5.03 ESKETAMINE, Nasal spray solution 28 mg, Spravato®, Janssen-Cilag Pty Ltd.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drugs), Authority Required (telephone/electronic) listing for esketamine nasal spray for the treatment of treatment resistant depression (TRD), initiated in conjunction with a newly prescribed oral antidepressant (OAD).

1.2 Listing was requested on a cost-effectiveness basis versus a newly prescribed OAD alone.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Adult patients with treatment resistant depression, 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.
Intervention	Esketamine nasal spray is to be initiated in conjunction with a newly initiated oral antidepressant. 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. Maintenance phase: • Weeks 5-8: 56 mg or 84 mg administered once weekly. • From week 9: 56 mg or 84 mg administered once weekly or every two weeks depending on dose and frequency that best maintains remission/response. Patients should continue therapy to maintain remission/response and must discontinue therapy if they relapse (i.e., a clinically significant worsening of symptoms). Patients over 65 years of age receive a dose of 28 mg during all phases.
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, health related 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 effectiveness and inferior in terms of safety compared with placebo plus a newly initiated oral antidepressant.

Source: Table 1-1 of the submission

2 Background

Registration status

2.1 Esketamine nasal spray was registered on the 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). Esketamine is to be initiated in conjunction with a newly initiated oral antidepressant'.

2.2 Esketamine was originally rejected by the TGA delegate on 10 September 2020, on the basis of the design of the pivotal trials; the failure of some of the pivotal trials to achieve the primary efficacy outcome; the magnitude of the safety risk management issues associated with the use of the product; and the potential for misuse/diversion of the product.

2.3 The sponsor appealed the decision on 1 December 2020 and the TGA delegate revoked the initial decision and made a new decision in substitution, to register esketamine on 27 January 2021. The substituted decision to register the product was made on the basis that the quality, safety and efficacy of the product for the purposes for which it is to be used had been satisfactorily established.

2.4 The ESC noted that, in addition to the indication in paragraph 2.1, esketamine was indicated in Europe for "adults with a moderate to severe episode of major depressive disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency". The ESC noted this indication was based on the ASPIRE-1 (NCT03039192) and ASPIRE-2 (NCT03097133) studies.

Clinical expert advice

2.5 Prior to the ESC meeting, the PBAC sought clinical advice regarding the likely place of esketamine in the treatment of TRD. The clinicians consulted considered:

- The proposed definition of TRD in the requested listing (failed to respond to at least two different antidepressants) did not reflect how treatment resistant depression would be defined in practice in Australia, and that other interventions for which longer term safety data are available, should be considered or trialled prior to considering treatment with esketamine;
- The requirement to commence a new antidepressant with esketamine is clinically inappropriate;
- There should be extensive monitoring requirements associated with administering esketamine given the potential adverse events which can be severe;
- The appropriate treatment duration is unclear and there is potential risk of ongoing use;
- There is a significant risk of use in indications other than TRD, including major depressive disorder (MDD), post-traumatic stress disorder, anxiety, obsessive compulsive disorder, chronic pain and acute suicidality.

2.6 The ESC noted this advice and considered the submission positioned esketamine inappropriately early in the treatment algorithm, which impacted on the comparator, interpretation of the clinical evidence, economic evaluation and financial estimates.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (effective) dispensed price for maximum quantity	Proprietary name and manufacturer
Initial treatment/Induction (Treatment weeks 1-4)					
ESKETAMINE Nasal spray device, 28 mg, 1	8	8	0	Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])	Spravato®, Janssen-Cilag Pty Ltd
ESKETAMINE Nasal spray device, 28 mg, 2	8	16	0	Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])	Spravato®, Janssen-Cilag Pty Ltd
ESKETAMINE Nasal spray device, 28 mg, 3	8	24	0	Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])	Spravato®, Janssen-Cilag Pty Ltd
Continuing treatment/~~Maintenance period 1 (Treatment weeks 5-8)~~					
ESKETAMINE Nasal spray device, 28 mg, 1	4	4	~~0~~ *2*	Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])	Spravato®, Janssen-Cilag Pty Ltd
ESKETAMINE Nasal spray device, 28 mg, 2	4	8	~~0~~ *2*	Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])	Spravato®, Janssen-Cilag Pty Ltd
ESKETAMINE Nasal spray device, 28 mg, 3	4	12	~~0~~ *2*	Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])	Spravato®, Janssen-Cilag Pty Ltd
~~Continuing treatment/Maintenance period 2 (Treatment week 9 onwards)~~					
~~ESKETAMINE Nasal spray device, 28 mg, 1~~	~~4~~	~~4~~	~~2~~	~~Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])~~	~~Spravato®, Janssen-Cilag Pty Ltd~~
~~ESKETAMINE Nasal spray device, 28 mg, 2~~	~~4~~	~~8~~	~~2~~	~~Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])~~	~~Spravato®, Janssen-Cilag Pty Ltd~~
~~ESKETAMINE Nasal spray device, 28 mg, 3~~	~~4~~	~~12~~	~~2~~	~~Public Hospital: $[redacted] ($[redacted]) Private Hospital/Community Access: $[redacted] ($[redacted])~~	~~Spravato®, Janssen-Cilag Pty Ltd~~

Category / Program:	Section 100 – Highly Specialised Drugs Program PBS Esketamine nasal spray Program
Prescriber type:	Medical Practitioners
Severity:	Moderate to severe
Condition:	Major depressive disorder
PBS Indication:	Treatment resistant depression

Treatment phase:	Initial treatment/induction
Restriction:	Authority Required – Telephone, Electronic
Treatment criteria:	Psychiatrists or under the supervision of a psychiatrist
Clinical criteria:	Patient must have received and not achieved an adequate response to at least two different antidepressant medications at adequate doses and duration to treat the current moderate to severe depressive episode. AND Patient must have moderate to severe depression symptoms AND Treatment must be used in combination with a newly initiated oral antidepressant AND Patient must not receive more than 4 weeks of treatment under this restriction
Population criteria:	Patients must be aged 18 years or greater
Prescriber Instructions:	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 professional following administration in a healthcare facility
Administrative Advice:	Care must be taken to comply with the provisions of the state/territory law for prescribing this drug

Category / Program:	Section 100 – Highly Specialised Drugs Program PBS esketamine nasal spray program
Prescriber type:	Medical Practitioners
Severity:	Moderate to severe
Condition:	Major depressive disorder
PBS Indication:	Treatment resistant depression
Treatment phase:	Continuing treatment~~/maintenance period 1~~
Restriction:	Authority Required – Telephone, Electronic
Treatment criteria:	Psychiatrists or under the supervision of a psychiatrist
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have responded adequately *during the initial treatment phase* ~~to the treatment by week 4 for continuing~~ treatment AND Patient must not receive more than 4 weeks of treatment under this restriction. *AND* *Patient must not have relapsed while receiving treatment with this drug for this condition during subsequent treatment cycles.*
Population criteria:	Patients must be aged 18 years or greater
Prescriber Instructions:	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 professional following administration in a healthcare facility
Administrative Advice:	Care must be taken to comply with the provisions of the state/territory law for prescribing this drug

~~**Category / Program:**~~	~~Section 100 – Highly Specialised Drugs Program~~ ~~PBS esketamine nasal spray program~~
~~**Prescriber type:**~~	~~Medical Practitioners~~
~~**Severity:**~~	~~Moderate to severe~~
~~**Condition:**~~	~~Major depressive disorder~~

~~**PBS Indication:**~~	~~Treatment resistant depression~~
~~**Treatment phase:**~~	~~Continuing treatment/maintenance period 2~~
~~**Restriction:**~~	~~Authority Required – Telephone, Electronic~~
~~**Treatment criteria:**~~	~~Psychiatrists or under the supervision of a psychiatrist~~
~~**Clinical criteria:**~~	~~Patient must have previously received PBS-subsidised treatment with this drug for this condition~~ ~~AND~~ ~~Patient must not have relapsed while receiving treatment with this drug for this condition~~
~~**Population criteria:**~~	~~Patients must be aged 18 years or greater~~
~~**Prescriber Instructions:**~~	~~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 professional following administration in a healthcare facility~~
~~**Administrative Advice:**~~	~~Care must be taken to comply with the provisions of the state/territory law for prescribing this drug~~

3.2 The submission proposed an effective and published price for esketamine nasal spray with a special pricing arrangement.

3.3 The sponsor requested that esketamine nasal spray be administered via a special Section 100 program, similar to the program implemented for botulinum toxin medicines (Section 100 Botulinum Toxin Program). The special program would be implemented to manage the administration requirements for esketamine nasal spray, including the need for supervised dosing and post-administration monitoring, and to limit the number of co-payments that a patient would be required to pay to one in any given monthly period. It is unclear how the establishment of a new Section 100 program would facilitate the supervised dosing and post-administration monitoring requirements of esketamine or how it would address the number of co-payments a patient would pay per month.

3.4 The dispensing and storage of esketamine nasal spray will be subject to a number of requirements, including:

- Patients are not permitted to handle the drug until ready for administration in the clinic.
- Administration of esketamine nasal spray must be under the supervision of a healthcare professional on a bi-weekly, weekly, or fortnightly basis, patient dependent. The sponsor stated that in order to avoid disadvantaging any patient, the eventual arrangement for the delivery of esketamine nasal spray should not result in more than one monthly PBS co-payment, should include timely script delivery, and avoid patients having to pay additional consultation fees to see a physician and/or nurse for each administration. The treatment model which would allow these requirements to be met in Australian clinical practice was unclear in the submission. The submission stated that the use of esketamine nasal spray will most likely occur in private psychiatry practices, but it is unclear whether private psychiatry practices will have the staffing and infrastructure available to support

the administration and monitoring requirements, and what the potential costs to patients would be.

- Schedule 8 drug administration and State/Territory requirements to be fulfilled.

3.5 The Pre-Sub-Committee Response (PSCR) stated the sponsor is currently working with treatment sites (private and public psychiatry clinics and hospitals) to ensure that health care professionals (HCPs) (psychiatrists, nurses and other staff) are trained and the required facilities are in place for the safe use of esketamine, in accordance with the product information (PI) and as required by the TGA Risk-Management Plan. The PSCR stated that following prescription by a psychiatrist (or a medical practitioner in consultation with a psychiatrist) at the treatment site, the prescription is delivered to a nominated (onsite) pharmacy. The dispensed drug is then securely delivered to and stored in a S8 medication safe at the treatment site. Upon presentation at the treatment site patients have a pre-administration check by the onsite psychiatrist. Next, the patient self-administers the drug and remains in the room for monitoring in accordance with the PI, all completed under the supervision of an HCP who in most instances will be a mental health nurse. The patient is then assessed for release, which includes the patient having organised transport as they cannot drive until after an overnight restful sleep.

3.6 Treatment with esketamine nasal spray is to be initiated in conjunction with a new OAD. The proposed restriction does not specify which oral agents should be initiated alongside esketamine nasal spray. Only four oral antidepressants were allowed in the induction clinical trials, two of which were selective serotonin reuptake inhibitors (SSRIs) and two of which were serotonin and norepinephrine reuptake inhibitors (SNRIs). The impact of allowing any OAD, especially those with different mechanisms of action, is unclear. In other jurisdictions, including the EMA and Canada, esketamine is approved for use only in conjunction with SSRIs and SNRIs. The PSCR noted the sponsor was amenable to restricting the newly initiated OAD alongside esketamine to the SSRI and SNRI classes. The ESC considered that, while it was consistent with the TGA indication and the presented clinical evidence for esketamine, initiation of two new medicines for TRD at the same time (i.e., esketamine and a newly initiated OAD) was inconsistent with good clinical practice. The Pre-PBAC Response stated the proposed restriction does not specify the exact timing of initiating a new OAD and that each could be initiated separately to assess tolerability while being unlikely to impact the efficacy of esketamine as observed in the clinical trials.

