

An addendum to this public summary document has been included at the end of the document.

7.01 ESKETAMINE, Nasal spray solution 28 mg in 0.2 mL (2 actuations) Spravato[®], Janssen-Cilag Pty Ltd.

1 Purpose of submission

- 1.1 The standard re-entry submission requested Section 100 (Highly Specialised Drug Program) Authority Required (Telephone/Online) listing for esketamine for the treatment of treatment-resistant depression (TRD).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus a newly initiated OAD.

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

Component	Description
Population	Adults with major depressive disorder, who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate to severe depressive episode.
Intervention	Esketamine hydrochloride is to be administered in conjunction with an oral antidepressant, under the supervision of a healthcare professional. Dosing depends on age and phase of treatment. Patients receive either 1 device (28 mg dose), 2 devices (56 mg dose) or 3 devices (84 mg dose) and are treated twice per week (weeks 1-4 of treatment), weekly (weeks 5-8), and weekly or fortnightly thereafter. Evidence of therapeutic benefit should be evaluated at the end of induction phase (4 weeks) to determine need for continued treatment. After depressive symptoms improve, treatment should continue for at least 6 months, with patients monitored to determine continuing response. Esketamine is discontinued once a patient relapses or when a patient recovers. <u>For most patients, the maximum treatment duration is 12 months per major depressive episode. A proportion of patients will require treatment beyond 12 months per major depressive episode. These would generally be (but not specifically limited to) patients who were continuing to respond to treatment but had not achieved remission or recovery. Retreatment with esketamine is clinically appropriate for patients who have responded to treatment with esketamine in a previous major depressive episode, after a break of at least 4 months between esketamine treatments.</u>
Comparator	Initiation of a new oral antidepressant.
Outcomes	Change in depression severity (using the Montgomery-Asberg Depression Rating Scale (MADRS) total score), incidence of clinical response and remission, occupational, social and family functioning, quality of life, incidence of adverse events.
Clinical claim	Esketamine nasal spray in combination with a newly initiated oral antidepressant is superior in terms of efficacy and inferior in terms of safety when compared to a newly initiated oral antidepressant alone.

Source: Table 1-1, of the submission.

Note: Underlined text indicates changes/additions to the July 2023 resubmission.

Note: Unlike the clinical evidence presented in the resubmission and the approved TGA indication, the requested restrictions do not require concomitant treatment with an oral antidepressant to be newly initiated.

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). Spravato [esketamine] is to be initiated in conjunction with a newly initiated oral antidepressant”.

Previous PBAC consideration

2.2 This is the fourth PBAC consideration of esketamine. Esketamine was previously considered for the treatment of patients with TRD at the July 2021, July 2022 and July 2023 PBAC meetings.

2.3 The matters of concern from the July 2023 meeting are summarised in Table 2 below.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Restriction	The PBAC noted that there needed to be some flexibility regarding the maximum 12-month treatment duration and allowing retreatment may be appropriate for some patients after a reasonable period of time off treatment (para 7.4, esketamine Public Summary Document (PSD), July 2023 PBAC meeting)	Restrictions were proposed for patients receiving up to 12 months of treatment (majority of patients); patients treated beyond 12 months (new restriction); and patients who have previously responded to esketamine and require retreatment for a new MDE (new restriction)
Clinical evidence	The PBAC recalled its previous view that the claim of superior comparative effectiveness may be reasonable, although the magnitude and clinical importance of the observed benefits was uncertain (para 7.10, esketamine PSD, July 2023 PBAC meeting).	The comparative clinical evidence is unchanged.
Economic analysis	The PBAC noted the economic model included a single course of treatment, and considered that while it was uncertain how many patients would receive more than one course of treatment over a 5 year period, it was likely to be a high proportion of patients (para 7.1, esketamine PSD, July 2023 PBAC meeting).	The economic model allows for a proportion of patients who have responded to initial treatment to be retreated if they subsequently relapse into MDD provided they have had a minimum 4 month treatment break.
	The PBAC noted that it would be appropriate to allow for a maximum treatment duration of 12 months per patient; and that stakeholders considered there needed to be some flexibility regarding the maximum treatment duration (para 7.4, esketamine PSD, July 2023 PBAC meeting).	Observed Australian supply data of esketamine from the sponsor’s early access program was used to inform the proportion of patients treated beyond 12 months.

Component	Matter of concern	How the resubmission addresses it
	<p>PBAC and ESC noted that some inputs to the economic model remained uncertain (paras 6.65, 7.13, esketamine PSD, July 2023 PBAC meeting):</p> <ul style="list-style-type: none"> - assumed rates of hospitalisation based on UK data remained uncertain; - use of the STAR*D study to inform some of the transition probabilities given it may not reflect contemporary practice; - the 5 year time horizon; - the EQ-5D-5L utility values which were mapped to a UK value set; - the frequency of dosing and doses likely to be used in practice; and - the administration and monitoring costs. 	<p>Australian data are used to inform health care resource use.</p> <p>The resubmission acknowledged concerns regarding whether the STAR*D study reflects contemporary practice, but argued that current practice has generally not changed significantly since the study was conducted and STAR*D remains the best available data to inform the economic evaluation.</p> <p>Other ESC/PBAC concerns were not addressed in the resubmission (uncertainties regarding the time horizon, health state utilities, dosing used in clinical practice and administration and monitoring costs).</p>
Financial estimates	<p>The PBAC considered the uptake of esketamine in new patients was likely overestimated (26% in Year 1, 45% in Year 6, average 39%) (para 7.15, esketamine PSD, July 2023 PBAC meeting).</p>	<p>The resubmission revised uptake rates in new patients to 31% in Year 1, to 39% in year 6, an average of 36%</p>
	<p>The PBAC considered the sponsor's assumption of retreatment rates (40% applied to all esketamine patients) uncertain, and that retreatment should have been modelled as a proportion of responders/remitters and risk of subsequent episodes of TRD, rather than added into subsequent lines of therapy with uptake rate (Table 18, esketamine PSD, July 2023 PBAC meeting)</p>	<p>The resubmission assumed a higher retreatment rate of 100% but applied to a smaller patient pool of patients who responded to initial esketamine treatment and who had subsequently relapsed. Of patients treated in Year 1, 61% receive retreatment over 6 years.</p>
	<p>The PBAC noted that the appropriate duration of treatment with esketamine remains uncertain but it would be appropriate to allow for a maximum treatment duration of 12 months per patient (para 7.4, esketamine PSD, July 2023 PBAC meeting).</p>	<p>The resubmission modified the financial estimates to reflect a maximum treatment duration of 12 months for █% of the initial and retreated population, with █% continuing beyond 12 months of therapy; based on data from the sponsor's early access program.</p>
	<p>The PBAC noted that uncertainties regarding the use of esketamine, which impact the cost-effectiveness and financial estimates, could potentially be addressed with a managed access program (para 7.16, esketamine PSD, July 2023 PBAC meeting)</p>	<p>The resubmission argued that a managed access program for esketamine is not feasible or practical, and instead sought to address outstanding uncertainties through revised hospitalisation inputs in the economic model base case, and a revised risk sharing arrangement with a higher rebate █% compared to █% in the July 2023 resubmission) for any use above the subsidisation caps.</p>

Source: Table (unlabelled) of the submission.

