,000 to < \$45,000 per QALY for plausible changes in hospitalisation days and demonstrates esketamine remains cost-effective. Furthermore, the Response discussed the Gillain 2021⁷ study, a retrospective cohort study of 125 patients in Belgium with hospital length of stay data for TRD/MDD episodes, with the cohort incurring 0.05 hospital episodes per month for patients in the major depressive episode state, translating to approximately 2.2 inpatient days per month, which is higher than used in the Australian model of 1.4 days per month. On that basis, the Response argued the Denee 2021 data was likely not an overestimate and in the absence of Australian hospitalisation data, Denee 2021 is applicable to the Australian context.
- 6.57 The results of the stepped economic evaluation presented in the resubmission are summarised in Table 15 below.

⁷ Gillain, B., Degraeve, G., Dreesen, T. et al. Real-World Treatment Patterns, Outcomes, Resource Utilization and Costs in Treatment-Resistant Major Depressive Disorder: PATTERN, a Retrospective Cohort Study in Belgium. *PharmacoEconomics Open* 6, 293–302 (2022). <https://doi.org/10.1007/s41669-021-00306-2>

Table 15: Results of the stepped economic evaluation

Step and component	Esketamine	Placebo	Increment
Trial based four-week induction phase¹			
Costs	\$█	\$17	\$█
Proportion of responders (Day 28)	62.1%	45.4%	16.7%
Proportion in remission (Day 28)	46.5%	26.8%	19.7%
Incremental cost/additional responder			\$ ¹
Incremental cost/additional patient in remission			\$ ²
Induction and maintenance phases over 52 weeks with treatment discontinuation²			
Costs	\$█	\$68	\$█
Years in response, remission, or recovery	0.428	0.229	0.199
Incremental cost/MDE-free life-year gained			\$ ³
As for Step 2a, with subsequent treatment costs and consequences included (based on STAR*D study)			
Costs	\$█	\$222	\$█
Years in response, remission, or recovery	0.507	0.343	0.164
Incremental cost/MDE-free life-year gained			\$ ⁴
As for Step 2b, with health care resource use included			
Costs	\$█	\$24,154	\$█
Years in response, remission, or recovery	0.507	0.343	0.164
Incremental cost/MDE-free life-year gained			\$ ³
As for Step 2c, with utilities derived from TRANSFORM-2 and -3 applied to time in health states			
Costs	\$█	\$24,154	\$█
QALYs	0.644	0.573	0.070
Incremental cost/QALY gained			\$ ⁵
As for Step 3b, extrapolated from 52 weeks to 5 years and includes AE cost/disutility (undiscounted)			
Costs	\$█	\$112,977	\$█
QALYs	3.077	2.927	0.151
Incremental cost/QALY gained			\$ ²
As for Step 4a, using 5.0% discount rate; current resubmission base case			
Costs	\$█	\$100,328	\$█
QALYs	2.732	2.592	0.141
Incremental cost/QALY gained			\$ ¹

Source: Table 325, p112 of the resubmission.

Abbreviations: DPMQ, dispensed price for maximum quantity; OAD, oral anti-depressant; QALY, quality adjusted life year.

¹ Proportion of responders and in remitters from TRANSFORM-2 and -3 weighted by the proportion of the Australian population aged < 65 and ≥ 65 years; esketamine and oral AD drug costs included; administration costs applied to esketamine arm only.

² Time spent in response, remission and recovery states based on TRANSFORM-2 and -3, SUSTAIN-1 and STAR*D data; esketamine and oral antidepressant drug costs included; administration costs applied to esketamine arm only; esketamine drug and administration cost applied to patients on treatment only.

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$15,000 to < \$25,000

³ \$55,000 to < \$75,000

⁴ \$75,000 to < \$95,000

⁵ \$135,000 to < \$155,000

- 6.58 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 impact on the stepped economic evaluation.
- 6.59 During the evaluation, a stepped economic evaluation was conducted from the July 2022 base case to the current resubmission base case, to assess the impact of changes included in the current resubmission's model. Compared with the July 2022 model, limiting esketamine treatment to one year and reducing the esketamine price (which

both decreased the ICER) and using a higher administration fee for esketamine and removing the administration fee for the placebo arm (which increased the ICER) had the largest impact on the current resubmission’s model.

6.60 Based on the economic model, treatment with esketamine nasal spray plus a newly initiated oral antidepressant versus treatment with a newly initiated oral antidepressant in patients with TRD is associated with an incremental cost per QALY gained of \$25,000 to < \$35,000. This compares to an incremental cost per QALY gained of \$45,000 to < \$55,000 in the July 2022 resubmission.