3.7 The restriction is based on a TRD definition of inadequate response to at least 2 antidepressants (inadequate response not defined). The definition of TRD may vary, and increasingly clinicians may be relying less upon pharmacological criteria to define TRD. The definition is also complicated by the lack of consensus in describing acute antidepressant responses, and what determines a treatment failure (i.e. inadequate dose or duration of pharmacotherapy, or nonadherence to treatment).

3.8 The proposed restriction is generally consistent with the eligibility criteria of the key trials. However, the included trials excluded patients with comorbid conditions,

particularly psychotic disorders, due to potential safety concerns. These patients would be eligible for treatment under the proposed restriction. The benefits and harms of treatment with esketamine nasal spray in populations with psychotic disorders are unknown. The PSCR noted the sponsor was amenable to including a caution or note regarding use in patients with a presence or history of psychosis in the restriction.

3.9 The proposed continuation rules are unclear, and interpretations may vary between clinicians. The product information state that evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine the need for continued treatment, however the criteria for assessing therapeutic benefit is unclear. The proposed restriction for continuing treatment/maintenance period 1 specifies that the patient must have 'responded adequately'. In practice, this may vary between some reduction in symptoms, and achieving complete remission of depressive symptoms and may typically be evaluated over a longer timeframe than four weeks. It is unclear what criteria will be used to evaluate response in clinical practice.

3.10 The proposed restriction for continuing treatment/maintenance period 2 specifies that the patient 'must not relapse'. In practice, the definition of relapse may also vary in terms of clinical symptoms and timeframes. It is unclear whether the proposed restriction, and the definitions used in the clinical trials, align with the clinical definition of relapse.

3.11 Although prescribing of esketamine nasal spray by a psychiatrist or in consultation with a psychiatrist is appropriate, access to psychiatrists in many areas of Australia is poor. As a result, there may be equity issues associated with access to this treatment.

3.12 The ESC noted that intravenously delivered ketamine is currently available in private treatment settings for a number of (off-label) psychiatric conditions including depression, post-traumatic stress disorder, obsessive-compulsive disorder and acute suicidal ideation and considered there was a high risk of leakage to these conditions.

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. Treatment-resistant depression (TRD) is the clinical term for a subpopulation of MDD patients that have not achieved an adequate response to conventional pharmacological antidepressant therapy.

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 2020 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.

4.5 Treatment options recommended in the 2020 RANZCP Guidelines for managing patients with TRD include optimising current antidepressant use, 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.

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.

4.8 Esketamine administration and monitoring requirements were not well described in the submission. In the esketamine clinical trials, administration occurred over a 20-minute period following a consultation to assess suitability for treatment. The Australian product information suggests that blood pressure is checked at 40 minutes and thereafter as needed, with transient increases in systolic and/or diastolic blood pressure lasting approximately 1-2 hours.

4.9 The clinical management algorithm presented in the submission positions esketamine nasal spray, initiated with a new OAD, for use in patients with TRD who have previously failed treatment with two prior OADs in the same depressive episode. Esketamine nasal spray is included in the submission alongside other pharmacological management options like switching antidepressant therapy, combination antidepressant therapy, and augmentation. The submission stated that esketamine nasal spray will most likely displace ECT or rTMS rather than replace them. Given that there are no clear lines of therapy in the treatment of depression, and the place in therapy of esketamine nasal spray is unclear and emerging, the integration of esketamine alongside non-pharmacological treatment options in practice is unclear.

4.10 The PSCR argued the place in therapy of esketamine was based on clinical guidelines and argued that the requested placement of esketamine after failure with at least two OADs was reasonable. The PSCR further argued that augmentation is only indicated for partial response to OADs and specialised interventions such as ECT were reserved for after failure of all pharmacotherapy options. The ESC considered that, given the range of available established options for MDD (including TRD) and the limited clinical evidence available for esketamine, the proposed restriction placed esketamine too early in the treatment algorithm.

4.11 The Pre-PBAC Response stated the proposed place in the treatment algorithm was consistent with the TGA approved indication, the clinical trial evidence and the most commonly accepted definition of TRD. The response noted that the requirement for patients to have failed at least two OADs was a minimum requirement and some patients would have trialled additional treatment options, which was also reflected in the clinical trial as 32.7% of patients in the TRANSFORM-2 study had received at least three OADs and 20.1% had received augmentation therapy. The PBAC agreed with the ESC and considered that given the effectiveness and safety of other treatment options are established in practice esketamine should be placed later in the treatment algorithm for TRD.

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

5 Comparator

5.1 The submission nominated switching to a new antidepressant as the main comparator. The choice of comparator was supported by utilisation data from the 10% PBS sample, and by expert psychiatrists, both of which suggested that switching to a new antidepressant is the most commonly used therapeutic strategy in a patient with TRD. The submission noted that this was consistent with the design of the phase III clinical studies where esketamine nasal spray was used as add-on to a patient switching to a new anti-depressant and compared to placebo plus switching to a new anti-depressant.

5.2 There are several therapeutic strategies that are recommended for use in patients with TRD including:

- Switching to another antidepressant;
- Adding on another antidepressant (combination therapy);
- Augmentation with lithium or an antipsychotic (e.g. olanzapine or aripiprazole);
- Physical treatments like ECT or rTMS, which are less commonly used and typically reserved where pharmacological approaches have failed; and
- Psychotherapy, such as cognitive-behavioural therapy.

5.3 Based on the 10% PBS sample analysis provided in the submission, a significant proportion of patients use either combination therapy, or add-on another agent (approximately 35.3%). The included data, based on PBS prescriptions, does not capture use of other potential comparators such as ECT, rTMS, or psychological therapies. The data provided in the submission summarising the 10% PBS sample data were not sufficient to verify the claims made in the submission.

5.4 The submission stated ECT and rTMS were not considered as comparators as esketamine nasal spray would most likely displace these therapies for TRD, rather than replace.

5.5 As noted above (paragraph 2.6), the ESC considered the submission positioned esketamine inappropriately early in the treatment algorithm, and positioning further down the treatment algorithm would impact on the appropriate comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician clarified the clinical management of TRD and the possible role of esketamine, noting its novel mechanism of action. The clinician also stated it was inappropriate to continue a treatment that was no longer providing benefit and therefore commencing a new OAD on or around commencement of esketamine was clinically appropriate. The clinician stated that the focus of treatment should be to achieve functional recovery and symptom remission for patients, which was demonstrated in the clinical trials for esketamine. The PBAC considered the hearing did not provide any further insight regarding the appropriate use of esketamine in clinical practice.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (6) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the burden of living with TRD and noted the high clinical need for novel therapies to treat the condition. Some comments noted that ketamine may also provide some benefits to patients with TRD and other mental illnesses.

6.3 The PBAC noted the comments received from the Mental Illness Fellowship of Australia which were strongly supportive of additional treatment options being available for TRD. The Fellowship noted the adherence benefits and rapid response that some patients achieve with esketamine compared to other antidepressant options. The Fellowship noted esketamine would likely be used as a third line treatment option and would provide an alternative for patients that have had no improvement using existing treatments. The Fellowship noted that ECT, used when all alternative pharmacological approaches have been exhausted, is still a feared treatment for some patients and having esketamine available as an additional treatment option would be welcomed.

Clinical studies

6.4 The submission was based on three short-term (induction), double blind, randomised controlled trials (RCTs) (TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3) and three long-term studies (SUSTAIN-1, SUSTAIN-2 and SUSTAIN-3), comparing esketamine nasal spray with a newly initiated OAD with intranasal placebo plus a newly initiated OAD.

6.5 Details of the studies presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
TRANSFORM-2 (NCT02418585)	A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression (TRANSFORM-2)	Internal study report; 6 November 2017
	Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. (2019). Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study.	Am J Psychiatry; 176(6): 428-38.
	Hudgens S, Floden L, Blackowicz M, Jamieson C, Popova V, Fedgchin M, et al. (2021). Meaningful Change in Depression Symptoms Assessed with the Patient Health Questionnaire (PHQ-9) and Montgomery-Åsberg Depression Rating Scale (MADRS) Among Patients with Treatment Resistant Depression in Two, Randomized, Double-blind, Active-controlled Trials of Esketamine Nasal Spray Combined With a New Oral Antidepressant.	J Aff Dis; 281: 767-775
	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
	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
	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
	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

Trial ID	Protocol title/ Publication title	Publication citation
	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
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 2.2-2, pp.74-76 of the submission

6.6 The key features of the included evidence are summarised in the table below.

Table 3: Key features of the included evidence

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

Source: Table 2.3-1, p.82; Table 2.3-2, p.83; Table 2.3-3, p.86; Table 2.3-3, p.87 of the submission; Table 2.1, pp.1-3; Table 2.2, pp. 3-4; Table 2.3, pp.5-7, Attachment 13 of the submission

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

6.7 The submission used the results from the TRANSFORM-2 trial as the pivotal evidence of short-term response during treatment induction as it enrolled adult patients (age 18-64) and evaluated flexibly-dosed esketamine, consistent with the product information. Results of TRANSFORM-1 (adult patients 18-64 years; fixed esketamine

dose regimens) and TRANSFORM-3 (adults age ≥65 years; flexible dose regimen) were used as supportive evidence. The ESC considered that the design of the TRANSFORMS studies, which required initiation of two new pharmacotherapies at the same time (i.e., esketamine and an OAD) is inconsistent with how TRD is managed in practice.

6.8 SUSTAIN-1 had a complex trial design, incorporating five phases: screening (4-7 weeks), induction (4 weeks open-label esketamine treatment), optimisation (12 weeks open-label esketamine treatment); maintenance (variable length of time, until relapse or until a maximum of up to 84 relapses occurred in patients with stable remission, or earlier based on interim analysis results); and follow up (2 weeks). Patients could enter the trial by direct entry or after TRANSFORM-1 or TRANSFORM-2. Only patients who achieved stable response or remission using esketamine nasal spray in combination with a newly initiated oral antidepressant during initiation and optimisation were eligible to be randomised in the double-blind maintenance phase to either continue with esketamine with an oral antidepressant, or discontinue esketamine and continue the oral antidepressant only. 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 (NICE, 2018). 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 unlikely reflective of how esketamine cessation would be undertaken in practice.

6.9 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.

6.10 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.

Comparative effectiveness

Short term studies (TRANSFORM trials)

6.11 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 4.

Table 4: 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[a] change from baseline to Day 28		ANCOVA[b] change from baseline to Day 28	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
TRANSFORM-2[c]						
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-1[d,e]						
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)[g]	-	-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)
TRANSFORM-3[e,f]						
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)

Source: Table 2.51, p.136 of the submission; Table 2.50, p.54 Attachment 11 of the submission

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

[a] Tests for treatment effects based on (MMRM with change from baseline as the response variable applied the fixed effect model terms for treatment (intranasal esk + oral AD, oral AD + intranasal placebo), day, country, class of oral antidepressant (SNRI or SSRI), and treatment-by-day, and baseline value as a covariate. A negative difference favours esketamine

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

[c] For TRANSFORM-2, the difference from placebo is the least-squares mean difference between Esk + oral AD and oral AD + placebo

[d] 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

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

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

[f] 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

[g] although nominally significant, could not be formally evaluated owing to a pre-specified testing sequence that required stopping after the higher dose failed.