Abbreviations: MDD, major depressive disorder; MDE, major depressive episode; TRD, treatment resistant depression

2.4 The Pre-Sub-Committee Response (PSCR) raised, and the ESC noted that, following the July 2023 PBAC meeting, the sponsor presented its approach for a resubmission to the Chairs of the PBAC and Department staff, focusing on:

- the available data to support retreatment and use beyond 12 months;
- the appropriate economic model structure to capture the cost-effectiveness of retreatment and use beyond 12 months;
- potential alternative data source for the rate of hospitalisation; and
- the feasibility of a Managed Access Program and/ or a Risk-Sharing Arrangement to address outstanding uncertainties.

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

3 Requested listing

3.1 Five separate restrictions were requested (i) initial induction treatment (weeks 1-4) (ii) initial maintenance treatment (weeks 5-52) (iii) treatment beyond 12 months (for either initial treatment or retreatment, weeks 53 onwards) (iv) retreatment induction (weeks 1-4), and (v) retreatment maintenance (weeks 5-52).

3.2 The criteria below incorporates changes proposed by the Secretariat with additions in italics and deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Published (effective) Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESKETAMINE					
Initial treatment/induction (Treatment weeks 1-4) and retreatment (weeks 1-4)					
Nasal spray device 28 mg, 1	Public Hospital: \$1 (\$1) Private Hospital/Community access: \$1 (\$1)	8	8	0	Spravato
Nasal spray device 28 mg, 2	Public Hospital: \$1 (\$1) Private Hospital/Community access: \$1 (\$1)	8	16	0	Spravato
Nasal spray device 28 mg, 3	Public Hospital: \$1 (\$1) Private Hospital/Community Access: \$1 (\$1)	8	24	0	Spravato
Continuing treatment (weeks 5-52), retreatment (weeks 5-52), and use beyond 12 months (weeks 53 and beyond)					
Nasal spray device 28 mg, 1	Public Hospital: \$1 (\$1) Private Hospital/Community Access: \$1 (\$1)	4	4	2	Spravato
Nasal spray device 28 mg, 2	Public Hospital: \$1 (\$1) Private Hospital/Community Access: \$1 (\$1)	4	8	2	Spravato
Nasal spray device 28 mg, 3	Public Hospital: \$1 (\$1) Private Hospital/Community Access: \$1 (\$1)	4	12	2	Spravato

Category / Program: Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals; Community Access}
Prescriber type: <input type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
Administrative Advice: Care must be taken to comply with the provisions of the state/territory law for prescribing this drug
Administrative Advice: No increases quantity or repeats will be authorised
Administrative Advice: Special Pricing Arrangements apply
Condition: Major depressive disorder

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Indication: Major depression Major depressive disorder
Treatment Phase: Induction treatment – first use in a major depressive disorder episode (weeks 1-4 of treatment with this drug) where the intended administered dose is [28 mg / 56 mg / 84 mg]
Clinical criteria:
The condition must be inadequately responsive(see Note) to at least two anti-depressant drug therapies from different pharmacological classes prior to the first administered dose of this drug
AND
Clinical criteria:
The treatment must be for a new episode of active, major depression
AND
Clinical criteria:
The treatment must not exceed each of: (i) An administered dose beyond 84 mg; (ii) a quantity that of drug after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceeds 8 doses over a period of 4 weeks of treatment when dosed within the Product Information recommended dosage
AND
Clinical criteria:
Patient must be undergoing concomitant treatment with an oral anti-depressant drug therapy
AND
Clinical criteria:
[Section 100 Public Hospital only] Must be treated in a public hospital outpatient clinic
[Section 100 Private Hospital only] Must be treated in a hospital that is not a public hospital
AND
Treatment criteria:
Must be treated by a psychiatrist
AND
Treatment criteria:
Prescribing Instructions:
Patient must be undergoing supervision by a healthcare professional at the time the drug is administered
AND
Population criteria:
Patient must be at least 18 years of age
Prescribing Instructions: optional (free text)
<p>Prescribing Instructions: [Section 100 Public Hospital] The psychiatrist must complete the authority application on each and every occasion. By seeking an authority application, the psychiatrist is declaring each of:</p> <ul style="list-style-type: none"> (i) they are affiliated with the public hospital at which the patient is receiving treatment at, (ii) has completed prescribing accreditation required by the pharmaceutical manufacturer of this drug, (iii) understands prior to prescribing this drug that these prescription details are to be provided only to the public hospital's pharmacy where it is known to have completed dispensing accreditation required by the pharmaceutical manufacturer (iv) has made suitable arrangements to forward the prescription directly to the public hospital's pharmacy, but only where it is an accredited dispenser, (v) has provided written direction on the prescription for the drug to be supplied directly to the healthcare professional who will supervise drug administration, at a prescribed frequency (vi) has provided written direction on the prescription to store/retain any un-administered drug/repeat prescriptions on the premises of the pharmacy <p>[Section 100 Private Hospital] The psychiatrist must complete the authority application on each and every occasion. By seeking an authority application, the psychiatrist is declaring each of:</p> <ul style="list-style-type: none"> (i) has completed prescribing accreditation required by the pharmaceutical manufacturer of this drug,

~~(ii) understands prior to prescribing this drug that these prescription details are to be provided only to the private hospital's pharmacy (or approved pharmacy provider) where it is known to have completed dispensing accreditation required by the pharmaceutical manufacturer~~
~~(iii) has made suitable arrangements to forward the prescription directly to the private hospital's pharmacy (or approved pharmacy provider), but only where it is an accredited dispenser,~~
~~(iv) has provided written direction on the prescription for the drug to be supplied directly to the healthcare professional who will supervise drug administration, at a prescribed frequency~~
~~(v) has provided written direction on the prescription to store/retain any un-administered drug/repeat prescriptions on the premises of the pharmacy~~

~~[Section 100 Community Access]~~ The psychiatrist must complete the authority application on each and every occasion. By seeking an authority application, the psychiatrist is declaring each of:

~~(i) has completed prescribing accreditation required by the pharmaceutical manufacturer of this drug,~~
~~(ii) understands prior to prescribing this drug that these prescription details are to be provided only to a pharmacy where it is known to have completed dispensing accreditation required by the pharmaceutical manufacturer, including an appropriate hospital based pharmacy to the prescribing setting, if relevant.~~
~~(iii) has made suitable arrangements to forward the prescription directly to a pharmacy, but only where it is an accredited dispenser,~~
~~(iv) has provided written direction on the prescription for the drug to be supplied directly to the healthcare professional who will supervise drug administration, at a prescribed frequency~~
~~(v) has provided written direction on the prescription to store/retain any un-administered drug/repeat prescriptions on the premises of the pharmacy~~

Administrative Advice:

For the purposes of this restriction, 'inadequately responsive' means:

(i) the therapies are listed on the Australian Register of Therapeutic Goods and the approved Product Information list 'Major depression/depressive disorders' in the indications section;
 (ii) the prescribed anti-depressants have at least 2 different pharmacological mechanisms of action (e.g. a serotonin-selective reuptake inhibitor and a tricyclic antidepressant meets this requirement);
 (iii) patient non-compliance with treatment has been excluded as a cause of treatment non-response/inadequate response;
 (iv) the prescribed anti-depressants have been prescribed at a therapeutic dose;
 (v) the prescribed anti-depressants have been prescribed for at least 4-6 continuous weeks
 (vi) the prescribed anti-depressants have been prescribed concomitantly with psychological therapy where psychological therapy is/has been considered clinically appropriate by the prescriber

No increase in the maximum quantity or number of units may be authorised.