6.61 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 \$|; based on an average duration of treatment of 5.5 months (\$| and 11.4 months in July 2022).
- An additional 0.36 years (4.3 months) free from major depressive disorder, which would save \$11,651 in disease management costs, and be associated with improved quality of life (5.8 months and \$14,932 in July 2022).

6.62 The results of key sensitivity analyses are summarised in Table 16 below.

Table 16: Results of sensitivity analyses

	Incremental cost (\$)	Incremental QALYs	ICER (\$)	% change in ICER
Base case		0.1407	1	-
Discount rate (base case: 5%)				
0%		0.1506	2	-20%
3.5%		0.1435	2	-6%
Time horizon (base case: 5 years)				
1 year		0.0682	5	417%
3 years		0.1272	3	43%
7 years		0.1438	2	-9%
10 years		0.1446	2	-11%
Probabilities of remission and response in induction phase (base case: remission 46.9% ESK+OAD vs 27.1% OAD; response 15.7% ESK+OAD vs 18.7% OAD from TRANSFORM-2 and -3 weighted average)				
Increase ESK+OAD probabilities by 20%		0.1924	6	-67%
Decrease ESK+OAD probabilities by 20%		0.0892	7	144%
Probability of remission only in induction phase (base case: remission 46.9% ESK+OAD vs 27.1% OAD from TRANSFORM-2 and -3 weighted average)				
Increase ESK+OAD probability of remission by 20%		0.1807	6	-56%
Decrease ESK+OAD probability of remission by 20%		0.1007	8	100%
Maintenance transition probabilities (base case values for ESK+OAD and OAD arms derived from SUSTAIN-1)				
OAD transitions same as for ESK+OAD		0.0532	9	656%
Increase probabilities to MDE by 20%; decrease response to remission probability by 20%: ESK+OAD arm		0.1194	3	55%
Decrease probabilities to MDE by 20%; increase response to remission probability by 20%: ESK+OAD arm		0.1626	2	-42%
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)				
Increase probabilities by 20%		0.1514	2	-28%

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	Incremental cost (\$)	Incremental QALYs	ICER (\$)	% change in ICER
Decrease probabilities by 20%		0.1279	³	40%
Esketamine utilisation and costs				
Use of 56 mg dose only		0.1407	⁶	-56%
Use of 84 mg dose only		0.1407	³	45%
All patients receive twice weekly dosing during initiation		0.1407	⁴	10%
All patients receive once weekly dosing during maintenance weeks 9+		0.1407	⁸	73%
All patients receive once fortnightly dosing during maintenance weeks 9+		0.1407	²	-12%
Health care resource use (base case: estimates of primary care, specialist, and ED visits and hospitalisation days by health state based on Denee 2021)				
Estimates increased by 20%		0.1407	⁶	-59%
Estimates decreased by 20%		0.1407	³	59%
Hospitalisation days per 28 days increased by 20%		0.1407	⁶	-56%
Hospitalisation days per 28 days decreased by 20%		0.1407	³	56%
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)				
Health state utilities from TRANSFORM-2 using Canadian value set		0.1255	⁴	12%
Utility values from Yrondi 2021 (0.41; 0.63; 0.80; 0.90)		0.1554	²	-9%
Utility values from NICE committee papers (0.417; 0.764; 0.866; 0.866)		0.1478	²	-5%
Utility values used in Ross (2019) based on Sapin (2004) (0.58; 0.72; 0.85; 0.85)		0.0882	³	59%
Impact of removing the 12 months maximum treatment duration of esketamine treatment				
Maximum treatment cap removed		0.1642	⁷	151%
Alternative administration/monitoring costs for esketamine (submission base case \$228.70 per administration)				
Increase by 50%		0.1407	³	+69%
Decrease by 50%		0.1407	⁶	-69%

Source: Table 330, p120 of the resubmission and 'Attachment 3.3 - Esketamine TRD CE model' spreadsheet provided with the resubmission.

Abbreviations: ESK, esketamine; MDE, major depressive episode; NICE, National Institute for Health and Care Excellence; OAD, oral anti-depressant.

The redacted values correspond to the following ranges:

- ¹ \$25,000 to < \$35,000
- ² \$15,000 to < \$25,000
- ³ \$35,000 to < \$45,000
- ⁴ \$25,000 to < \$35,000
- ⁵ \$115,000 to < \$135,000
- ⁶ \$5,000 to < \$15,000
- ⁷ \$55,000 to < \$75,000
- ⁸ \$45,000 to < \$55,000
- ⁹ \$155,000 to < \$255,000

6.63 The results were most sensitive to the probability of achieving remission or response at treatment induction, transition probabilities in the maintenance period, the time horizon, health care resource use (particularly use and cost of hospitalisations), the effectiveness of the subsequent treatment mix, the probability of the risk of recurrence from the recovery health state, the esketamine dosing schedule in the maintenance period (weekly/fortnightly), and utility values. Overall, the cost-effectiveness of esketamine nasal spray is highly uncertain.