6.12 Of the three short-term induction trials, only TRANSFORM-2 showed a statistically significant treatment effect with esketamine nasal spray compared with placebo. The mean difference between treatment arms (favouring esketamine) was around 4 MADRS points using a mixed-effect model for repeated measures MMRM analysis... The confidence intervals were wide, and the lower bound fell below the nominated MCID (2 MADRS points), suggesting that treatment effects are variable, and a proportion of patients do not derive any additional benefit from treatment with

esketamine. The ESC noted other studies have suggested a difference of 7 to 9 points in the MADRS is clinically important (Leucht 2017) and noted a difference of 6.5 was considered clinically important in the power calculations for TRANSFORM-2. The Pre-PBAC Response stated the threshold applied in Leucht 2017 was to an absolute change from baseline and not a between-group difference, as reported in the TRANSFORM-2 trial and reiterated the absolute change in MADRS for the esketamine + OAD group was -21.5 points. The PBAC 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.

6.13 The other two short-term induction studies, TRANSFORM-1 and TRANSFORM-3, failed to demonstrate a statistically significant treatment effect of esketamine nasal spray.

6.14 The proportion of responders and remitters at day 28 in the TRANSFORM-2 trial are summarised in Table 5. 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. The ESC noted the definition of remission was less stringent than applied in other studies, which defined remission as ≤ 8 (Leucht 2017).

Table 5: Proportion of responders and remitters at day 28 based on MADRS total score, TRANSFORM-2 (full analysis set)

	Esketamine + OAD N = 114	Placebo + OAD N = 109
Response (≥50% improvement MADRS score)		
Observed cases, n/N (%)	70/101 (69.3)	52/100 (52)
LOCF, n/N (%)	71/112 (63.4)	54/109 (49.5)
Remission (MADRS total score ≤12)		
Observed cases, n/N (%)	53/101 (52.5)	31/100 (31)
LOCF, n/N (%)	54/112 (48.2)	33/109 (30.3)

Source: Table 2.55, p.142; Table 2.56, p.143 of the submission

6.15 Based on changes in the MADRS score, at day 28, response rate was 69% in the esketamine nasal spray treatment group versus 52% for the intranasal placebo group (a risk-difference of 17%). At day 28, the remission rate was 53% in the esketamine nasal spray treatment group versus 31% for the intranasal placebo group (a risk difference of 22%). Response and remission in practice are more likely to be determined based on an assessment of both clinical symptoms and overall level of functioning, rather than using the MADRS.

6.16 The results for the EQ-5D-5L Visual Analogue Scale, health status index, and sum score across dimensions in the TRANSFORM-2 trial are summarised in Table 6.

Table 6: EQ-5D Visual Analogue Scale, health status index and sum scores in the TRANSFORM-2 trial

	Esketamine + oral AD		Placebo + oral AD	
	N	Mean (SD)	N	Mean (SD)
EQ VAS score				
Baseline	114	40.9 (20.24)	109	38.4 (20.27)
End point (day 28)	111	69.4 (19.91)	105	59.8 (23.50)
Health status index				
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)
Sum score				
Baseline	114	38.2 (14.83)	109	40.0 (15.35)
End point (day 28)	111	15.5 (15.43)	105	22.3 (18.81)

Source: TEFEQ5D01A, p.2853 TRANSFORM-2 clinical study report

Abbreviations: AD, antidepressant; SD, standard deviation; VAS, visual analogue scale

Note: EQ-VAS score from 0 (the worst health you can imagine) to 100 (the best health you can imagine), 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), and Sum score from 0 to 100, where Sum score=(sum of the scores from the 5 dimensions minus 5) * 5.

6.17 Participants in both arms of the TRANSFORM-2 trial experienced improvements in quality of life as measured by the EQ-5D-5L VAS and sum score between baseline and end of study, favouring treatment with intranasal esketamine. Similar results were obtained in the TRANSFORM-1 and TRANSFORM-3 trials.

Maintenance study (SUSTAIN-1)

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 7.

Table 7: Results of primary efficacy outcome (time to relapse)[a] in the SUSTAIN-1 trial (stable remitters and responders)

	Esketamine + AD	Placebo + AD	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 2.5.11, p.149 and Table 2.5.12, p.152 of the submission

Abbreviations: AD, antidepressant; CI, confidence interval; NE, not estimable

[a] Based on Kaplan-Meier product limit estimates

[b] Hazard 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 in the placebo arm 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 PSCR stated it is unlikely that a pharmacologic withdrawal effect contributed to the relapse rate in the placebo arm given the short half-life of esketamine. The PSCR stated a post-hoc analysis found that most esketamine treated patients did not have dissociative symptoms before randomisation into SUSTAIN-1 (or after) as these symptoms tend to reduce over time. The PSCR and pre-PBAC response stated there was no evidence of functional unblinding and noted a post-hoc analysis performed for NICE found that most patients in the placebo arm of SUSTAIN-1 who relapsed early did not experience dissociation effects before or after randomisation. The ESC and PBAC noted that esketamine has a distinct side effect profile (including nausea, vertigo, dysgeusia and somnolence) and given these patients had prior exposure to esketamine considered the risk that some unblinding had occurred could not be excluded.

Comparative harms

6.21 A summary of treatment-emergent adverse events from the TRANSFORM-2, TRANSFORM-1 and TRANSFORM-3 trials is presented in Table 8.

Table 8: Incidence of adverse events in the double-blind induction phase of the TRANSFORM trials (safety analysis set)

	TRANSFORM-2		TRANSFORM-1			TRANSFORM-3	
	ESK + OAD N = 115	PBO + OAD N = 109	ESK 56 mg + OAD N = 115	ESK 84 mg + OAD N = 116	PBO + OAD N = 113	ESK + OAD N = 72	PBO + OAD N = 65
TEAE	98 (85.2)	90 (78.3)	100 (87.0)	103 (88.8)	77 (68.1)	51 (70.8)	39 (60.0)
TEAE possibly related to intranasal drug [a]	90 (78.3)	39 (35.8)	89 (77.4)	92 (79.3)	54 (47.8)	42 (58.3)	22 (33.8)
TEAE possibly related to oral antidepressant [a]	39 (33.9)	26 (23.9)	44 (38.3)	43 (37.1)	34 (30.1)	13 (18.1)	11 (16.9)
TEAE leading to death	1 (0.9)	0	0	0	0	0	0
1 or more serious TEAE	1 (0.9)	1 (0.9)	2 (1.7)	0	0	3 (4.2)	2 (3.1)
TEAE leading to intranasal drug withdrawn [b]	8 (7.0)	1 (0.9)	1 (0.9)	7 (6.0)	2 (1.8)	4 (5.6)	2 (3.1)
TEAE leading to oral antidepressant withdrawn [b]	4 (3.5)	0	0	1 (0.9)	2 (1.8)	1 (1.4)	1 (1.5)
Most common TEAE (≥10%)							
Dissociation	30 (26.1)	4 (3.7)	30 (26.1)	32 (27.6)	4 (3.5)	9 (12.5)	1 (1.5)
Nausea	30 (26.1)	7 (6.4)	31 (27.0)	37 (31.9)	12 (10.6)	13 (18.1)	3 (4.6)
Vertigo	30 (26.1)	3 (2.8)	24 (20.9)	24 (20.7)	2 (1.8)	8 (11.1)	2 (3.1)
Dysgeusia	28 (24.3)	13 (11.9)	17 (14.8)	20 (17.2)	17 (15.0)	4 (5.6)	3 (4.6)
Dizziness	24 (20.9)	5 (4.6)	32 (27.8)	26 (22.4)	10 (8.8)	15 (20.8)	5 (7.7)
Headache	23 (20.0)	19 (17.4)	23 (20.0)	24 (20.7)	19 (16.8)	9 (12.5)	2 (3.1)
Somnolence	15 (13.0)	7 (6.4)	24 (20.9)	21 (18.1)	13 (11.5)	-	-
Vision blurred	14 (12.2)	3 (2.8)	8 (7.0)	9 (7.8)	0	-	-
Paraesthesia	13 (11.3)	1 (0.9)	19 (16.5)	11 (9.5)	3 (2.7)	4 (5.6)	2 (3.1)
Anxiety	12 (10.4)	5 (4.6)	10 (8.7)	9 (7.8)	7 (6.2)	2 (2.8)	5 (7.7)
Blood pressure increased	11 (9.6)	0	8 (7.0)	11 (9.5)	5 (4.4)	9 (12.5)	3 (4.6)
Vomiting	11 (9.6)	2 (1.8)	7 (6.1)	14 (12.1)	2 (1.8)	5 (6.9)	1 (1.5)
Hypoesthesia	8 (7.0)	1 (0.9)	14 (12.2)	16 (13.8)	2 (1.8)	4 (5.6)	1 (1.5)
Fatigue	5 (4.3)	6 (5.5)	12 (10.4)	8 (6.9)	5 (4.4)	9 (12.5)	5 (7.7)

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

6.22 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. More people in the esketamine treatment arms withdrew from treatment due to an AE compared with the placebo treatment arms in the included trials.

6.23 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, paresthesia, anxiety, hypoesthesia oral, hypoesthesia, 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.

6.24 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 9.

Table 9: 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 oral antidepressant [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 leading to intranasal drug withdrawn [b]	22 (5.0)	5 (1.1)	4 (2.6)	3 (2.1)
TEAE leading to oral antidepressant withdrawn [b]	8 (1.8)	2 (0.4)	3 (2.0)	0
Most common TEAE (≥10%)				
Dizziness	97 (22.2)	61 (13.4)	31 (20.4)	7 (4.8)
Dysgeusia	90 (20.6)	79 (17.4)	41 (27.0)	10 (6.9)
Somnolence	65 (14.9)	63 (13.8)	32 (21.1)	3 (2.1)
Headache	60 (13.7)	57 (12.5)	27 (17.8)	14 (9.7)
Paraesthesia	48 (11.0)	24 (5.3)	11 (7.2)	0
Sedation	44 (10.1)	-	10 (6.6)	1 (0.7)

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

6.25 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.

6.26 The most common treatment-emergent adverse events in SUSTAIN-1 included dysgeusia, vertigo, dissociation, somnolence, dizziness, headache, nausea, vision blurred, and hypoesthesia oral and were consistent with the types of adverse events observed in the induction phase.

6.27 The submission noted that 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.

6.28 Across all studies, adverse events of drug abuse, drug abuser, drug dependence, drug detoxification, drug rehabilitation, drug tolerance, drug tolerance increased, or drug use disorder were not identified. There were no reports from the investigational sites of any subjects requesting an increase either in the dose of esketamine nasal spray or in the frequency of treatment sessions (as a potential early indicator of drug-seeking behaviour). It may be difficult to observe these outcomes in a tightly regulated trial setting; it is unclear whether potential abuse or misuse may occur in clinical practice and this is likely to be dependent upon the model used for administration. Increased blood pressure or increased heart rate, dizziness/vertigo, and anxiety in all studies were primarily mild or moderate in severity. Suicidality-related adverse events were reported as severe in only a small number of subjects, and most were considered either not related or doubtfully related to esketamine nasal spray treatment in the opinion of the investigator and therefore likely associated with the underlying disease. There were very low reported cases of cystitis (9 subjects in SUSTAIN-1, 5 subjects in SUSTAIN-2 and 8 subjects in SUSTAIN-3) and impaired cognition (1 subject in SUSTAIN-3) in the esketamine nasal spray studies. Adverse events such as impaired cognition may not be observable over short-term trial durations.

Benefits/harms

6.29 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 with treatment-resistant depression treated with esketamine nasal spray + a newly initiated OAD in comparison to intranasal placebo + a newly initiated OAD:

- Approximately 17 more patients would have a response, defined as a ≥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.