No increase in the maximum number of repeats may be authorised.

Special Pricing Arrangements apply.

Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

Prescriber Instruction:

Authority required (telephone and online) – General PBS administration Concept ID 25796

Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia.

Category / Program:

Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals; Community Access}

Prescriber type: Medical Practitioners

Restriction Level / Method:

Authority Required – Telephone/Electronic/Emergency

Administrative Advice:

Insert administrative notes here that may apply across multiple restrictions; otherwise delete this row

Condition: Major depressive disorder

Indication: ~~Major depression~~ Major depressive disorder

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Treatment Phase: Continuing treatment – up to week 52 (weeks 5-52 of the same treatment episode) where the intended administered dose is [28 mg / 56 mg / 84 mg]
Clinical criteria:
The treatment must be to continue existing PBS-subsidised treatment for the same episode of major depression
OR
The treatment must be to transition once only a patient from non-PBS to PBS-subsidised supply, where each of the following is true: (i) the condition has been inadequately responsive (see Note) to at least two anti-depressant drug therapies from different pharmacological classes prior to the first administered dose of this drug, (ii) non-PBS supply was prescribed by a psychiatrist when the patient was at least 18 years of age
AND
Clinical criteria:
The treatment must not exceed each of: (i) an administered dose beyond 84 mg, (ii) a quantity of drug, after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceed a quantity sufficient to treat the patient for 12 weeks (i.e. the listed maximum quantity is based on once weekly dosing – where fortnightly dosing is prescribed, the authority application is to seek no more than half the listed maximum quantity of this listing)
AND
Treatment criteria:
Patient must be undergoing concomitant treatment with an oral anti-depressant drug therapy
AND
Treatment criteria:
Patient must not be undergoing PBS-subsidised treatment with this drug beyond week 52 of the same episode of major depression. <i>Treatment must not exceed a total of 48 weeks' treatment under this restriction.</i>
AND
Treatment criteria:
[Section 100 Public Hospital only] Must be treated in a public hospital outpatient clinic
[Section 100 Private Hospital only] Must be treated in a hospital that is not a public hospital
AND
Treatment criteria:
Must be treated by a psychiatrist
AND
Treatment criteria:
Prescribing Instructions:
Patient must be undergoing supervision by a healthcare professional at the time the drug is administered
AND
Population criteria:
Patient must be at least 18 years of age
Prescriber Instruction:
Authority required (telephone and online) – General PBS administration Concept ID 25796 Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia.
Administrative Advice: Where treatment exceeding a total of 52 weeks' is required in the current major depressive episode, further continuing authority and prescribing must be sought under the relevant PBS item.
Category / Program:
Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals; Community Access}
Prescriber type: <input type="checkbox"/> Medical Practitioners
Restriction Level / Method:
<input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency

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Administrative Advice: Insert administrative notes here that may apply across multiple restrictions; otherwise delete this row
Condition: Major depressive disorder
Indication: Major depression Major depressive disorder
Treatment Phase: Extended continuing treatment – beyond 52 weeks’ treatment (weeks 53 and beyond of the same treatment episode) where the intended administered dose is [28 mg / 56 mg / 84 mg]
Clinical criteria: The treatment must be to continue existing PBS-subsidised treatment for the same episode of major depression in patients who have received 12 months 52 weeks of treatment with esketamine
AND
Clinical criteria: The treatment must not exceed each of: (i) an administered dose beyond 84 mg, (ii) a quantity of drug, after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceed a quantity sufficient to treat the patient for 12 weeks (i.e. the listed maximum quantity is based on once weekly dosing – where fortnightly dosing is prescribed, the authority application is to seek no more than half the listed maximum quantity of this listing)
AND
Treatment criteria: Patient must be undergoing concomitant treatment with an oral anti-depressant drug therapy
AND
Treatment criteria: [Section 100 Public Hospital only] Must be treated in a public hospital outpatient clinic
[Section 100 Private Hospital only] Must be treated in a hospital that is not a public hospital
AND
Treatment criteria: Must be treated by a psychiatrist
AND
Treatment criteria: Prescribing Instructions: Patient must be undergoing supervision by a healthcare professional at the time the drug is administered
AND
Population criteria: Patient must be at least 18 years of age
Prescriber Instruction: Authority required (telephone and online) – General PBS administration Concept ID 25796 Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia.

Category / Program: Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals; Community Access}
Prescriber type: <input type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
Administrative Advice: Insert administrative notes here that may apply across multiple restrictions; otherwise delete this row
Condition: Major depressive disorder
Indication: Major depression Major depressive disorder
Treatment Phase: Induction treatment – re-treatment in a major depressive disorder episode
Clinical criteria:

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The treatment must be for a recurrence of symptoms in an episode of active, major depression, following prior treatment with esketamine
AND
Clinical criteria:
The treatment must not exceed each of: (i) An administered dose beyond 84 mg; (ii) a quantity of drug after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceed 8 doses over a period of 4 weeks of treatment when dosed within the Product Information recommended dosage
AND
Clinical criteria:
Patient must be undergoing concomitant treatment with an oral anti-depressant drug therapy
AND
Clinical criteria:
[Section 100 Public Hospital only] Must be treated in a public hospital outpatient clinic
[Section 100 Private Hospital only] Must be treated in a hospital that is not a public hospital
AND
Treatment criteria:
Must be treated by a psychiatrist
AND
Treatment criteria:
Prescribing Instructions:
Patient must be undergoing supervision by a healthcare professional at the time the drug is administered
AND
Population criteria:
Patient must be at least 18 years of age
Prescriber Instruction:
Authority required (telephone and online) – General PBS administration Concept ID 25796 Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia.

Category / Program:
Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals; Community Access}
Prescriber type: <input type="checkbox"/> Medical Practitioners
Restriction Level / Method:
<input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
Administrative Advice:
Insert administrative notes here that may apply across multiple restrictions; otherwise delete this row
Episodicity: optional
Severity: optional
Condition: Major depressive disorder
Indication: Major depression Major depressive disorder
Treatment Phase: Continuing treatment – re-treatment up to week 52 Re-treatment – Continuing treatment (weeks 5-52 of the same treatment episode) where the intended administered dose is [28 mg / 56 mg / 84 mg]
Clinical criteria:
The treatment must be to continue existing PBS-subsidised treatment for the same episode of major depression treated under PBS item number <the item number to be added is the item number for the initial retreatment (weeks 1-4) restrictions>.
AND
Clinical criteria:
The treatment must not exceed each of: (i) an administered dose beyond 84 mg, (ii) a quantity of drug, after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceed a quantity sufficient to treat the patient for

12 weeks (i.e. the listed maximum quantity is based on once weekly dosing – where fortnightly dosing is prescribed, the authority application is to seek no more than half the listed maximum quantity of this listing)
AND
Clinical criteria:
The treatment must be to continue existing PBS-subsidised treatment for the same episode of major depression treated under PBS item number <the item number to be added is the item number for the initial retreatment (weeks 1-4) restrictions>.
AND
Clinical criteria:
Patient must not be undergoing PBS-subsidised treatment with this drug beyond week 52 of the same episode of major depression
AND
Treatment criteria:
[Section 100 Public Hospital only] Must be treated in a public hospital outpatient clinic
[Section 100 Private Hospital only] Must be treated in a hospital that is not a public hospital
AND
Treatment criteria:
Must be treated by a psychiatrist
AND
Treatment criteria:
Prescriber Instruction:
Patient must be undergoing supervision by a healthcare professional at the time the drug is administered
AND
Population criteria:
Patient must be at least 18 years of age
Prescriber Instruction:
Authority required (telephone and online) – General PBS administration Concept ID 25796 Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia.