- 6.64 The ESC noted the sensitivity analysis removing the 12 month treatment cap resulted in an increase in the ICER from \$25,000 to < \$35,000/ QALY to \$55,000 to < \$75,000/ QALY. The ESC noted including the 12 month treatment cap resulted in a 66% decrease in incremental costs (from \$| to \$|) and a 14% decrease in incremental benefits (from 0.1642 QALYs to 0.1407 QALYs). More specifically the 12 month treatment cap reduced the cost of esketamine in the model from \$| to \$| (36% reduction) which is larger than the reduction in incremental QALYs (14%). The ESC noted this may reflect that the use of esketamine beyond 12 months is less cost-effective than the use in the initial 12 months, however the impact of the 12 month treatment cap on efficacy was unknown and hence the magnitude of the reduction in the ICER associated with the treatment cap (60%) was highly uncertain.
- 6.65 The ESC considered some of the issues with the economic model raised in the July 2022 advice had been addressed (in part or in full), including more conservative maintenance of treatment effects (by applying the transition risks of the PBO + OAD group to patients who discontinue esketamine), removal of monitoring costs from the placebo + OAD arms of the model, the addition of adverse event costs for hypertension and bladder-related events and changes to how adverse event costs and disutilities were applied (see paragraph 6.41). The ESC considered the following inputs remained uncertain:
- Hospitalisations avoided with esketamine treatment decreased in the current resubmission (paragraph 6.55 refers) however the uncertain applicability of the source data (Denee 2021) to the Australian setting remained. The model generates a large number of hospitalisations over the time horizon (46.5 days for esketamine and 52.3 days for placebo);
 - Use of the STAR*D study to inform some of the transition probabilities given it may not reflect contemporary practice;
 - The 5 year time horizon, noting a median 18 to 19 weeks of exposure to esketamine in the SUSTAIN-1 trial;
 - The EQ-5D-5L utility values which were mapped to a UK value set.
 - The frequency of dosing and doses likely to be used in practice (paragraph 6.50 refers); and
 - The administration and monitoring costs. The ESC considered it was unclear what the likely true cost of administration and monitoring would be in practice, and noted the ICER was moderately sensitive to an increase or decrease of 50% of these assumed costs (refer Table 16). The ESC noted the administration and monitoring costs contributed to 35% of the esketamine drug and administration cost (see paragraph 6.48) which is why the ICER is sensitive to assumptions regarding this cost.

Drug cost/patient/treatment phase

Table 17: Drug costs per patient for esketamine

Value	Esketamine trials ¹	Economic model	Financial estimates
ESKETAMINE DRUG COSTS			
Acute treatment phase (Weeks 1-4)			
Mean dose	TRANSFORM-2: 70.8 mg (2.530×28 mg devices) TRANSFORM-3: 59.8 (2.136×28 mg devices)	68.9 mg ² (2.462×28 mg devices)	70.8 mg ³ (2.530×28 mg devices)
Unit cost (DPMQ) per 28 mg device ⁴	-	\$	\$
Average sessions per week	TRANSFORM-2: 1.851 TRANSFORM-3: 1.844	1.850 ²	-
Adherence	Not reported	Not explicitly modelled	92.5%
Cost/patient/4-week period	-	\$	\$
Persistence	TRANSFORM-2: 84.5% TRANSFORM-3: 86.1%	100%	100%
Maintenance phase (Week 5+)			
Mean dose	Weeks 5 - 40: 72.9 mg (2.605×28 mg devices) ⁵ Week 41+: 72.0 mg (2.571×28 mg devices) ⁵	Weeks 5 - 40: 72.9 mg (2.605×28 mg devices) Week 41+: 72.0 mg (2.571×28 mg devices)	Week 5-8: 70.8 mg (2.530×28 mg devices) Week 9+: 72.9 mg (2.605×28 mg devices)
Unit cost per 28 mg device	-	\$	Week 5-8: \$ ⁸ Week 9-52: \$ ⁸
Average sessions per week	Weeks 5 - 8: 0.992 ⁶ Weeks 9 - 40: 0.711 ⁶ Week 41+: 0.675 ⁶	Weeks 5 - 8: 0.992 Weeks 9 - 40: 0.711 Week 41-52: 0.675	-
Adherence	Not reported	Not explicitly modelled	Weeks 5 - 52: 73.83% Weeks 53+: 67.46%
Cost/patient/4-week period ⁷	-	Weeks 5 - 8: \$ Weeks 9 - 40: \$ Week 41-52: \$	Weeks 5 - 8: \$ Weeks 9-52: \$
OAD COSTS			
Cost/patient/4-week period	-	\$17.13 ⁸	Not included
Adherence	Varies by treatment	100%	Not included
Persistence	TRANSFORM-2: 89.2% TRANSFORM-3: 90.9%	100%	Not included

Source: '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.