6.30 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 + an OAD compared to those who discontinued treatment with esketamine nasal spray, instead receiving an intranasal placebo + 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

6.31 The submission described esketamine nasal spray in combination with a newly initiated 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.

6.32 The ESC considered the claim of superior effectiveness was poorly supported:

- Of the three randomised induction trials, only TRANSFORM-2 demonstrated an improvement in MADRS for esketamine over placebo that was statistically significant. The magnitude of the improvement observed in the other two trials was similar although not statistically significant. The ESC noted the 4 point change in the MADRS observed in TRANSFORM-2 at 4 weeks met the MCID nominated in the submission of 2 points, but also noted that studies have considered a difference of at least 7 to 9 points to be clinically important.
- The 4 week duration of TRANSFORM-2 was insufficient to see a maximal response from the newly initiated OAD.
- Esketamine nasal spray produced antidepressant effects relatively fast compared with other oral antidepressants, however long-term data about the maintenance of treatment effect is currently unavailable. The SUSTAIN-1 trial suggested that participants who discontinue esketamine after improvement are more likely to relapse in comparison with those who do not discontinue esketamine. However, some authors have commented that this type of withdrawal trial design tends to overemphasise the efficacy of maintenance treatment, as the comparison group is at extremely high risk of relapse considering that treatment is abruptly stopped soon after improvement (NICE, 2018).
- The optimum duration of therapy is yet to be determined. Current guidelines suggest at least 6 months, and ideally more than one year of maintenance treatment with pharmacotherapies for people with major depression, with longer treatment durations suggested for patients with recurrent episodes (Malhi et al., 2021). Patients in the intranasal placebo arm of the SUSTAIN-1 trial, who discontinued treatment after 12 or 16 weeks of treatment, experienced more relapse episodes than those continuing treatment. As the durability of benefit has not been established, it is unclear for how long esketamine should be prescribed to prevent relapse.

6.33 The ESC noted there is a lack of long-term safety data for esketamine. Presently it is thought that esketamine may share some of the well-known risks associated with ketamine (e.g. drug abuse, dissociation, altered consciousness; Ballard & Zarate, 2020), however there are no studies directly comparing the two (Malhi et al., 2021). 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.

6.34 The PBAC considered that the claim of superior comparative effectiveness of esketamine + new OAD to a new OAD alone may be reasonable, however the magnitude and clinical importance of the observed benefits was uncertain.

6.35 The PBAC considered that the claim of inferior comparative safety of esketamine + new OAD to a new OAD alone was reasonable.

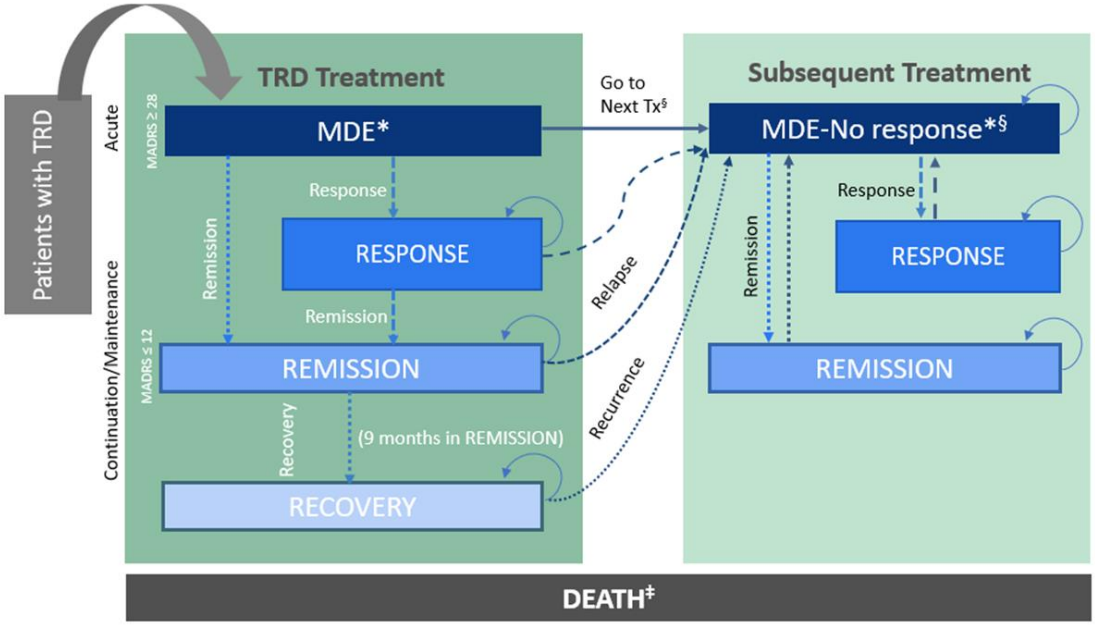
Economic analysis

6.36 As noted above (paragraph 2.6), the ESC considered the submission positioned esketamine inappropriately early in the treatment algorithm and that the results from the economic model are unlikely to be directly applicable to later line use.

6.37 The submission presented a stepped economic evaluation of the additive effects of using esketamine nasal spray with a newly initiated OAD, compared to a newly initiated OAD for the treatment of patients with moderate to severe TRD. The economic evaluation was based on two direct randomised trials (TRANSFORM-2 and SUSTAIN-1) with additional modelled data. The ESC noted the economic model did not utilise all available RCT data for esketamine. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis. The Pre-PBAC Response argued it was reasonable to only use data from the TRANSFORM-2 RCT (as well as the SUSTAIN-1 study for some inputs) as only the TRANSFORM-2 trial was reflective of the dosage regimens in the approved TGA Product Information.

6.38 The model structure is summarised in Figure 1 and Table 10.

Figure 1: Model structure



Source: Figure 6, p.210 of the submission

Table 10: Summary of model structure, key inputs and rationale

Component	Description
Treatments	Esketamine nasal spray with a newly initiated OAD; intranasal placebo with a newly initiated OAD
Outcomes	Quality-adjusted life-years MDE-free life years Proportions of patients with remission and response
Time horizon	5 years (compared with 4 weeks double-blind induction phase in TRANSFORM-2, and a median duration of maintenance treatment of 17.7 weeks in stable remitters, and 19.4 weeks in stable responders, in the esketamine + OAD treatment arms of the SUSTAIN-1 trial)
Method used to generate results	Markov cohort analysis with multiple lines of treatment
Health states	Major Depressive Episode (MDE) Response Remission Recovery Death
Cycle length	Four weeks
Transition probabilities	Initial Treatment: Probabilities of response and remission in the induction phase based on data from TRANSFORM-2. Maintenance setting: Probabilities of transitions from response to remission, loss of response, relapse from remission, and recurrence from recovery to the MDE health state were based on data from SUSTAIN-1. Patients transition to the recovery health state after 36 weeks (9 cycles) in remission. Subsequent Treatment: Response, remission, loss of response and relapse rates were based on the fourth-line treatment outcomes from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Treatment discontinuations: Based on the mean value of an exponential curve fitted to treatment discontinuations due to any cause from the SUSTAIN-1 trial
Health related quality of life	Patient-level EQ-5D-5L data from day 28 of the TRANSFORM-2 trial was retrospectively transformed into health state utilities using a Canadian value set. The ESC noted Australian utility values are available and should have been used.
Costs	Mean dose and frequency of administration during induction and maintenance periods were based on data from the TRANSFORM-2 and SUSTAIN-1 trials. Esketamine drug costs based on the proposed effective DPMQ, with a weighted public/private split (20/80) Oral antidepressant drug costs based on weighted average of antidepressant agents prescribed in a 10% PBS sample analysis, with costs applied based on costs of agents on the PBS website Disease management costs (GP visits, specialist visits, community health centre visits, hospitalisations, emergency department visits) by health state based on a UK study by Denee et al. (2021). Hospitalisation costs were estimated based on AR-DRG items. Emergency department costs were based on URG items. GP and specialist visit costs were based on MBS items A scenario analysis was conducted using a societal perspective including indirect costs to patients due to loss in productivity because of TRD, based on a study of both absenteeism and presenteeism data for varying levels of MDD by Stewart et al. (2003)

Source: Table 3.1, p.200 of the submission

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; GP, general practitioner; MBS, Medicare Benefits Schedule; MDD, major depressive disorder; MDE, major depressive episode; OAD, oral antidepressant; PBS, Pharmaceutical Benefits Scheme; TRD, treatment resistant depression; UK, United Kingdom; URG, urgency related groups

6.39 The STAR*D study, used to inform transition probabilities for subsequent treatment, was conducted between 2001 and 2006 and some of the included treatments are not commonly used in Australia for the treatment of depression (e.g. bupropion; triiodothyronine augmentation). Additionally, some patients were treated with non-

pharmacological therapy (cognitive therapy alone or as a second-line add-on to citalopram therapy). The ESC considered the STAR*D study may not reflect contemporary treatment practises for TRD and the appropriateness of using it to inform transition probabilities was uncertain.

6.40 Patients who receive subsequent treatment may: remain in the MDE state, experience remission or response, experience relapse, or die. Patients who experience a relapse transition back to the MDE state, where they again have a chance to achieve remission or response. The model did not allow recovery to be achieved in the subsequent treatment mix.