Note: The private hospital/community access DPMQs in the resubmission were incorrectly calculated (mark-ups were not based on the highest maximum quantity for each pack; the dangerous drug free for supplying a Schedule 8 medicine was excluded).

- 3.3 The resubmission proposed an effective and published price for esketamine nasal spray with a special pricing arrangement. The published price remained unchanged from the previous resubmission. The proposed effective ex-manufacturer price (EMP) in the resubmission (\$ per 28 mg device) was lower than that proposed in the July 2023 resubmission (\$ per 28 mg device).
- 3.4 Consistent with the July 2023 resubmission, the resubmission incorporated the listing of esketamine nasal spray under the Section 100 Highly Specialised Drugs (HSD) program, with Community Access listing sought (in addition to Public Hospital and Private Hospital) to enable patients to obtain esketamine from community pharmacies. The resubmission stated that in the event the PBAC considers esketamine does not meet the Section 100 (Highly Specialised Drugs) criteria, the proposed Community Access listing would be implemented in the General Schedule, with relevant changes to facilitate such a listing.
- 3.5 The proposed restriction is broadly consistent with the approved TGA indication of treatment for TRD (defined as prior failure of 2 antidepressants for that episode)

- initiated in combination with a new OAD, with the exception that the proposed restriction does not specify that the co-administered OAD must be newly initiated.
- 3.6 The requested restriction for initial induction therapy does not specify that patients must not have been treated with esketamine before, meaning patients who have not responded to previous esketamine treatment could access further treatment with esketamine using this restriction.
- 3.7 The resubmission stated that the intent of the separate restriction for continuing therapy was because patients who fail to show an adequate response to esketamine after 4 weeks should discontinue treatment with esketamine, and will be ineligible for continuing treatment. However, the requested restriction for continuing treatment did not include any criteria requiring patients to have demonstrated a response to their induction treatment. In addition, the requested restriction did not specify that patients must continue to demonstrate a response to treatment during the maintenance treatment period, and should discontinue treatment with esketamine if no longer responding.
- 3.8 The resubmission proposed that patients requiring treatment for longer than 12 months obtain Authority approval to receive additional esketamine, with proposed wording added to the Administrative Advice for the continuing treatment restriction: ‘patients continuing to respond to esketamine but who haven’t entered remission or for whom ceasing treatment would be clinically inappropriate are able to apply, under Authority to continue use beyond 12 months’. The resubmission suggested if the PBAC considered a separate restriction was not necessary, the proposed maintenance restriction (weeks 5-52) could include wording that allowed (under Authority approval) an increase in the number of repeats for those patients requiring further treatment beyond 12 months.
- 3.9 The requested restriction for continuing treatment beyond 12 months did not include any criteria requiring patients to have demonstrated a response to their treatment during weeks 5-52. In addition, the requested restriction did not specify that patients must continue to demonstrate a response to treatment beyond 12 months, and should discontinue treatment with esketamine if no longer responding.
- 3.10 PSCR, acknowledged the requested restrictions inadvertently failed to preclude use by patients who have been previously treated with esketamine and the initial maintenance treatment restriction did not include a requirement to demonstrate a response to initial treatment. The Response clarified the economic model and financial estimates were applied to an appropriate patient population which includes requirements for response to treatment for continuation and prior response for re-treatment.
- 3.11 The resubmission did not include a limit to the duration of additional treatment beyond 12 months. The resubmission argued that this use is likely to be rebated back to the Commonwealth, given the proposed RSA which applies subsidisation caps above the level of expected use. The evaluation considered the level of expected use

in the resubmission is uncertain and already incorporates a proportion of patients treated beyond 12 months, with an average treatment duration of 32 months (initial treatment) or 26 months (retreatment). The resubmission proposed a reimbursement of 100% for any potential use above specified subsidisation caps. The ESC noted the risks (such as extent of use beyond 12 months) can only be managed through an RSA if the utilisation estimates have not been overestimated.

- 3.12 The resubmission proposed two retreatment restrictions, one for the first four weeks of treatment (induction period) and one for weeks 5-52 of retreatment (maintenance). The resubmission stated that the intent of the restriction is that patients who have previously received and responded to esketamine are eligible for retreatment once they have relapsed and they are experiencing a new major depressive episode.
- 3.13 The ESC considered the proposed restrictions could be consolidated and still achieve the intent of allowing treatment beyond 12 months and re-treatment where appropriate.
- 3.14 Consistent with previous advice from the PBAC to inform the restrictions for esketamine using the MBS listing for repetitive transcranial magnetic stimulation (rTMS) which was designed to identify and treat the same patient population (para 3.13, esketamine Public Summary Document (PSD), July 2022 PBAC meeting), the resubmission proposed that the patient must have relapsed following the previous treatment with esketamine and the patient must not have received esketamine in the previous 4 months before an application for retreatment.
- 3.15 The requirement for a minimum 4 month break from esketamine before retreatment is permitted may result in patients who are responding to the treatment choosing to stay on treatment indefinitely rather than risk relapse.
- 3.16 Unlike the MBS listing for rTMS retreatment, the wording of the proposed initial retreatment restriction for esketamine does not require a patient to have achieved remission following the previous esketamine treatment (only to have demonstrated a 'satisfactory clinical response'). The requested restriction for continuing retreatment did not include any criteria requiring patients to have demonstrated a response to the induction phase of retreatment.
- 3.17 The resubmission incorporated grandfathering provisions for 300 patients currently treated under the sponsor's early access program in the continuing treatment restriction. The resubmission acknowledged that patients receiving esketamine through the EAP were not limited to a maximum of 12 months treatment and it will not be possible to determine how many months of treatment each individual patient has received.
- 3.18 The proposed restrictions were 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 (para 6.11, esketamine PSD, July 2022 PBAC meeting). In the July 2023 resubmission, the proposed restriction included a caution in prescriber notes regarding this and other populations who were excluded from the trials, including personality disorders, alcohol and substance use disorders, and those with suicidal ideation. The requested restriction in the current resubmission omitted these cautions; and that dosing frequency and dosage should be individualised to the lowest frequency and dosage to maintain remission/response. The requested restriction also did not specify that patients must be monitored by a healthcare professional following administration in a healthcare facility, and that post-cessation monitoring is recommended.