Abbreviations: DPMQ, dispensed price for maximum quantity.

¹ TRANSFORM-2 and TRANSFORM-3 for acute treatment phase and SUSTAIN-1 for maintenance phase.

² Based on a weighted average of TRANSFORM-2 and -3 data, based on the proportion of the Australian population aged <65 (83%) and ≥65 (17%) years.

³ Based on TRANSFORM-2 data

⁴ Based DPMQs in Section 3 and a weighted Public/Private (20%/80%) hospital split;

⁵ assuming a 7.6%/43.4%/48.9% split between 28 mg, 56 mg and 84 mg doses.

⁶ The source data could not be verified during the evaluation.

⁷ Weeks 5-8 assuming a 7.6%/43.4%/48.9% split between 28 mg, 56 mg and 84 mg doses. Weeks 9-52 assuming a 3.1%/14.5%/22.3% split across 28 mg, 56 mg, and 84 mg weekly doses, and assuming a 4.6%/21.9%/33.6% split across 28 mg, 56 mg, and 84 mg fortnightly doses⁸ Average cost of PBS-listed antidepressants weighted by market share according to PBS data from January 2022 to December 2022.

Estimated PBS usage & financial implications

6.66 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. Key changes in the financial model in the resubmission include:

- Analysis of the 100% PBS dataset conducted by the DUSC Secretariat to identify the unique number of treatment resistant depression (TRD) patients in the third-line plus setting (3L+)
- Extrapolating growth in prevalence using a parametric function, rather than using an annual rate derived from survey data
- Limiting maximum treatment duration to a maximum of 12 months per episode
- Inclusion of the 28 mg dose for patients aged 65 years or older
- Removing GP prescribers and allowing psychiatrist prescribing only
- Including fortnightly dosing frequency for continuing patients beyond week 9 of therapy
- Including retreatment with esketamine in a subsequent episode of MDD for a proportion of patients.

6.67 Table 18 summarises the key inputs for the financial estimates.

Table 18: Key inputs for financial estimates

Data	Value applied and source	Comment
Number of patients meeting criteria for TRD	DUSC Secretariat PBS 100% sample analysis. 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 from January 2018-September 2022 (57,227 in Year 1)	It is unclear whether the method used to conduct the 100% PBS sample analysis captured all relevant patients with TRD and those with TRD initiating a new treatment, as non-pharmaceutical interventions and diagnosis information are not captured. 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	A logarithmic function was applied to the 100% PBS trend data from 2019 to 2021 to extrapolate growth of TRD. The average annual growth rate applied ranges from 2.1% - 4.8%	The availability of a new treatment may result in an increase in patients initiating a new therapy. The growth rate of this population over time is highly uncertain.
Prescription setting	100% PBS sample analysis. The PBS 100% patient line combination data shows that between 2019 to 2021, 18.6% to 19.6% of all patient initiations occurred in the psychiatry setting, with the average across the 3 years being 19.1%. The remaining patient initiations occurring within GP or other settings, are not included as part of the eligible patient population. No growth rate in psychiatrist prescribing was applied.	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=600). At the time of submission, these patients had been on treatment for an average of 15.17 weeks (or 3.5 months). This was deducted from the maximum treatment duration of 52 weeks (or 12 months), and as such these patients are anticipated to be on PBS-subsidised treatment for approximately 36.83 weeks (or 8.5 months) following listing. The adherence rate and doses per period were assumed to align with that of the continuing (week 9+) groups as these patients have already been initiated prior to PBS listing.	The total number of patients who are self-funded and may be eligible for PBS treatment, or who are currently treated using off-label ketamine and may switch following listing, is unclear and may be greater than that estimated by the sponsor.
Uptake rates	Uptake rates vary in line with number of prior treatment failure, and time since listing.	The uptake of esketamine is considered highly uncertain. 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, and potential out-of-pocket costs associated with administration in the absence of any alternative funding arrangements.
Proportion of patients who retreat with esketamine in subsequent episodes of TRD	Sponsor assumption (assumed 40% of patients who initiated would receive retreatment for a subsequent episode of MDD). Factored into uptake rates starting in the 3rd year of the financial model (i.e. 2 years after the initial episode).	There is no clinical data to support retreatment, however patients who had previously responded to esketamine may benefit from retreatment in subsequent episodes. The assumed proportion of patients who elect retreatment may be under- or overestimated, as patients who achieve response or remission with an agent in a prior episode of TRD or MDD are likely to trial this agent in subsequent episodes. This should have been modelled as a proportion of responders/remitters and risk of subsequent episodes of TRD, rather than added into subsequent lines of therapy with uptake rate.
Dose distribution	Distribution derived from the proportion of patients aged 18-64 years, and 65 years and over in the DUSC Secretariat dataset (92.4%, and 7.6% respectively). This informed the split between the 28 mg dose and the 56 mg/84 mg doses. 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). Use in the SUSTAIN trial was used to inform the mean daily doses in the maintenance phases (2.6053). 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 dose distribution among the PBS population may differ from the distribution in the clinical trial setting. The dose split used to define the elderly population, based on the population split in the 100% PBS dataset, differed from the population split used in the economic model (based on ABS population projections; 17.1% aged 65 years and older). The source data used to derive the average devices per session could not be verified.
Dose frequency	Derived from the proportion of patients maintained on either weekly or fortnightly dosing in the SUSTAIN-1 trial.	Dose frequency in clinical practice may differ from that observed in the clinical trial setting.