6.41 Key drivers of the model are summarised in Table 11.

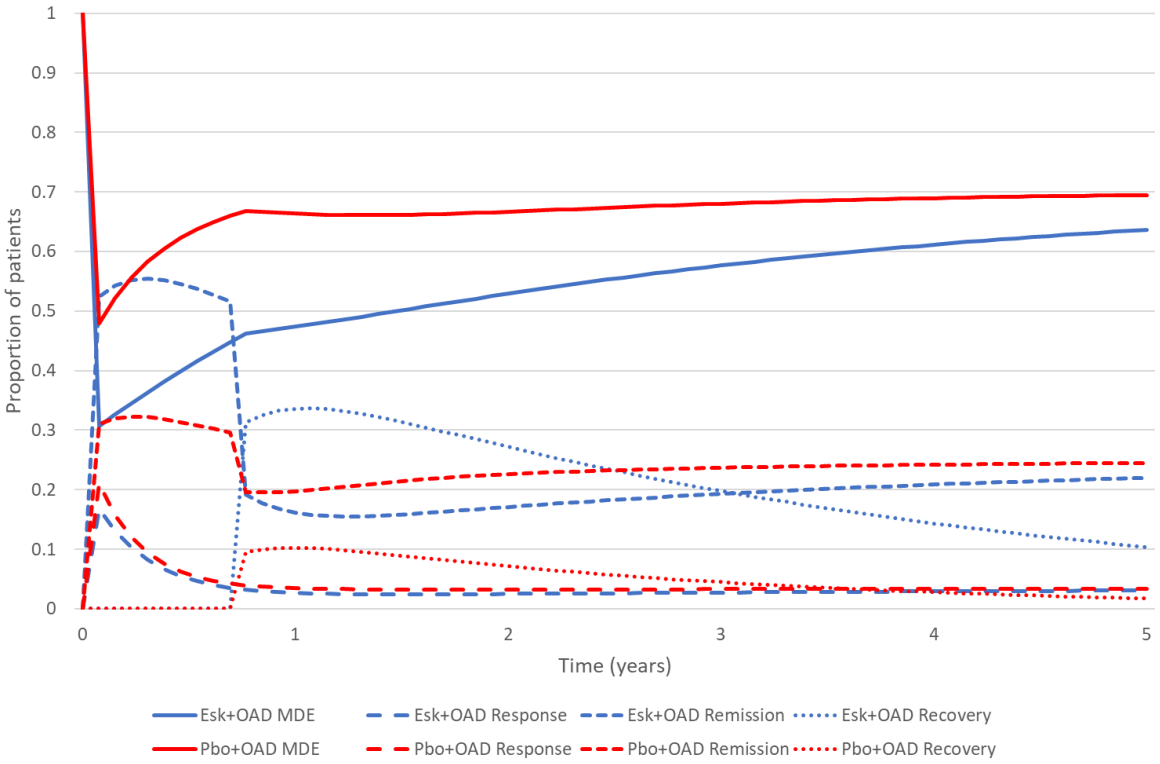
Table 11: Key drivers of the model

Description	Method/Value	Impact
Transition probabilities in the maintenance phase	The application of transition probabilities derived from the SUSTAIN-1 trial in the model assumes that these outcomes will continue to occur at a constant rate and beyond the duration of the trial. This may not be appropriate, based on the relatively short duration of the trial (10-17 weeks in the maintenance period). There is only limited data to inform the long-term use and outcomes associated with esketamine nasal spray treatment. Further, the SUSTAIN-1 trial was not an accurate reflection of clinical practice in the placebo treatment arm. The withdrawal trial design increased the risk of relapse in responders and remitters randomised to placebo, and likely overstates the comparative effectiveness of esketamine nasal spray in preventing relapse.	High, favours esketamine
Application of the recovery health state	In the model, patients who remain in the remission state for nine consecutive cycles following initial treatment (esketamine plus OAD, OAD alone) achieve recovery. Only a small proportion of patients in the OAD alone arm achieve recovery in the model, which is likely to be underestimated due to the high placebo relapse rate resulting from the abrupt withdrawal design of SUSTAIN-1 trial, which informs estimates. Further, the model does not allow patients using subsequent therapy to achieve recovery, which does not reflect real-world outcomes of antidepressant treatment. Prospective observational studies have shown that the median time to recovery from a major depressive episode is approximately 20 weeks (Corvell et al., 1994; Solomon et al., 1997), a finding which was consistent in treated patients with multiple recurrent episodes (up to five), and for individuals in the community who have not sought treatment. This approach strongly favours esketamine as more patients in the OAD alone arm transition to subsequent therapy.	High, favours esketamine
Healthcare resource use and costs	The model generates a large number of hospitalisations over the time horizon, based on resource use estimates from a UK retrospective chart review (Denee 2021). The data were based on a relatively small and heterogeneous sample. The applicability of this study to the Australian setting is unclear and the reductions in hospitalisations generated in the model may not be realised in practice.	Moderate, favours esketamine
Costs of administration and monitoring	The mechanism for delivering, supervising, and monitoring esketamine nasal spray in Australia was not well defined in the submission. Esketamine nasal spray represents a novel treatment paradigm, and the mechanism for administration needs to be clarified. The administration cost in the model (based on a 15 minute psychiatrist consultation), which was inappropriately applied to both treatment arms, is likely to greatly underestimate the costs of administration and monitoring.	High, favours esketamine
Treatment discontinuations	An exponential parametric curve was fitted to pooled data from stable responders and stable remitters with esketamine discontinuation for any reason in the SUSTAIN-1 trial to model treatment discontinuations. Treatment discontinuations are only applied as a reduction in drug costs in all health states from week 5 onwards. The application of treatment persistence as a reduction to drug costs only beyond the observed trial period is inappropriate, as treatment persistence would also impact the effectiveness and safety of the treatment (i.e. non-persistent patients will reduce drug costs but also receive reduced benefits/harms of treatment).	High, favours esketamine

Source: Constructed during the evaluation.

6.42 The model trace is summarised in Figure 2.

Figure 2: Markov trace



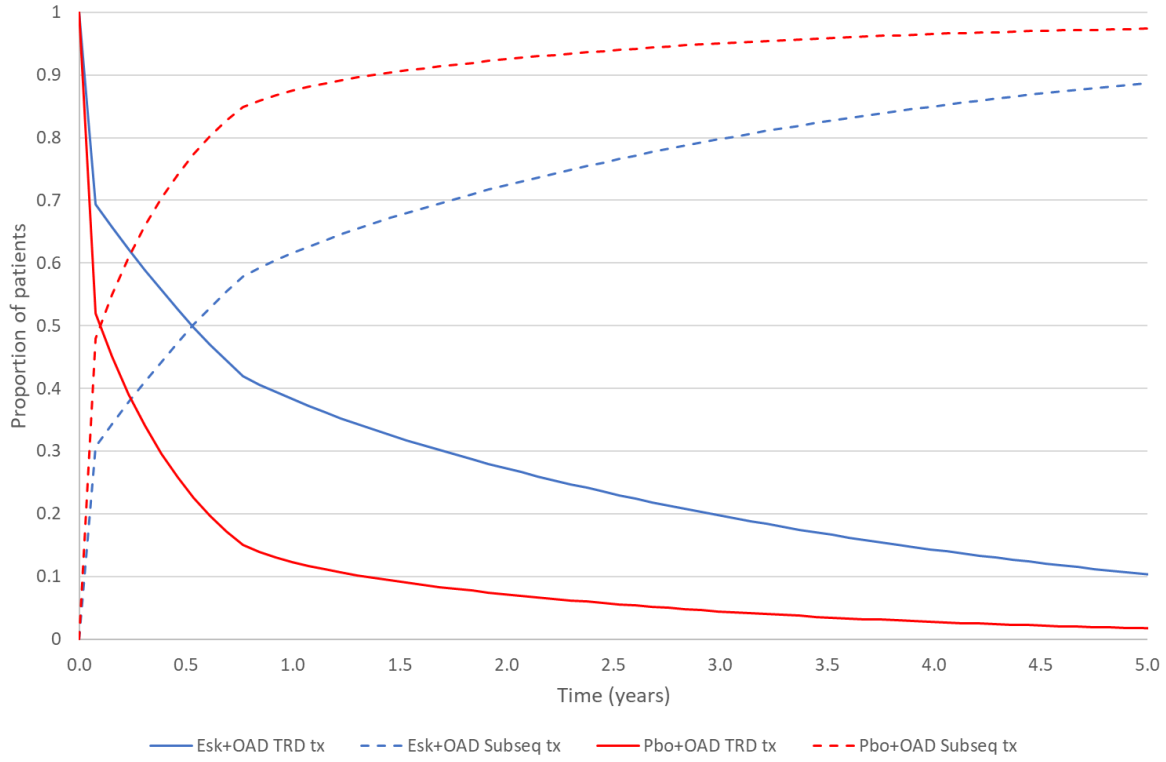
Source: constructed during the evaluation using Attachment 19- Esketamine TRD CE model spreadsheet
Abbreviations: Esk, esketamine; MDE, major depressive episode; OAD, oral antidepressant; Pbo, placebo

6.43 The model is driven by a greater proportion of patients in the placebo arm in the MDE health state, and a smaller proportion of patients in the placebo arm in the recovery health state. Although this is consistent with the higher remission rate and lower relapse rate observed in the esketamine nasal spray arm of the TRANSFORM-2 and SUSTAIN-1 trials, which leads to a higher proportion achieving recovery in the esketamine nasal spray with OAD treatment arm, there is no evidence to suggest this would be maintained indefinitely. Only a small proportion of patients in the placebo arm achieve recovery. This does not meet face validity; larger proportions of patients achieve recovery in current clinical practice than are modelled in the placebo treatment arm. The low recovery rates in the OAD only treatment arm are based on the higher relapse rates observed in the SUSTAIN-1 trial and the inability to achieve recovery with subsequent treatment, which are unlikely to be realised in practice. The PSCR argued that not including a recovery health state for subsequent therapy was justified by the low probability of recovery in TRD patient who received multiple therapies (based on the STAR-D study), and further argued the model did not attribute any QALY benefit to patients achieving recovery with the subsequent treatment in the esketamine arm of the model and was therefore conservative. The ESC considered the exclusion of a recovery state in subsequent treatment was inappropriate and did not reflect clinical practice, particularly with esketamine placed early in the treatment algorithm and the availability of later line treatment options. The ESC considered a

five year time horizon resulted in any difference between treatment arms in the proportion of patients in the recovery health state early in the model being maintained for a long period of time.

6.44 Figure 3 is a trace showing the proportion of patients in the initial versus subsequent TRD treatments, by treatment arm in the model.

Figure 3: Proportions of patients in TRD treatment (ESK+OAD or OAD alone) versus subsequent treatment



Source: constructed during the evaluation using Attachment 19- Esketamine TRD CE model spreadsheet
Abbreviations: Esk, esketamine; OAD, oral antidepressant; Pbo, placebo

6.45 Table 12 summarises the incremental costs for health care resource items used in the economic evaluation.

Table 12: Disaggregated summary of cost impacts (discounted) in the economic evaluation

Cost description	Esketamine + oral antidepressant	Oral antidepressant	Increment
COSTS BY RESOURCE ITEM			
Treatment costs	**$[redacted]**	**$986**	**$[redacted]**
- esketamine	$[redacted]	$0	$[redacted]
- oral antidepressant	$287	$110	$177
- subsequent therapies	$699	$876	-$177
Administration	**$1,524**	**$770**	**$754**
Monitoring	**$0**	**$0**	**$0**
Adverse events	**$0**	**$0**	**$0**
Disease management costs	**$76,820**	**$93,937**	**-$17,116**
- primary care visits	$229	$257	-$28
- specialist visits	$643	$686	-$44
- ED visits	$3,135	$3,878	-$742
- hospitalisations	$72,813	$89,116	-$16,303

Source: Table 3.26 of the submission; and 'Attachment 19 – Esketamine TRD CE model' Excel spreadsheet provided with the submission

6.46 The difference in costs between treatment arms was driven by esketamine drug costs, which were offset by reduced disease management costs (primarily costs of hospitalisations). It is unclear whether such a significant reduction in hospitalisations will occur in practice. The source data for resource use by health state was based on a retrospective chart review study (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 noted Denee 2021 was a UK study which may have limited applicability to the Australian context.

6.47 The costs of administration and monitoring associated with esketamine treatment had a limited effect on incremental costs given the small unit cost, and the application to the OAD treatment arm in the model. In practice, the costs of administration and monitoring will potentially be significantly greater than those included in the model, depending upon the final practice model used to deliver and administer esketamine nasal spray.

6.48 The results of the stepped economic evaluation are summarised below.

Table 13: Results of the stepped economic evaluation

Step and component	Esketamine+OAD	OAD	Increment
Step 1: Trial-based four-week induction phase (proportions of patients with response and in remission from TRANSFORM-2 trial; esketamine and oral antidepressant drug costs; administration costs applied to both arms)			
Costs	$[redacted]	$303	$[redacted]
Proportion of responders (Day 28)	69.3%	52.0%	17.3%
Proportion in remission (Day 28)	52.5%	31.0%	21.5%
Incremental cost/additional responder			**$[redacted]**[3]
Incremental cost/additional patient in remission			**$[redacted]**[3]
Step 2: Modelled induction and maintenance phases over 52 weeks (based on TRANSFORM-2 and SUSTAIN-1 data); esketamine and oral antidepressant drug costs; administration costs applied to both arms[2], treatment discontinuation, subsequent treatment costs and consequences included (based on STAR*D study), health care resource use included (primary care, specialist and ED visits and hospitalisation days)[1, 2].			
Costs	$[redacted]	$21,427	$[redacted]
Years in response, remission, recovery	0.5521	0.3595	0.1926
Incremental cost/MDE-free life year gained			**$[redacted]**[4]
Step 3: utilities derived from TRANSFORM-2 applied to time in health states, disutilities associated with adverse events included, half-cycle correction applied			
Costs	$[redacted]	$21,046	$[redacted]
QALYs	0.7279	0.6509	0.0770
Incremental cost/extra QALY gained			**$[redacted]**[5]
Step 4: extrapolated from 52 weeks to 5 years, costs and outcomes discounted at 5%			
Costs	$[redacted]	$96,693	$[redacted]
QALYs	3,0372	2.8132	0.2240
Incremental cost/extra QALY gained (base case)			**$[redacted]**[6]

Source: Table 3.25 of the submission and 'Attachment 19 - Esketamine TRD CE model' spreadsheet provided with the submission.
Abbreviations: MDE, major depressive episode; OAD, oral antidepressant

[1] In Step 1, the proportion of responders and proportion in remission are not mutually exclusive, however in Step 2, the proportion of responders has been adjusted to remove the proportion in remission to make the model health states mutually exclusive.