- 3.19 The DUSC previously noted that there is a significant risk of use outside the proposed restriction in patients with: depression that is not treatment resistant, post-traumatic stress disorder (PTSD), anxiety, chronic pain, insomnia, fibromyalgia, suicidality and other conditions; with ketamine currently used in many of these additional indications. The DUSC considered there is the potential for a large cohort of patients currently being treated with ketamine infusions to move to esketamine nasal spray (para 6.68, esketamine PSD, July 2022 PBAC meeting). There is potential for use outside the proposed population.
- 3.20 The PBAC noted a number of outstanding issues related to the proposed restriction criteria that need to be resolved.

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

4 Population and disease

- 4.1 The proposed population (adults with TRD) was unchanged from the previous submissions.
- 4.2 Treatment options recommended in the 2020 RANZCP Guidelines for managing patients with TRD include optimising current antidepressant use (appropriate dose for an appropriate period of time), switching to a different antidepressant, combining two antidepressants, augmenting treatment by adding an antipsychotic or lithium to the existing antidepressant, and using non-pharmacologic physical therapies such as electroconvulsive therapy (ECT) and rTMS (Mahli 2021).
- 4.3 Esketamine, the S-enantiomer of racemic ketamine, is an antidepressant with a novel mechanism of action. It is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Ketamine, administered by either intramuscular or intravenous route, is approved as an anaesthetic drug by the TGA, but is not currently approved or indicated for use in treating depression. Ketamine is not listed on the PBS for any indication.
- 4.4 The clinical management algorithm and proposed place in therapy is broadly unchanged from the July 2023 resubmission. The clinical management algorithm

positions esketamine in combination with an OAD following failure of 2 different OADs (of adequate dose and duration) in the same depressive episode.

- 4.5 All patients treated with esketamine undergo initial treatment for 4 weeks, with response assessed at week 4. Treatment is ceased for non-responders. Patients who demonstrate a response continue to receive maintenance treatment. Patients who achieve remission and recovery during this period would cease treatment. The resubmission stated that a maximum of 12 months will be sufficient treatment for the majority of patients, however a proportion would continue treatment for longer than 12 months. Patients treated for longer than 12 months per episode would include, but not be limited to, those responding to treatment with esketamine but who have not entered remission or recovery, or patients who may experience anxiety when approaching the 12 month limit that may exacerbate their depression. Patients who have previously responded to treatment with esketamine and who have subsequently had a recurrence of their depression and are experiencing a new major depressive episode are eligible for retreatment. The effect of stopping treatment with esketamine in responders, and therefore the optimum treatment duration, is unknown. The SUSTAIN-1 trial suggested that participants who discontinue esketamine after improvement are more likely to relapse in comparison with those who do not discontinue esketamine.

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

5 Comparator

- 5.1 The resubmission nominated a newly initiated OAD drug as the main comparator. The PBAC previously considered that this was reasonable (para 7.9, esketamine PSD, July 2023 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (17) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with esketamine including rapid improvement in mood, good remission rates, reduction in suicidal ideation and reduction in hospital admissions. Health care professionals described esketamine as an effective, rapid, and well-tolerated treatment for a substantial number of patients, with good remission rates. They commented that the medication has a rapid and life-changing impact on symptoms and quality of life,

improving mood and reducing suicidal ideation. The comments described esketamine as providing hope to patients where other treatments have failed, but access and affordability remain significant barriers to patients.

- 6.3 Individuals living with TRD described the impact of TRD on every facet of daily life and the enduring feelings of despair, worthlessness and hopelessness that come with it. Individuals also described the hope for effective treatments that could help them escape these feelings and reclaim their lives, and the importance of the opportunity to try esketamine or ketamine, based on the available evidence. Individuals also highlighted affordability as a critical barrier to access, both in terms of the drug and the cost of administration and monitoring, both for intranasal and intravenous treatment options, with one individual highlighting the substantial cost of treatment in the first month for the drug and associated psychiatrist and nurse administration/monitoring fees.
- 6.4 The PBAC noted the advice received from the Royal Australian College of Psychiatrists (RANZCP), noting that the College has a Clinical Memorandum on the use of ketamine (including esketamine) in psychiatric practice, which includes an outline of its practical application for TRD, and highlights that short-term efficacy for adults with TRD has been established. RANZCP also noted that a priority for the College is ensuring patients have access to evidence based treatments, with affordability being a component of access. Further, the College also noted that ketamine is not recommended as a first-line treatment and should only be initiated after due consideration of the available evidence, and there is currently limited guidance on translating research findings into practice with respect to dosing and safety and effectiveness with long-term use.

Clinical studies

- 6.5 Compared to the July 2023 resubmission, the key changes in the clinical evidence were:
- Updated non-comparative efficacy and safety results of the SUSTAIN-3 trial, representing patients with a mean cumulative exposure of up to 6.5 years for esketamine. The PBAC has previously considered only safety data from SUSTAIN-3.
 - Inclusion of two studies examining use of esketamine among US patients with TRD over a 12 month period.
 - Inclusion of data from the sponsor's Australian early access program on the proportion of patients retreated with esketamine after a break of 4 or more months, and the proportion continuing treatment beyond 12 months.
 - Additional information from the most recent Periodic Benefit Risk Evaluation Report (PBRER) for esketamine.
- 6.6 The resubmission was based on three short-term (induction), double blind, randomised controlled trials (RCTs) (TRANSFORM-1, TRANSFORM-2, and

TRANSFORM-3) and three long-term studies (SUSTAIN-1, SUSTAIN-2, and SUSTAIN-3), comparing esketamine nasal spray with a newly initiated OAD versus intranasal placebo with a newly initiated OAD. All of these studies have previously been seen by the PBAC.

6.7 Details of the studies presented in the resubmission are provided in Table 3.

Table 3: Studies and associated reports presented in the resubmission (shaded study has not previously been considered by the PBAC).

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

Trial ID	Protocol title/ Publication title	Publication citation
TRANSFORM-3 (NCT02422186)	Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects with Treatment-resistant Depression	Internal study report; 12 July 2018
	Citrome L, DiBernardo A, Singh J. (2020). Appraising esketamine nasal spray for the management of treatment-resistant depression in adults: Number needed to treat, number needed to harm, and likelihood to be helped or harmed.	J Aff Dis; 271 (228-238).
	Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, et al. (2020). Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients with Treatment-Resistant Depression-TRANSFORM-3.	Am J Geriatr Psychiatry; 28(2):121-141.
SUSTAIN-1 (NCT02493868)	A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression	Internal study report; 15 August 2018
	Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. (2019). Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial.	JAMA Psychiatry; 76(9):893-903
	Citrome L, DiBernardo A, Singh J. (2020). Appraising Esketamine Nasal Spray for the Management of Treatment-Resistant Depression in Adults: number Needed to Treat, Number Needed to Harm, and Likelihood to be Helped/Harmed.	J Aff Dis; 271:228-238.
SUSTAIN-2 (NCT02497287)	An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression	Internal study report; 14 August 2018
	Wajs E, Aluisio L, Holder R, Daly EJ, et al. (2020) Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: Assessment of long-term safety in a phase 3, open-label study (sustain-2).	J Clin Psychiatry; 81:3.
	Nijs M, Wajs E, Aluisio L, Turkoz I, et al. (2020) Managing esketamine treatment frequency toward successful outcomes: Analysis of phase 3 data.	Int J Neuropsychopharmacol; 23:7 (426-433).
SUSTAIN-3 (NCT02782104)	An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment-resistant Depression	Internal study report; 21 May 2019
	Zaki N, Chen L, Lane R, et al. Long-term safety and maintenance of response with esketamine nasal spray in treatment-resistant depression: Final results of the SUSTAIN-3 study.	Poster presented at Psych Congress 2023, Nashville USA.