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Data	Value applied and source	Comment
Duration	Maximum duration of treatment limited to 1 year (52 weeks), to align with proposed restriction.	The maximum treatment duration aligns with the proposed restriction, but it is unclear what the clinical impact of this may be in practice.
Adherence	92.5% for initial treatment, and 73.8% for continuing treatment. 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.127-128; Section 4.3, p.128-140 of the resubmission; 'Attachment 4.1 Esketamine UCM March 2023 Resubmission-BASE' Excel workbook

Abbreviations: AEMP, approved ex-manufacturer price; GP, general practitioner; MDD, major depressive disorder; TRD, treatment-resistant depression; Yr, Year.

6.68 The estimated net cost of listing esketamine on the PBS/RPBS for TRD is summarised in Table 19 below.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of TRD patients in third line setting and over	█ ¹	█ ¹	█ ²	█ ²	█ ²	█ ²
Patients initiated in the psychiatry setting (19.1%)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Grandfathered patients	█ ⁴	-	-	-	-	-
Total new patients available for esketamine treatment	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Proportion of patients electing treatment (average uptake across lines of prior therapies without retreatment)	26%	34%	41%	45%	45%	45%
Proportion of patients assumed to retreat in subsequent episodes	-	-	8%	11%	13%	16%
Uptake of esketamine across all lines, including retreatment	26%	34%	49%	55%	58%	61%
Total patients treated with esketamine (including grandfathered patients and retreated patients)	█ ⁴	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Total patients treated with esketamine (July 2022)	█ ⁴	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Total scripts	█ ⁶	█ ⁶	█ ⁷	█ ⁸	█ ⁸	█ ¹
Total scripts (July 2022)	█ ³	█ ⁶	█ ⁸	█ ¹	█ ¹	█ ²
Net cost to the PBS/RPBS	\$█ ⁹	\$█ ¹⁰	\$█ ¹¹	\$█ ¹³	\$█ ¹³	\$█ ¹⁴
Net PBS/RPBS costs (July 2022)	\$█ ⁹	\$█ ¹¹	\$█ ¹²	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁵

Source: Table 4-2, p134; Table 4-3, p135; Table 4-6, p138; Table 47, p138; Table 49, p140; Table 410, p141 of the resubmission; 'Attachment 4.1 Esketamine UCM March 2023 Resubmission (BASE)' spreadsheet.

The redacted values correspond to the following ranges:

- ¹ 50,000 to < 60,000
- ² 60,000 to < 70,000
- ³ 10,000 to < 20,000
- ⁴ 500 to < 5,000
- ⁵ 5,000 to < 10,000
- ⁶ 20,000 to < 30,000
- ⁷ 30,000 to < 40,000
- ⁸ 40,000 to < 50,000