[2] Modelled drug and administration costs assuming patients with non-response, relapse or remission receive OAD only.

The redacted values correspond to the following ranges:

[3] *$15,000 to < $25,000/QALY gained*

[4] *$45,000 to < $55,000/QALY gained*

[5] *$95,000 to < $115,000/QALY gained*

[6] *$25,000 to < $35,000/QALY gained*

6.49 Incorporating the costs and consequences of maintenance treatment, including health care resource use, applying health state utilities and extrapolation of the model to five years had the largest impacts on the stepped economic evaluation. The ESC noted the extrapolation from 52 weeks to 5 years had a significant impact on the ICER which suggested short-term treatment (average modelled duration of treatment with esketamine was 1 year) had a long-term impact. The ESC considered there was limited clinical evidence available to justify this assumption.

6.50 Based on the economic model, treatment with esketamine nasal spray plus a newly initiated OAD versus treatment with a newly initiated OAD in patients with TRD is associated with a cost per QALY gained of $25,000 to < $35,000.

6.51 The submission presented an alternative base case scenario conducted using a societal perspective, which includes indirect costs to patients due to loss in productivity associated with TRD. Incorporating indirect costs resulted in a cost per QALY gained of $5,000 to < $15,000 for esketamine nasal spray plus OAD versus OAD alone.

6.52 The results of key sensitivity analyses are summarised below.

Table 14: Results of sensitivity analyses

	Incremental cost	Incremental QALYs	ICER
Base case	**$** [redacted]	**0.2240**	**$** [redacted] 1
Time horizon (base case 5 years)			
1 year	$ [redacted]	0.0750	$ [redacted] 2
3 years	$ [redacted]	0.1736	$ [redacted] 3
Probabilities of remission in induction phase (base case: remission 52.5% ESK+OAD vs 31.0% OAD; from TRANSFORM-2)			
Decrease ESK+OAD probability of remission by 20%	$ [redacted]	0.1713	$ [redacted] 4
Increase ESK+OAD probability of remission by 20%	$ [redacted]	0.2766	$ [redacted] 5
Maintenance (base case values for ESK+OAD and OAD arms derived from SUSTAIN-1)			
Increase probabilities to MDE by 20%; decrease response to remission probability by 20%: ESK+OAD arm	$ [redacted]	0.1735	$ [redacted] 3
Increase probabilities to MDE by 20%; decrease response to remission probability by 20%: OAD arm	$ [redacted]	0.2507	$ [redacted] 5
Subsequent treatment remission and response (base case: remission 4.5%/cycle; response 1.1%/cycle; assuming response estimates in STAR*D study double-count remission estimates and are based on a 12-week duration)			
Response 5.8%/cycle (no double-counting assumed)	$ [redacted]	0.2027	$ [redacted] 4
STAR*D probabilities adjusted to 4-weekly estimates based on time to response (8.3 weeks)/remission (7.4 weeks)	$ [redacted]	0.1942	$ [redacted] 4
Subsequent treatment loss or response and relapse from remission (base case: remission to MDE 12.8%/cycle; response to MDE 22.8%/cycle)			
Increase probabilities by 20%	$ [redacted]	0.2334	$ [redacted] 1
Decrease probabilities by 20%	$ [redacted]	0.2116	$ [redacted] 4
Recurrence of MDE from recovery (base case: 2.427% ESK+OAD; 3.558% OAD)			
Same probability of recovery to MDE in each arm, based on placebo: 0.03558	$ [redacted]	0.1777	$ [redacted] 3
Same probability of recovery to MDE in each arm, based on esketamine: 0.02427	$ [redacted]	0.2094	$ [redacted] 4
Use of 56 mg dose only	$ [redacted]	0.2240	$ [redacted] 6
Use of 84 mg dose only	$ [redacted]	0.2240	$ [redacted] 4
All patients receive once weekly dosing during maintenance weeks 9+	$ [redacted]	0.2240	$ [redacted] 7
All patients receive once fortnightly dosing during maintenance weeks 9+	$ [redacted]	0.2240	$ [redacted] 6
Cost of administration and monitoring (base case MBS item 300 (<15 min), $45.35 (benefit of $38.55 inappropriately applied); applied to both treatment arms)			
MBS item 304 (30-45 min) $139.30 applied to esketamine arm only	$ [redacted]	0.2240	$ [redacted] 3
MBS item 308 (>75 min) $223.10 applied to esketamine arm only	$ [redacted]	0.2240	$ [redacted] 7
Treatment discontinuation (probability of discontinuing esketamine 1.7% per cycle; affects drug and administration costs only)			
Treatment discontinuations only applied for the duration of the SUSTAIN-1 maintenance period (weeks 5-40)	$ [redacted]	0.2240	$ [redacted] 3
Health care resource use (base case: estimates of primary care, specialist, and ED visits and hospitalisation days by health state based on Denee 2021)			
Hospitalisation days per 28 days increased by 20%	$ [redacted]	0.2240	$ [redacted] 6
Hospitalisation days per 28 days decreased by 20%	$ [redacted]	0.2240	$ [redacted] 4
Health state utility values (base case derived from TRANSFORM-2 trial data: MDE 0.516; response 0.833; remission 0.899; recovery 0.899)			
Utility values from Yrondi 2021 (0.41; 0.63; 0.80; 0.90)	$ [redacted]	0.2926	$ [redacted] 5

	Incremental cost	Incremental QALYs	ICER
Utility values from NICE committee papers (0.417; 0.764; 0.866; 0.866)	$[redacted]	0.2634	$[redacted][1]
Utility values used in Ross (2019) based on Sapin (2004) (0.58; 0.72; 0.85; 0.85)	$[redacted]	0.1606	$[redacted][4]

Source: Table 3.31 of the submission and 'Attachment 19 - Esketamine TRD CE model' spreadsheet provided with the submission.
Abbreviations: ED, emergency department; ERG, Evidence Review Group; MBS, Medicare Benefits Schedule; MDE, major depressive episode; min, minutes; NICE, National Institute for Health and Care Excellence
The redacted values correspond to the following ranges:
[1] *$25,000 to < $35,000/QALY gained*
[2] *$95,000 to < $115,000/QALY gained*
[3] *$45,000 to < $55,000/QALY gained*
[4] *$35,000 to < $45,000/QALY gained*
[5] *$15,000 to < $25,000/QALY gained*
[6] *$5,000 to < $15,000/QALY gained*
[7] *$55,000 to < $75,000/QALY gained*

6.53 The results were sensitive to several inputs, particularly the time horizon, probability of achieving remission or response at treatment induction, transition probabilities in the maintenance period, 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), costs of administration and monitoring, treatment discontinuations, and utility values.

6.54 The ESC noted the base case ICER was highly dependent on the values chosen for a number of inputs and many of the input values are not robust and are likely to vary in practice. Therefore, the ESC considered that, overall, the base case ICER was not robust.

6.55 The model did not allow recovery to be achieved in the subsequent treatment mix and this could not be tested in sensitivity analyses due to the structure of the model. The ESC considered this may have a significant impact on the cost effectiveness of esketamine nasal spray as discussed in paragraph 6.43.

6.56 The PSCR reiterated the inclusion of MBS item 300 (< 15 mins psychiatrist consultation) to account for monitoring costs was reasonable, noting it was likely administration would be supervised by a nurse but there is no appropriate MBS item for account for nurse time. The ESC considered the costs of administering esketamine were highly uncertain but it was likely they were significantly underestimated in the economic model.

6.57 The PSCR stated it was reasonable to apply a monitoring cost in the model comparator arm as patients in SUSTAIN-1 benefitted from the more frequent visits to the clinic as a result of the administration of placebo and whilst this may not fully reflect Australian practice, the clinical data informing the model inherently capture the benefit. The PSCR stated good modelling practice dictates that the cost for this benefit should be included. The ESC considered the economic model should capture resource use the way treatment is delivered in clinical practice and administration and monitoring costs would not be incurred for a patient being treated with a newly initiated OAD. The ESC

therefore considered it was not appropriate to include administration and monitoring costs in the placebo + OAD treatment arm in the economic model.

6.58 The ESC noted the ICER was sensitive to the dose and the dose interval in the maintenance phase (once or twice weekly) and the submission did not provide adequate information to asses if the assumptions applied in the economic model were reasonable.

6.59 The ESC noted treatment discontinuations were applied in the model as a reduction in drug costs only in all heath states from week 5 onwards, with those who discontinue treatment continuing to accrue effectiveness in line with estimates from the clinical trials. The ESC considered this was inappropriate, as treatment persistence would also impact the effectiveness and safety of the treatment. The ESC noted the average modelled duration of treatment with esketamine was 1 year but the appropriate duration of treatment in clinical practice is uncertain.

6.60 The ESC considered it would be appropriate for the economic model to capture the significant safety concerns associated with the use of esketamine.

6.61 The ESC advised a substantially revised economic model would be needed to assess the cost-effectiveness of esketamine. The ESC considered the following issues need to be addressed:

- model structure needs to account for the subsequent therapies (paragraph 6.43);
- inclusion of clinical data from only one clinical trial for esketamine in the economic model;
- more conservative maintenance of treatment effect assumptions (paragraph 6.43);
- duration of treatment, treatment discontinuations and dose likely to be used in clinical practice (paragraphs 6.58 and 6.59);
- appropriate cost of administration (paragraph 6.47);
- the applicability of the disease management costs (paragraph 6.46);
- account for safety concerns (paragraph 6.60).

6.62 The PBAC noted a number of additional ICERs were provided in the pre-PBAC response but did not consider them to be informative given the underlying issues with economic model.