Source: Table 2-4, p.69 of the July 2022 resubmission; Section 2.2.1.1, p47 of the resubmission

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

Table 4: Key features of the included evidence

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

Source: Table 2-5, p.78; Table 2-6, p.79; Table 2-7, p.85; Table 2-8, p.86 of the July 2022 resubmission; Table 2.1, p.1; Table 2.2, p.3; Table 2.3, p.5, Attachment 2.5 of the July 2022 resubmission
 Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant; RCT, randomised controlled trial; TRD, treatment-resistant depression

Comparative effectiveness

6.9 Results were unchanged from the July 2021, July 2022, and July 2023 submissions. The results of the primary efficacy endpoint for the TRANSFORM trials (change in MADRS total score from baseline to the end of the 4-week double-blind induction phase), are summarised in Table 5 below.

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

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

Source: Table 2-13, p.114 of the July 2022 resubmission; Table 2.50, Attachment 2.6 of the July 2022 resubmission

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

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

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

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

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

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

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

In TRANSFORM-1, the comparison for 56 mg was considered statistically significant only if the analysis was significant for 84 mg. As tests showed that the 84 mg dose treatment arm was not statistically significantly different from placebo, 56 mg was not formally evaluated MADRS Total score ranges from 0 to 60; a higher score indicates a more severe condition and negative change in score indicates improvement.

6.10 Of the three short-term induction trials, only TRANSFORM-2 showed a statistically significant treatment effect with esketamine nasal spray compared with placebo. The PBAC previously considered the observed difference in the esketamine + OAD arm compared to a new OAD alone of 4 points on the MADRS scale was of uncertain clinical significance (para 6.13, esketamine PSD, July 2022 PBAC meeting). The confidence intervals are wide, and the lower bound falls below the nominated minimum clinically important difference (MCID), suggesting that treatment effects are variable, and the between-group difference falls below published MCIDs. This suggests that a significant

proportion of patients do not derive any additional benefit from treatment with esketamine.

- 6.11 The proportion of responders and remitters at day 28 of the TRANSFORM-2 and TRANSFORM-3 trials are summarised in Table 6 below. A subject was defined as a responder at a given time point if the percent improvement (decrease) in MADRS total score from baseline was $\geq 50\%$. Subjects who had a MADRS total score of ≤ 12 were considered remitters. This was not a standard definition of remission; other trials have used a more stringent cut-off of < 10 or < 7 to define remission, however the potential impact of this on the trial results is unclear. These outcomes were used to inform the transition probabilities in the economic model.

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

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

Source: Table 2-17, p.123; Table 2-18, p.125; Table 2-19, p.126; Table 2-20, p.127 of the July 2022 resubmission.

DB, double-blind; LOCF, last observation carried forward; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral anti-depressant

- 6.12 The results for the EQ-5D-5L health status index in the TRANSFORM trials are summarised in Table 7 below.

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

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

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

Abbreviations: OAD, oral antidepressant; SD, standard deviation

Note: Health Status Index ranges from -0.148 to 0.949 and is anchored at 0 (health state valued equal to dead) and 1 (full health). In each of the trials, patient-level EQ 5D-5L data were transformed into health state utilities using the Canadian value set.

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

6.14 In the SUSTAIN-1 trial, the primary efficacy endpoint was the time from randomisation (in the maintenance phase) to the first relapse in patients who previously achieved stable remission with esketamine nasal spray by the end of the optimisation phase. Time to relapse in the stable remitters and stable responders sets are summarised in Table 8 below.

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

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

Source: Table 2-25, p.136; Table 2-26, p.139 of the July 2022 resubmission

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

^aBased on Kaplan-Meier product limit estimates

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

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

6.16 Remission and response from baseline (maintenance) to endpoint in the SUSTAIN-1 trial is summarised in Table 9 below.

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

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

Source: Table 2-28, p.143; Table 2-29, p.144 of the July 2022 resubmission

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

- 6.17 Remission was achieved or maintained by a higher percentage of subjects in the esketamine nasal spray treatment groups. Remission during the maintenance phase among stable remitters decreased less over time in the esketamine nasal spray group compared with the intranasal placebo group (33.6% versus 57.9%), which indicates fewer patients lose remission over the trial period. Similarly, in stable responders, remission was achieved or maintained by a higher percentage of subjects in the esketamine nasal spray treatment groups compared with patients in the intranasal placebo treatment groups. The reduction over time was smaller in the esketamine nasal spray group, indicating fewer patients lost remission over the trial time period when treated with esketamine nasal spray and an OAD versus continuing on an OAD alone.
- 6.18 Response was also maintained or lost at a slower rate by a higher percentage of subjects in the esketamine nasal spray treatment groups. Response during the maintenance phase among stable remitters decreased from 100% of patients in both the esketamine nasal spray treatment group and intranasal placebo group at baseline to 75.3% and 55.8%, respectively, at endpoint. This suggests that fewer patients lost response over the trial period with esketamine nasal spray. Similarly, subjects with response in stable responders decreased from 100% in the esketamine nasal spray treatment group and 100% in the intranasal placebo group at baseline to 66.1% and 33.9% of subjects, respectively, at endpoint. Fewer patients lost response over the trial time period when treated with esketamine nasal spray.
- 6.19 The resubmission provided additional data from the long-term optimisation/maintenance phase of the SUSTAIN-3 study (Zaki, Chen et al. 2023), an open-label long term extension safety study of esketamine nasal spray in adult and elderly people with TRD, who previously participated in TRANSFORM-1, TRANSFORM-

2, SUSTAIN-1, SUSTAIN-2, TRANSFORM-3 or TRD3006 (Chen 2023) studies. Patients entered either a 4 week induction phase followed by an optimisation/maintenance phase of variable duration (n=458), or directly entered the optimisation/maintenance phase (n=690) based on their status at the end of the parent study. Mean esketamine exposure was 42.9 months (SD 24.2 months). Of the 1,110 individuals who participated in the optimisation/maintenance phase, 38.7% discontinued the study, primarily due to adverse events (6.0%), withdrawal by participant (5.3%) and lack of efficacy (4.7%).