⁹ \$30 million to < \$40 million

¹⁰ \$40 million to < \$50 million

¹¹ \$60 million to < \$70 million

¹² \$90 million to < \$100 million

¹³ \$70 million to < \$80 million

¹⁴ \$80 million to < \$90 million

¹⁵ \$100 million to < \$200 million

- 6.69 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 \$80 million to < \$90 million in Year 6, an estimated net cost of \$300 million to < \$400million over the first six years of listing.
- 6.70 The ESC noted removing the assumption regarding retreatment resulted in an estimated net cost to the PBS/RPBS of \$60 million to < \$70 million in Year 6 and an estimated net cost of \$300 million to < \$400 million over the first six years of listing.
- 6.71 There were a number of potential issues associated with the estimation of use and financial impact of PBS listing esketamine nasal spray:
- The PBAC previously considered the estimated number of patients likely to initiate treatment with esketamine was not well justified and likely to be substantially overestimated (para 7.13, esketamine PSD, July 2022 PBAC meeting). Compared with the July 2022 resubmission, estimated patient numbers in the current resubmission were greater in most years. This is due to the use of the 100% PBS dataset to determine patients at 3rd line and above, whilst the previous analysis restricted included patients to 3rd line only and the inclusion of assumptions regarding retreatment.
 - 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 (para 6.68, esketamine PSD, July 2022 PBAC meeting).
 - The net financial impact is reduced in the current resubmission compared with the July 2022 resubmission, primarily because duration of treatment is limited to a maximum of 12 months in the financial model. Although a reduced treatment duration may address some of the financial uncertainty associated with listing esketamine, there is significant clinical uncertainty remaining about appropriate duration of treatment and withdrawing treatment with esketamine in stable responders or remitters.
 - 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 adherence (para 6.68, esketamine PSD, July 2022 PBAC meeting). Access and adherence to treatment may also be constrained by funding mechanisms for administration and monitoring, particularly if these costs are met by patients.

- 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 6.68, esketamine PSD, July 2022 PBAC meeting).
- 6.72 The PSCR (pg. 3) noted the likely extent of use of esketamine was discussed at the stakeholder meeting in February 2023, where the stakeholders present considered the overall approach used in the July 2022 re-submission was 'reasonable'. The PSCR also noted that while the uptake rate was not specifically discussed at the stakeholder meeting, argued the uptake rate applied in the submission was reasonable. The PSCR reiterated the uptake of esketamine was assumed to be highest in patients who have failed more treatment options. The ESC considered the likely uptake of esketamine was highly uncertain (see paragraph 6.67).
- 6.73 The Pre-PBAC Response argued that market research undertaken by the Sponsor indicated only a small proportion of TRD patients were currently receiving treatment with ketamine, and argued it was unlikely patients would switch if they were already receiving ketamine.
- 6.74 The ESC recalled the PBAC had previously considered the number of treated patients to be substantially overestimated (paragraph 7.13, esketamine PSD, July 2022 PBAC meeting). The ESC noted the uptake rates (excluding retreatment) applied in the resubmission were only slightly lower than the previous assumptions in the psychiatry setting (26% in Year 1 to 45% in Year 6 compared to 30% in Year 1 and 50% in Year 6). The ESC noted there are a number of factors including access to accredited treatment centres, the burden of twice weekly, weekly, or fortnightly appointments, and the lack of a clear funding mechanism for the administration and monitoring of treatment and considered uptake was likely to be lower than predicted. The ESC considered that, given the revised patient estimates are higher in the resubmission and issues that may limit access remain, a reduction in uptake rates may be appropriate. The Pre-PBAC Response argued the uptake rates were reasonable and appropriate given the high unmet need for a novel therapy for the treatment of TRD.
- 6.75 The ESC noted re-treatment assumptions were included in the utilisation estimates and considered the question of whether re-treatment should be supported, and any limitations remained a matter for PBAC. The ESC noted that, as the economic model only included one treatment course over the 5 year time horizon, the cost effectiveness of re-treatment has not been considered.

Quality Use of Medicines

- 6.76 The sponsor noted that esketamine is the first nasal spray medication listed on the ARTG for adults with TRD. As a Schedule 8 drug with a unique mode of delivery, the sponsor has developed an appropriate QUM strategy and accompanying activities for esketamine.
- 6.77 The resubmission stated that patients will only be able to access esketamine nasal spray under a controlled clinical model of care at sponsor accredited esketamine treatment sites, which must meet a strict set of criteria to be eligible to be set up as an esketamine treatment site which includes maintaining appropriate facilities for patient administration and monitoring, access to emergency care and pharmacy. The sponsor noted that as of March 2023, 78 sites have been accredited (30 in March 2022).
- 6.78 The ESC considered the current model of delivery, being restricted to psychiatrists in only a limited number of sponsor-accredited facilities (with very few public hospital based sites) was likely to result in inequities in treatment access. Furthermore, the ESC considered the lack of a clear funding mechanism for the administration and monitoring of esketamine treatment was likely to significantly exacerbate equity of access issues, as these out of pocket costs may be substantial and some patients who would otherwise be eligible for treatment with esketamine will be unable to afford and/or access treatment.
- 6.79 The Pre-PBAC Response argued the equity issues raised by the ESC relate to the health system broadly, where there is an acknowledged shortage of psychiatrists, especially for rural and remote patients. It was also stated that while the current number of public hospital based administration sites was low, anticipated this would increase with a PBS listing for esketamine.