Drug cost/patient/treatment phase

Table 15: 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	70.8 mg (2.530×28 mg devices)	70.8 mg (2.530×28 mg devices)	70.8 mg (2.530×28 mg devices)
Unit cost per 28 mg device	-	$[redacted][2]	$[redacted][3]
Average doses per week	1.851	1.851	-
Adherence	Not reported	Not explicitly modelled	92.5%
Cost/patient/4-week period	-	$[redacted]	$[redacted]
Persistence	84.5%	100%	100%
Maintenance phase (Week 5+)			
Mean dose	Weeks 5 - 40: 72.9 mg (2.605×28 mg devices)[4] Week 41+: 72.0 mg (2.571×28 mg devices)[4]	Weeks 5 - 40: 72.9 mg (2.605×28 mg devices) Week 41+: 72.0 mg (2.571×28 mg devices)	Week 5+: 72.9 mg (2.605×28 mg devices)
Unit cost per 28 mg device	-	$[redacted][5]	$[redacted][6]
Average doses per week	Weeks 5 - 8: 0.992[4] Weeks 9 - 40: 0.711[4] Week 41+: 0.675[4]	Weeks 5 - 8: 0.992 Weeks 9 - 40: 0.711 Week 41+: 0.675	-
Adherence	Not reported	Not explicitly modelled	Weeks 5 - 52: 73.83% Weeks 53+: 67.46%
Cost/patient/4-week period	-	Weeks 5 - 8: $[redacted] Weeks 9 - 40: $[redacted] Week 41+: $[redacted]	Weeks 5 - 52: $[redacted] Weeks 53+: $[redacted]
Persistence[7]	91.4%	Y1: 33.04% Y2: 18.85% Y3: 10.94% Y4: 6.35% Y5: 3.69%	Y1: 48.40% Y2: 22.67% Y3: 13.09% Y4: 7.60% Y5: 4.41% Y6: 2.56%
ORAL ANTIDEPRESSANT COSTS			
Cost/patient/4-week period	-	$17.20[8]	Not included
Adherence	Varies by treatment (≥91.7% in TRANSFORM-2)	100%	Not included
Persistence	89.2%	100%	Not included

Source: Table 3.12 Table 2.4-15; Section 4.2.1.5.2 of the submission. 'Drug costs' and 'Drug cost – details' worksheets of the 'Esketamine TRD CE model', Attachment 19 of the submission; 'Compliance and persistence', 'Scripts – proposed' and 'Impact – proposed (eff)' worksheets of the 'Utilisation cost model – esketamine TRD' Excel workbook, Attachment 25 of the submission.

Abbreviations: DPMQ, dispenses price for maximum quantity.

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

[2] Based on a weighted Public/Private (20%/80%) hospital DPMQ of $[redacted] for 28 mg dose (8 x 28 mg units).

[3] Based on a weighted Public/Private (20%/80%) hospital DPMQ of $[redacted] for 56 mg dose (16 x 28 mg units) and $[redacted] for 84 mg dose (24 x 28 mg units), assuming a 47%/53% split between 56 mg and 84 mg doses.

[4] The source data could not be verified during the evaluation.

[5] Based on a weighted Public/Private (20%/80%) hospital DPMQ of $[redacted] for 28 mg dose (4 x 28 mg units).

[6] Based on a weighted Public/Private (20%/80%) hospital DPMQ of $[redacted] for 56 mg dose (8 x 28 mg units) and $[redacted] for 84 mg dose (12 x 28 mg units), assuming a 39%/61% split between 56 mg and 84 mg doses.

[7] Economic model persistence based on the proportion of patients remaining on esketamine at the end of each treatment year; financial estimates persistence based on average annual persistence.

[8] Average cost of PBS-listed antidepressants weighted by market share according to PBS data from February 2020 to January 2021.

Estimated PBS usage & financial implications

6.63 The submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of esketamine for TRD.

Table 16: Key inputs for the financial estimates

Parameter	Value applied and source	Comment
Prevalence of MDD (2007)	4.1%. Based on the 2007 National Survey of Mental Health and Wellbeing, 4.1% of Australians aged 16 to 85 years had previously been diagnosed with MDD in their lifetime, and reported symptoms of depression in the past 12 months.	While patients reported symptoms of depression in the prior 12 months, this may not have represented a major depressive episode. Additionally, patients may have been receiving treatment for MDD but not experienced symptoms in the prior 12 months.
Prevalence of MDD (2022-2027)	6.08% in year 1 to 6.94% in year 6. Based on the results of the 2017/18 National Health Survey, 10.4% of Australians had depression or feelings of depression, an increase from 8.9% in the 2014/15 National Health Survey. The submission estimated an average annual growth of 5.3% for 2014/2015 to 2017/18 and assumed that the growth in 12-month MDD prevalence was half this rate (2.66%).	The applicability of the Australian National Health Survey results (which were based on self-reported depression or feelings of depression rather than a clinical diagnosis of depression) to the prevalence of MDD was unclear. The growth assumption used to inflate the 2007 estimate did not appear to be well supported.
Proportion of adult MDD patients who have TRD	33%. Based on the results of the STAR*D study, which reported a cumulative remission rate of 67% following four treatments. The study recruited outpatients with nonpsychotic MDD (N=3,671).	The study was conducted between 2001 and 2006 and included treatments not commonly used in Australia (e.g., bupropion; triiodothyronine augmentation). Additionally, treatments were protocol-specified, and some patients were treated with non-pharmacological therapy (cognitive therapy alone or as a second-line add-on to citalopram therapy). A large number of patients discontinued the study, and only a small number of patients received a fourth line of treatment (N=123).
Proportion of patients who are eligible and becoming available for treatment in the year	9% in year 1 to 11% in year 6. TRD patients with inadequate responses to two or more antidepressants in the current MDD episode and started a new treatment regimen in one year derived from a 10% PBS sample analysis conducted between November 2019 and October 2020 (28,820 / 386,669 = 7.5%). Assumed to increase each year due to PBS listing of esketamine.	It is unclear whether the method used to conduct the 10% PBS sample analysis captured all relevant patients with TRD and those with TRD initiating a new treatment. The availability of a new treatment may result in an increase in patients initiating a new therapy.
Proportion of patients starting treatment at the psychiatry setting	22.66% in year 1 to 26.27% in year 6. Proportion of TRD patients who have had inadequate responses to two or more antidepressants in the current MDD episode and started a new treatment regimen in the psychiatry setting based on a 10% PBS sample analysis. Out of 28,820 patients who initiated a new treatment from November 2019 to October 2020, 6,340 patients started the new treatment in the psychiatry setting (22.0%). The submission assumed a 3% increase per year due to increased GP referrals to psychiatrists.	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.
Uptake rate	30% in year 1 to 50% in year 6. Sponsor assumption based on expert opinion.	The uptake of esketamine is considered highly uncertain. Esketamine represents a novel treatment for a disorder that is resistant to

Parameter	Value applied and source	Comment
		standard therapies. However, uptake is likely to be constrained by the ability of treatment sites to comply with esketamine delivery, handling and monitoring requirements. It is unclear how many treatment sites will possess the required capacity to offer esketamine treatment.
Dose distribution between 56 mg and 84 mg dose	Initial: 56 mg - 47.0%; 84 mg - 53.0%. Continuing: 56 mg - 39.5%; 84 mg - 60.5%. Distribution derived from the mean daily dose of esketamine in the TRANSFORM-2 trial four-week initial treatment period (70.7 mg, equating to 2.5298 esketamine devices), and the average number of esketamine devices used per session in the SUSTAIN-1 maintenance phase (2.6053). 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 submission did not account for patients receiving a 28 mg dose. The recommended dose for patients aged ≥65 years is 28 mg, however, patients ≥65 years were excluded from the trials that informed dose distribution. The dose distribution among the PBS population may differ from the distribution in the clinical trial setting.
Persistence	48.4% in year 1 to 58.05% in year 6. Derived from the proportion of patients remaining on treatment each year in the economic model.	Differences between the clinical trial setting and Australian clinical practice may result in differences in persistence. The proposed restriction does not preclude repeat courses of esketamine, which were not accounted for in the financial estimates.
Compliance	92.5% for initial treatment, 73.8% for continuing treatment in the initiation year, and 67.5% in subsequent years. Derived from TRANSFORM-2 (initial treatment) and SUSTAIN-1 (maintenance) trial data.	Differences between the clinical trial setting and Australian clinical practice may result in differences in compliance. Difficulty in accessing supervised administration, the burden of twice weekly, weekly, or fortnightly appointments for administration, and the inability to drive for the rest of the day following treatment, may impact compliance.
Esketamine price	$[redacted] (28 mg pack); $[redacted] (56 mg pack); $[redacted] (84 mg pack). Proposed effective AEMP.	
Private/Public hospital use	Private: 80%; Public: 20%. Based on sponsor assumption.	The relative proportion between the public and private setting will be dependent on the participation of treatment centres, which is currently uncertain.
Psychiatrist consultations	$36.28. Based on MBS Item 300 (< 15 mins); 80% of the schedule fee.	Costs associated with esketamine administration and monitoring are likely to be substantially higher than estimated. The included MBS cost was inappropriately based on 80% of the schedule fee rather than 85%.

Source: Source: Section 4.1; Section 4.2; Section 4.5.2 of the submission.
Abbreviations: AEMP, approved ex-manufacturer price; COVID-19, coronavirus disease 2019; GP, general practitioner; MBS, Medicare Benefits Scheme; MDD, major depressive disorder; TRD, treatment-resistant depression; Yr, Year.

6.64 Table 17 presents the estimated net cost listing of esketamine on the PBS/RPBS for TRD.

Table 17: Estimated net cost of listing esketamine on the PBS/RPBS for TRD

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Eligible patients						
Australian population ≥18 years	[redacted][a]	[redacted][a]	[redacted][a]	[redacted][a]	[redacted][a]	[redacted][a]
Prevalence of MDD	6.08%	6.24%	6.41%	6.58%	6.76%	6.94%

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Prevalent MDD patients	[redacted]b	[redacted]b	[redacted]b	[redacted]b	[redacted]b	[redacted]b
Proportion with treatment-resistant depression (33.3%)	[redacted]c	[redacted]c	[redacted]c	[redacted]c	[redacted]c	[redacted]d
Proportion initiating new treatment	[redacted]e (9.0%)	[redacted]f (10.0%)	[redacted]f (10.7%)	[redacted]g (10.9%)	[redacted]g (11.0%)	[redacted]g (11.0%)
Patients treated by a psychiatrist	[redacted]h (22.7%)	[redacted]g (23.3%)	[redacted]g (24.0%)	[redacted]g (24.8%)	[redacted]g (25.5%)	[redacted]g (26.3%)
Initial treatment scripts						
Esketamine uptake	30%	40%	48%	49%	50%	50%
Initiating patients	[redacted]	[redacted]	[redacted]h	[redacted]h	[redacted]h	[redacted]h
Initial treatment scripts[1] - 56 mg scripts (47.0%) - 84 mg scripts (53.0%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing scripts - initiation year						
Continuing patients (48.4%)[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing scripts[1] - 56 mg scripts (39.5%) - 84 mg scrips (60.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing scripts - subsequent years						
Total continuing patients	[redacted]k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing scripts[1] - 56 mg dose (39.5%) - 84 mg dose (60.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS/RPBS						
Total scripts - 56 mg scripts - 84 mg scripts	[redacted]	[redacted]	[redacted]f	[redacted]g	[redacted]m	[redacted]m
Total PBS/RPBS cost - 56 mg scripts[3] - 84 mg scripts[4]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient copayments	$[redacted]w	$[redacted]w	$[redacted]w	$[redacted]w	$[redacted]w	$[redacted]w
Net PBS/RPBS cost	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Change in MBS Item 300 services	[redacted]m	[redacted]x	[redacted]x	[redacted]y	[redacted]y	[redacted]z
Change in MBS Item 300 cost	$[redacted]w	$[redacted]w	$[redacted]w	$[redacted]w	$[redacted]w	$[redacted]o
Net cost to Government	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4-2; Table 4-5; Table 4-8; Table 4-9 of the submission; 'Utilisation cost model – esketamine TRD' Excel workbook, Attachment 25 of the submission

Abbreviations: MBS, Medicare Benefits Scheme.

[1] Includes compliance of 92.5% for initiating patients, 73.8% for patients continuing in initiation year, and 67.5% in subsequent years.

[2] Average proportion of initiated patients receiving the continuing treatment in the initiation year, derived based on the treatment persistence in the economic model.

[3] Based on a weighted effective DPMQ (Public/Private 20%/80%) of $[redacted] for initial scripts and $[redacted] for continuing scripts.