- 6.20 Over 80% of patients remained on esketamine treatment for 12 months or more, with over half the participants still treated with esketamine after 3.5 years. The resubmission argued that the duration of treatment seen in the SUSTAIN-3 trial was unlikely to be realised in Australian clinical practice. The SUSTAIN-3 study was designed to meet ethical requirements for patients who had previously responded to treatment to continue to receive esketamine prior to registration and reimbursement. Patients were not required to discontinue treatment with esketamine and could remain on treatment indefinitely. The resubmission also noted that the study was conducted at the height of the COVID pandemic and for many patients, the ability to see a psychiatrist at each study visit may have been desirable. In addition, patients were not able to undergo retreatment in the trial, which may have encouraged patients to stay on treatment for longer than was necessary. It is unclear how the resubmission's proposed restriction for treatment beyond 12 months will impact the average duration of treatment. Under the proposed restriction, once a patient has been approved for esketamine use beyond 12 months, there is no time limit for continued treatment.
- 6.21 Maintenance of efficacy was measured using the MADRS total score, with 49.2% of patients (224/455) classed as responders ($\geq 50\%$ reduction in MADRS total score) at the end of the induction phase, and approximately 50% of patients in remission at various timepoints during the maintenance phase of the study.
- 6.22 The study also measured improvement in functioning and associated disability using the Sheehan Disability Scale total score, with results indicating maintenance of response from optimisation/maintenance phase baseline to endpoint.
- 6.23 Limitations of the SUSTAIN-3 study were listed in the resubmission, including the study design (open label with no comparator arm), limited generalisability of study findings due to potential bias relating to whether participants chose to continue (or not continue) from the parent study into this study, and no set duration of treatment or requirement to cease treatment at any time. In addition, sample size decreases at later time points in the study may have implications for the representativeness or generalisability of the findings. Given these limitations, the resubmission reiterated that SUSTAIN-3 cannot be used to inform the efficacy assumptions in the economic model, but rather provides supportive efficacy data and relevant long-term safety data.

- 6.24 The resubmission summarised the results of two US claims database studies (Teeples 2021; Karkare 2021) reporting real-world use of esketamine to provide data on use of esketamine beyond 12 months, and retreatment with esketamine after relapse. Both studies were only available as poster presentations, which limited the amount of available information.
- 6.25 Teeples 2021 (N=273; mean age 49.3 years; 66.3% female; median 12.4 months of follow-up) reported that 21.5% of patients receiving esketamine treatment for TRD (with available follow-up data) remained on treatment at 12 months; and, among the 188 patients who discontinued esketamine based on a >60 day gap, 21.3% restarted treatment over available follow up.
- 6.26 Karkare 2021 (N=229; mean age 44.3 years; 62.4% female; median 8.8 months follow-up) reported that 23.9% of patients receiving esketamine treatment for TRD (with available follow-up data) remained on treatment at 12 months; and, among the 133 patients who discontinued esketamine, 18.0% restarted treatment over available follow-up
- 6.27 While acknowledging the limitations of these studies, the resubmission noted that the proportion of patients discontinuing / remaining on treatment at 12 months in these real-world US TRD cohorts were consistent with the data reported in the SUSTAIN-1 trial. The resubmission argued that the proportion of patients receiving a second course of esketamine is likely to be an underestimate of the proportion of patients likely to receive retreatment in Australian clinical practice, as the US data had limited follow-up and the proportion retreated is likely to increase with time. The resubmission argued that these data are the best available, and the proportion of patients retreated was used to inform the base case economic model.
- 6.28 The resubmission included an analysis of supply data from the sponsor's early access program (EAP). These data indicate that only 1% of patients have so far been retreated with esketamine after a 4-month gap from treatment. The resubmission argued that retreatment was not encouraged in the EAP, with no limit on the duration of the initial course of therapy, and as such the observed retreatment rate in the EAP is significantly lower than what would be observed in clinical practice where retreatment is allowed and considered to be appropriate. The proportion of patients treated beyond 12 months (1%) was used to inform the economic model and financial implications. Limited details were provided on the EAP dataset. Of the 500 to < 5,000 unique patients included in the EAP data, <500 (1%) had their initial esketamine treatment less than one year prior to the data cut-off date, which may have underestimated the number of patients that would eventually be treated with esketamine beyond 12 months duration. However, the resubmission noted that the 1% of patients estimated to be treated beyond 12 months duration included patients with a break in supply, which may have overestimated patients treated for longer than a year. Overall, the estimates of use of esketamine beyond 12 months based on the EAP data were highly uncertain.

Comparative harms

6.29 Comparative harms were unchanged from the July 2021, July 2022, and July 2023 submissions.

6.30 A summary of treatment-emergent adverse events from the TRANSFORM trials is presented in Table 10 below.

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

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

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

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

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

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

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

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

6.33 A summary of treatment-emergent adverse events by phase, for the induction, optimisation, and maintenance phases of the SUSTAIN-1 trial is included in Table 11 below.

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

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

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

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

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

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

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

- 6.34 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.
- 6.35 The most common treatment-emergent adverse events in SUSTAIN-1 included dysgeusia, vertigo, dissociation, somnolence, dizziness, headache, nausea, vision blurred, and hypoaesthesia oral and were consistent with the types of adverse events observed in the induction phase. In the double blinded maintenance phase, these events occurred at a higher incidence in the esketamine nasal spray treatment arm compared with the intranasal placebo treatment arm.
- 6.36 The ESC previously noted that adverse events continued to be experienced at a greater incidence in the esketamine treatment group compared with the placebo treatment group in the SUSTAIN-1 trial, suggesting that adverse events may continue throughout maintenance treatment (para 6.32, esketamine PSD, July 2022 PBAC meeting). The resubmission stated that although esketamine nasal spray has a distinct side effect profile and patients treated with esketamine nasal spray are likely to experience these upon dosing into the maintenance phase, the majority of esketamine side effects are transient, self-limiting, and mostly mild or moderate in severity. At present, longer-term (>12 months) comparative safety of use of esketamine nasal spray is unknown. The longer term, repeated use of esketamine may potentially lead to adverse effects that are seen with longer-term, repeated use of ketamine, including abuse and addiction, neurotoxicity, bladder toxicity, and hepatotoxicity (UpToDate, 2024).

- 6.37 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.
- 6.38 Increased blood pressure or increased heart rate, dizziness/vertigo, and anxiety in all studies were primarily mild or moderate in severity. Suicidality-related adverse events were reported as severe in only a small number of subjects, and most were considered either not related or doubtfully related to esketamine nasal spray treatment in the opinion of the investigator and therefore likely associated with the underlying disease. There were very few reported cases of cystitis (9 subjects in SUSTAIN-1, 5 subjects in SUSTAIN-2 and 8 subjects in SUSTAIN-3) and impaired cognition (1 subject in SUSTAIN-3) in the esketamine nasal spray studies. Adverse events such as impaired cognition may not be observable over short-term trial durations.
- 6.39 The most frequently reported adverse events in the optimisation/maintenance phase of SUSTAIN-3 were consistent with those reported in previously included studies of esketamine, namely headache (36.9%), dizziness (33.9%), nausea (33.6%), dissociation (25.5%), nasopharyngitis (23.8%), somnolence (23.1%), and dysgeusia (20.2%). The most common adverse events leading to discontinuation of esketamine treatment (6.3% of participants) were increased blood pressure (0.5%) and dissociation (0.4%). The resubmission stated that only 0.6% of patients required treatment for dissociation, and there were no dissociation-related serious adverse events. Increased blood pressure was reported in 19.9% of patients with incidence rates generally similar throughout the induction and optimisation/maintenance phases. More than 95% of increased blood pressure adverse events occurred and resolved on the day of dosing. No cases of treatment-related interstitial/ulcerative cystitis was identified, with urinary tract infections reported in 15.8% of patients. The distribution of adverse events (other than increased blood pressure) over the maintenance period of the study is unknown. It is unclear whether these events were experienced at a consistent rate from the start of the maintenance period to the end of the study.
- 6.40 Serious adverse events were reported in 18.8% of patients, including those related to depression (2.0%), suicidality (2.4%), cholelithiasis (0.9%), COVID-19 (0.8%), pneumonia (0.6%), nephrolithiasis (0.5%), anxiety (0.4%), atrial fibrillation (0.4%), myocardial infarction, back pain, cellulitis, urinary tract infection, intentional overdose, lower limb fracture, headache, cholecystitis, intervertebral disc protrusion and osteoarthritis (0.3% each). Serious adverse events requiring hospitalisation occurred in 2.1% of patients. The study investigators considered that most of the serious adverse events reported were likely unrelated to esketamine. There were 9 (0.8%) deaths reported during the study period (COVID-related (n=3), pneumonia

(n=2), completed suicide, myocardial infarction, multiple injuries, unknown cause (n=1 each)), none of which were considered by the investigator to be related to esketamine.