Financial Management – Risk Sharing Arrangements

- 6.80 The resubmission noted potential uncertainty in the estimated utilisation of esketamine, including the number of patients eligible for treatment, and the expected 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.
- 6.81 The total value of the subsidisation cap over the 5-year period represents a 37% reduction from that proposed in the July 2022 resubmission. In addition, the resubmission proposed a reimbursement of $\frac{1}{2}$ % for any potential use above specified subsidisation caps. The ESC considered it was unclear whether a $\frac{1}{2}$ % rebate would be sufficient to address the significant uncertainties around the size of the eligible and treated populations, and uncertainties associated with the flexible dosing of esketamine.
- 6.82 Table 20 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	\$ ¹	\$ ²	\$ ³	\$ ⁴	\$ ⁴
Number of scripts in subsidisation caps	⁷	⁷	⁸	⁹	⁹
Number of devices in subsidisation caps	¹⁰	¹¹	¹²	¹³	¹³
July 2022 subsidisation caps ¹	\$ ¹	\$ ³	\$ ⁵	\$ ⁶	\$ ⁶

Source: Table 419, p147 of the resubmission; Table 4-13, p250 of the July 2022 resubmission.

¹ The July 2022 resubmission proposed a rebate of █% for any potential use above the subsidisation cap.

The redacted values correspond to the following ranges:

¹ \$30 million to < \$40 million

² \$40 million to < \$50 million

³ \$60 million to < \$70 million

⁴ \$70 million to < \$80 million

⁵ \$90 million to < \$100 million

⁶ \$100 million to < \$200 million

⁷ 20,000 to < 30,000

⁸ 30,000 to < 40,000

⁹ 40,000 to < 50,000

¹⁰ 100,000 to < 200,000

¹¹ 200,000 to < 300,000

¹² 300,000 to < 400,000

¹³ 400,000 to < 500,000

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of esketamine for the treatment of patients with treatment resistant depression (TRD). The PBAC noted, based on the stakeholder meeting, that it was proposed that a treatment course with esketamine be limited to a maximum of 12 months duration. The PBAC noted this was the key change in the resubmission which flowed into the economic and financial models. The PBAC noted the economic model included a single course of treatment however, the model time horizon of 5 years was retained. The PBAC considered that while it was uncertain how many patients would receive more than one course of treatment over a 5-year period, it was likely to be a high proportion of patients. The PBAC considered it was unlikely that esketamine would be cost-effective if additional courses of treatment were required within the 5-year period. The PBAC considered the financial estimates were overestimated due to optimistic assumptions regarding the uptake of esketamine in the context of likely barriers to access, although also noted the assumption of an additional treatment course in 40% of patient likely underestimated use.

7.2 The key reason for this outcome was due to the economic evaluation.

7.3 The PBAC noted and welcomed the input from individuals, clinicians and organisations, with comments highlighting the severe impact of TRD on daily life, the benefits of esketamine (and ketamine) in improving daily functioning and the importance of restoring hope to patients with TRD. The PBAC recalled this input was

similar to that received for its July 2021 and July 2022 consideration. The PBAC noted some of the consumer comments specifically referred to reduced suicidal ideation as a benefit of esketamine; however, patients with current or recent suicidal ideation were excluded from the clinical trials.