[4] Based on a weighted effective DPMQ (Public/Private 20%/80%) of $[redacted] for initial scripts and $[redacted] for continuing scripts.

The redacted values correspond to the following ranges:

[a] *> 10,000,000*

[b] *1,000,000 to < 2,000,000*

[c] *400,000 to < 500,000*

[d] *500,000 to < 600,000*

[e] *30,000 to < 40,000*

[f] *40,000 to < 50,000*

[g] *50,000 to < 60,000*

[h] *5,000 to < 10,000*

[i] 10,000 to < 20,000
[j] 500 to < 5,000
[k] <500
[l] 20,000 to < 30,000
[m] 60,000 to < 70,000
[n] $30 million to < $40 million
[o] $10 million to < $20 million
[p] $20 million to < $30 million
[q] $40 million to < $50 million
[r] $50 million to < $60 million
[s] $60 million to < $70 million
[t] $70 million to < $80 million
[u] $100 million to < $200 million
[v] $90 million to < $100 million
[w] $0 to < $10 million
[x] 100,000 to < 200,000
[y] 200,000 to < 300,000
[z] 300,000 to < 400,000

6.65 The estimated net cost to the PBS/RPBS based on the proposed effective price was $30 million to < $40 million in Year 1 of listing, increasing to $100 million to < $200 million in Year 6 with an estimated net cost of $600 million to < $700 million over the first six years of listing. The estimated net cost to Government over the first six years of listing was $700 million to < $800 million.

6.66 The DUSC considered the estimates presented in the submission were underestimated and noted the following:

- The estimated eligible population is uncertain due to a lack of recent Australian prevalence studies and assumptions relating to prevalence growth, the estimated proportion of patients with TRD and assumptions relating to the proportion of patients who fail at least two treatments for a major depressive episode each year.
- The financial impacts incorporated compliance, persistence and dose distribution estimates derived from the TRANSFORM-2 and SUSTAIN-1 clinical trials and the DUSC considered the applicability of the trial-based estimates to Australian clinical practice is unclear. The DUSC noted the submission did not account for patients receiving the 28 mg dose of esketamine.
- The costs associated with esketamine administration and monitoring appeared to be significantly underestimated.
- The optimum duration of treatment with esketamine is unclear and the DUSC noted the financial estimates did not account for repeat courses of esketamine.
- Difficulty in accessing supervised administration, the burden of twice weekly, weekly, or fortnightly appointments for administration, and the inability to drive for the rest of the day following treatment, may impact compliance.
- 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.

Quality Use of Medicines

6.67 The sponsor noted that the dispensing and storage of esketamine nasal spray will present a number of challenges including:

- Patients will not be permitted to handle the drug until ready for administration in the clinic.
- Administration of esketamine nasal spray must be under the supervision of a healthcare professional on a twice weekly, weekly, or fortnightly basis.
- The need for timely esketamine delivery.
- Compliance with State Government requirements relating to Schedule 8 drugs.

6.68 The submission stated that a controlled access program has been created in which the supply of esketamine will be restricted to sponsor-initiated treatment sites where a health care professional is trained to administer esketamine and monitor patients in accordance with the product information. The submission stated that the program has been developed to mitigate the potential risk of drug abuse, misuse and diversion.

6.69 Additional quality use of medicines issues noted during the evaluation include:

- Esketamine can cause transient increases in blood pressure. Patients with cardiovascular and cerebrovascular conditions should be carefully assessed before prescribing esketamine and treatment initiated only if the benefit outweighs the risk. The product information notes that esketamine should be used with caution in the presence or a history of psychosis; the presence or history of mania or bipolar disorder; hyperthyroidism that has not been sufficiently treated; significant pulmonary insufficiency; known uncontrolled bradyarrhythmias or tachyarrhythmias that lead to haemodynamic instability; or a history of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure.
- The potential for tolerance and dependence to develop during esketamine treatment, and the potential for withdrawal symptoms to occur following esketamine treatment cessation.
- There are potential risks to the patient and the general public if advice not to drive following esketamine dosing is disregarded.
- There is potential for use outside of the recommended age range. The efficacy and safety of esketamine have not been established in patients aged ≤17 years.
- There may be residual medicine contained in the delivery device following use, which will require disposal as per Schedule 8 medicine requirements.
- The esketamine devices are relatively bulky and may be difficult to store in treatment facility Schedule 8 drug safes.

- Treatment centres will require adequate facilities for the management of adverse events.

6.70 The DUSC noted the following additional Quality Use of Medicines issues:

- The restriction requiring treatment to be used in combination with a newly initiated oral antidepressant was problematic noting that clinical practice guidelines would never start two new treatments at the same time.
- There are significant access to treatment issues, as the availability and location of psychiatrists is limited in some areas of Australia.
- Esketamine can cause adverse side effects, which could have been underestimated in the submission due to limited longer term follow up and real-world utilisation data.

Financial Management – Risk Sharing Arrangements

6.71 The submission noted potential uncertainty in the utilisation of esketamine, including the number of patients eligible for treatment, and the number of treated patients. The submission proposed a Risk Sharing Arrangement consisting of a rebate of [redacted]% for use above specified subsidisation caps. The proposed subsidisation caps were set according to the estimated financial impacts over the first five years of listing.

6.72 Table 18 presents the subsidisation caps proposed in the submission.

Table 18: Proposed risk-sharing arrangement subsidisation caps

	Year 1	Year 2	Year 3	Year 4	Year 5
Value of subsidisation caps	$[redacted][1]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Proposed rebate for spend above cap	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Source: Table 4-14 of the submission.

The redacted values correspond to the following ranges:

[1] *$30 million to < $40 million*

[2] *$60 million to < $70 million*

[3] *$100 million to < $200 million*

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

7 PBAC Outcome

7.1 The PBAC did not recommend the Section 100 listing of esketamine for the treatment of treatment-resistant depression (TRD), defined as patients 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, as the role of esketamine nasal spray in clinical practice was unclear. The PBAC considered this reflected (i) the uncertainty regarding the clinical significance of observed benefit in the clinical trials, (ii) the optimal dose and duration of treatment for each individual patient being unclear, (iii) the lack of long-term safety together with the potential for tolerance and dependence, and (iv) it being unclear how esketamine would be appropriately integrated into clinical practice given the administration and monitoring

requirements. Based on these concerns the PBAC considered esketamine should be reserved for patients in whom alternative therapies beyond two different antidepressants have been considered.

7.2 The PBAC acknowledged there is a moderate to high clinical need for alternative treatment options for TRD and this was supported by the consumer comments received. However, the PBAC considered the proposed placement of esketamine after failure of two antidepressants was too early in the treatment algorithm, given the availability of established alternatives such as combination OAD therapy, augmentation therapy, psychotherapy, ECT and other physical interventions. The PBAC noted that the management of depressive disorders such as TRD are complex and considered that as the place in therapy of esketamine nasal spray is unclear and emerging, the integration of esketamine alongside non-pharmacological treatment options in practice, such as ECT, is unclear.

7.3 The PBAC noted the submission requested the formation of a new stand-alone Section 100 program for esketamine, on the basis that esketamine has unique administration requirements (i.e., it needed to be taken in the presence of a healthcare practitioner). The PBAC considered it was unclear why the administration requirements could not be managed under current PBS programs (such as the Section 100 Highly Specialised Drugs program) and why a separate Section 100 program for esketamine was required. The PBAC noted some information regarding how patients would access esketamine was provided in the PSCR but the sponsor should provide further detail in any resubmission to ensure the appropriate PBS program could be identified.

7.4 The PBAC considered substantial changes would be required to the proposed restriction for esketamine to reflect a more appropriate place in the treatment algorithm for TRD. The PBAC noted any proposed restriction criteria in a resubmission should address the issues raised in Section 3 where relevant.

7.5 The PBAC noted the use of esketamine in combination with a newly initiated OAD was consistent with the clinical evidence and the TGA indication but considered the PBS restrictions should allow flexibility to enable the treatment needs of individual patients to be considered.

7.6 The PBAC noted the nominated comparator was a newly initiated OAD and considered that, while this may be an appropriate comparator for esketamine in the proposed clinical positioning, it was too early in the treatment algorithm. The PBAC noted there are a number of PBS and non-PBS alternative treatment options that may be appropriate comparators if esketamine was positioned later in the treatment algorithm.

7.7 The PBAC noted the clinical evidence for esketamine consisted of three short-term, double blind, randomised controlled trials (RCTs) (TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3) comparing esketamine plus a newly initiated OAD to a newly initiated OAD alone and three long-term studies (SUSTAIN-1, SUSTAIN-2 and SUSTAIN-3). The PBAC noted the clinical and economic comparisons in the submission were based on

the TRANSFORM-2 and SUSTAIN-1 studies. The PBAC considered the results from TRANSFORM-1 and TRANSFORM-3 to be relevant, although acknowledged the use of a fixed dose of esketamine rather than the recommended flexible regimen. The PBAC noted TRANSFORM-3 was the only trial that included patients over 65 years of age and that esketamine is indicated in this patient population. The PBAC noted a statistically significant treatment effect of esketamine nasal spray was not demonstrated in TRANSFORM-1 and TRANSFORM-3.

7.8 The PBAC noted the TRANSFORM-2 trial reported a statistically significant improvement in MADRS score for patients treated with esketamine plus a newly initiated OAD compared to a new OAD alone with a mean improvement of 4.0 points (95%CI: -7.3, -0.6) (in an instrument where the total score ranges from 0 to 60) at 4 weeks. The PBAC noted a higher proportion of people treated with esketamine plus a newly initiated OAD achieved a 50% reduction in MADRS score at 4 weeks (69% vs 52%) and a higher proportion achieved remission (defined as a MADRS score ≤ 12) (53% vs 31%). The PBAC noted there were a number of issues that complicated the interpretation of these results (paragraph 6.31); however, considered that, on balance, esketamine was likely to be effective in some patients but the magnitude and clinical relevance of the benefit remained uncertain.

7.9 The PBAC noted the SUSTAIN-1 trial indicated a statistically significant reduction in median time to relapse compared to placebo in patients who responded to esketamine + an OAD and were later re-randomised to receive either esketamine or placebo (+ ongoing OAD). The PBAC agreed with the ESC and was concerned that given the adverse event profile of esketamine, the design of the trial (where every participant received esketamine initially) may lead to unblinding of some patients who were randomised to placebo (paragraph 6.20) and the PBAC considered this may overestimate the efficacy of esketamine.

7.10 The PBAC noted that patients in the esketamine arm of the clinical trials were more likely to experience adverse events such as dizziness, dissociation and vertigo and considered the submission reasonably described esketamine as having inferior comparative safety to placebo/new OAD alone. The PBAC noted there was limited data available regarding the long-term safety or potential for tolerance and dependence of esketamine.

7.11 Overall the PBAC considered the benefit of esketamine treatment had been overestimated in the economic model due to modelling a substantially higher proportion of patients as recovered over a relatively long period of time. The PBAC considered the modelled benefit was inconsistent with the totality of the clinical evidence. The PBAC considered the modelled costs to be uncertain noting the optimal dose and duration of esketamine treatment is unknown, and the issues relating to the costs associated with the administration of esketamine and the disease management costs, including those for subsequent therapies. The PBAC also considered the applicability of the model results if esketamine use was restricted to later in the treatment algorithm was unknown.

7.12 The PBAC considered the financial estimates provided in the submission are based on esketamine being positioned too early in the treatment algorithm and any resubmission would require substantial revision to reflect use later in the treatment algorithm.

7.13 The PBAC advised the submission was 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

The sponsor had no comment.