- 7.4 The PBAC noted input from the stakeholder meeting that the appropriate duration of treatment with esketamine remains uncertain, but it would be appropriate to allow for a maximum treatment duration of 12 months per patient. The PBAC noted the stakeholders considered there needed to be some flexibility regarding the maximum 12-month treatment duration and allowing retreatment may be appropriate for some patients after a reasonable period of time off treatment.
- 7.5 The PBAC reaffirmed its previous view that there is a moderate to high clinical need for additional treatment options for TRD.
- 7.6 The PBAC noted the proposed restriction criteria addressed a number of the issues raised during its previous consideration and as part of the stakeholder meeting, including limiting prescribing to psychiatrists, revision to be consistent with the rTMS MBS criteria and inclusion of a caution regarding use in specific patient populations that were excluded from the clinical trials.
- 7.7 The proposed restriction criteria limited esketamine to a maximum duration of 12 months per episode as supported by the stakeholder meeting. The PBAC considered there was a number of uncertainties associated with this, including how episodic treatment would be managed, the impact of ceasing treatment in responders and how to implement use beyond 12 months for some patients (as discussed in paragraphs 2.2 and 3.5).
- 7.8 The PBAC agreed with the input from the stakeholder meeting that it was appropriate that some patients who responded to esketamine in a depressive episode would use it again if they relapsed or experienced a new depressive episode. The PBAC considered that implementing an appropriate pathway for retreatment (including addressing the issues raised in paragraph 3.6) would require further consideration. The PBAC noted the financial estimates assumed 40% of patients would require retreatment and it considered that while it was uncertain how many patients would receive more than one course of treatment, it was likely to be a high proportion of patients.
- 7.9 The PBAC recalled its previous view that the nominated comparator of a newly initiated OAD alone was reasonable (paragraph 7.7, esketamine PSD, July 2022).
- 7.10 The PBAC noted no new clinical evidence was presented and the resubmission was supported by three induction (TRANSFORM-1/2/3) and three maintenance (SUSTAIN-1/2/3) studies. The PBAC recalled its previous view that the claim of superior comparative effectiveness may be reasonable, although the magnitude and clinical importance of the observed benefits was uncertain. The PBAC noted there is a body of evidence of effectiveness for intravenous and subcutaneously administered

racemic ketamine (paragraph 4.8 refers), which does provide additional data to support the use of esketamine. The PBAC noted the inclusion of a 12-month treatment cap per episode increased the uncertainty regarding the magnitude of clinical benefit that would be observed in clinical practice.

- 7.11 The PBAC recalled its previous view that a claim of inferior comparative safety compared to a new OAD alone was reasonable, however remained concerned there was limited longer-term safety data (paragraph 7.9, esketamine PSD, July 2022 PBAC meeting). The PBAC noted input received via Consumer Comments that the adverse event profile (dissociation, in particular) can be concerning for some patients and considered this may result in them needing additional care.
- 7.12 The PBAC noted the base case economic model in the resubmission resulted in an incremental cost effectiveness ratio (ICER) of \$25,000 to < \$35,000 per quality adjusted life year (QALY). The PBAC noted the economic model included a single course of treatment with an average duration of 5.5 months (based on a maximum treatment duration of 12 months), compared to 11.4 months in the previous resubmission (with no cap on the treatment duration); however, the model time horizon of 5 years was retained. The PBAC noted that if the time horizon was reduced to 12 months (to reflect a single treatment cycle) the ICER increased to \$115,000 to < \$135,000 per QALY. The PBAC also noted the cap on the treatment duration was a model driver with the ICER increasing to \$55,000 to < \$75,000 per QALY when removed (with the 5-year horizon retained). The PBAC considered that while it was uncertain how many patients would receive more than one course of treatment, it was likely to be a high proportion of patients. The PBAC considered it was unlikely that esketamine would be cost-effective if additional courses of treatment were required within the 5-year period.
- 7.13 The PBAC agreed with the ESC that some other inputs to the economic model, including assumed rates of hospitalisation and assumptions around administration and monitoring costs remained uncertain and likely favoured esketamine.
- 7.14 Overall, the PBAC considered esketamine was unlikely to be cost-effective.
- 7.15 The PBAC noted the estimated net cost of listing esketamine on the PBS/RPBS was \$30 million to < \$40 million in Year 1 of listing, increasing to \$80 million to < \$90 million in Year 6, an estimated net cost of \$300 million to < \$400 million over the first six years of listing. The PBAC considered the uptake of esketamine in new patients was likely overestimated (26% in Year 1, 45% in Year 6) and while the uptake in subsequent episodes was uncertain, considered it was likely underestimated (40% of patients who initiated treatment would receive retreatment). The PBAC recalled it had previously 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 (paragraph 7.13, esketamine PSD, July 2022 PBAC meeting).
- 7.16 The PBAC considered any resubmission needs to address the outstanding issues

related to the implementation, extent and cost effectiveness of use beyond the 12-month treatment cap and retreatment. The PBAC noted the uncertainties regarding the use of esketamine, which impact the cost-effectiveness and financial estimates, could potentially be addressed with a managed access program.

7.17 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 is disappointed that the PBAC did not recommend esketamine but welcomes the PBAC's recognition of the need for treatment options for TRD, their understanding of the severe impact of TRD on daily life, and their acceptance of the clinically meaningful benefits of esketamine. Janssen believes in the benefit that esketamine provides patients and hopes to have this treatment available through the PBS. Janssen will consider how we can resolve the remaining uncertainties so that Australian patients can access esketamine in a timely way.