- 6.41 The resubmission provided a PBRR covering the period 5 March 2022 – 4 March 2023. The resubmission stated that the safety profile for esketamine remains consistent with the profile established during clinical trials, and that esketamine continues to have a favourable benefit-risk profile for the treatment of patients with TRD. The important identified risks reported in the PBRR include drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and blood pressure increase. The important potential risks are cognitive disorders and memory impairment (long-term use), and interstitial cystitis (long-term use). Important missing information included use during pregnancy. No new safety concerns were identified.

Benefits/harms

- 6.42 The benefits and harms are unchanged from the July 2023 resubmission.
- 6.43 On the basis of the direct evidence presented in the submission (4 weeks of double-blind induction treatment in TRANSFORM-2), for every 100 patients aged 18-64 years with treatment-resistant depression treated with esketamine nasal spray plus an OAD in comparison to intranasal placebo plus an OAD:
- Approximately 17 more patients would have a response, defined as a $\geq 50\%$ reduction in symptoms of depression as measured on the MADRS.
 - Approximately 22 additional patients would experience remission, defined as a MADRS score ≤ 12 .
 - Approximately 16 patients would experience dizziness.
 - Approximately 22 patients would experience dissociation.
 - Approximately 23 patients would experience vertigo.
 - Approximately 10 patients would have an increase in blood pressure.
- 6.44 On the basis of the direct evidence presented in the submission (4 weeks of double-blind induction treatment in TRANSFORM-3), for every 100 patients aged 65 years and over with treatment-resistant depression treated with esketamine nasal spray plus an OAD in comparison to intranasal placebo plus an OAD:
- Approximately 14 more patients would have a response, defined as a $\geq 50\%$ reduction in symptoms of depression as measured on the MADRS.
 - Approximately 11 additional patients would experience remission, defined as a MADRS score ≤ 12 .
 - Approximately 13 patients would experience dizziness.
 - Approximately 11 patients would experience dissociation.

- Approximately 8 patients would experience vertigo.
 - Approximately 8 patients would have an increase in blood pressure.
- 6.45 On the basis of the direct evidence presented in the submission (double-blind maintenance treatment in SUSTAIN-1), for every 100 patients with treatment-resistant depression who achieved remission or response and continued treatment with esketamine nasal spray plus an OAD compared to those who achieved remission or response who then discontinued treatment with esketamine nasal spray, instead receiving an intranasal placebo plus an OAD in the maintenance phase:
- In those who achieved remission, approximately 19 fewer patients would experience relapse to depression.
 - In those who achieved response, approximately 32 fewer patients would experience relapse to depression.
 - Approximately 16 patients would experience dizziness.
 - Approximately 23 patients would experience dissociation.
 - Approximately 20 patients would experience vertigo.
 - Approximately 3 patients would have an increase in blood pressure.

Clinical claim

- 6.46 The clinical claim for the resubmission remained the same as the July 2023 resubmission, that is: esketamine nasal spray in combination with a newly initiated OAD is superior in terms of effectiveness and inferior in terms of safety, compared with a newly initiated OAD alone.
- 6.47 The PBAC previously considered that the claim of superior comparative effectiveness may be reasonable, although the magnitude and clinical importance of the observed benefits was uncertain (para 7.10, esketamine PSD, July 2023 PBAC meeting). The PBAC previously considered the claim of non-inferior safety was reasonable, however remained concerned there was limited longer-term safety data. The PBAC previously noted input received via Consumer Comments that the adverse event profile (dissociation, in particular) can be concerning for some patients and considered this may result in them needing additional care (para 7.11, esketamine PSD, July 2023 PBAC meeting).
- 6.48 The ESC noted there are several outstanding issues which should be considered:
- There are clinical questions which remain unanswered with the available clinical data, including how or when to cease or taper treatment in responders and the optimal duration of treatment.
 - The magnitude of the clinical benefit, and the subgroups most likely to respond to treatment, are uncertain. Only one of the included short-term induction trials showed a statistically significant difference in the primary outcome.

- There is limited long-term evidence for comparative efficacy or safety, or efficacy of retreatment.
- 6.49 The ESC noted there were limited clinical data for use of esketamine beyond 12 months and for retreatment, and acknowledged there was unlikely to be additional clinical data forthcoming; however, the ESC noted long-term efficacy and safety were uncertain.
- 6.50 The PBAC considered that the claim of superior comparative effectiveness was likely to be reasonable, however the magnitude of benefit remained uncertain.
- 6.51 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.52 The resubmission presented a stepped economic evaluation of esketamine nasal spray plus a newly initiated OAD versus a newly initiated OAD alone in patients with moderate to severe TRD. The economic analysis was based on evidence from the TRANSFORM-2, TRANSFORM-3 and SUSTAIN-1 trials, as well as additional modelled variables. The economic evaluation was presented as a cost-utility analysis.
- 6.53 The key changes to the economic evaluation in the current resubmission compared with the July 2023 submission include:
- Allowing patients who respond to initial esketamine treatment and subsequently relapse to be retreated after a treatment break of at least 4 months.
 - Allowing a proportion of patients to remain on esketamine beyond the maximum treatment duration of one year.
 - Using an alternative approach to estimating disease management costs based on South Australian data (Goldney 2007; previously based on a UK retrospective chart review study, Denee 2021).
 - Revising the effective AEMP of esketamine nasal spray from \$| to \$| per 28 mg device.
- 6.54 Table 12 summarises the key components of the economic evaluation.

Table 12: Key components of the economic evaluation

Component	Summary
Treatments	Esketamine + OAD versus placebo + OAD.
Time horizon	5 years in the model base case versus 4 weeks in the short-term induction trials (TRANSFORM trials), and a median exposure to intranasal esketamine of 17.7-19.4 weeks in the SUSTAIN-1 trial.
Outcomes	Quality adjusted life years
Type of analysis	Cost-utility analysis
Methods used to generate results	Markov state transition model with multiple lines of treatment.
Health states	Major depressive episode, response, remission, recovery, death
Cycle length	4 weeks.

Component	Summary
Transition probabilities	<p>Unchanged from the July 2023 model, except for the inclusion of esketamine retreatment and allowing a proportion of patients to continue treatment beyond the maximum of 12 months.</p> <p>Transitions from MDE to response or remission were based on patients who achieved remission or response in TRANSFORM-2 and TRANSFORM-3, weighted by the proportion of the Australian population aged <65 and ≥65 years.</p> <p>Probabilities of loss of response and relapse (from remission) in the esketamine plus OAD arm were based on the SUSTAIN-1 trial; maintenance transitions revert to those of the placebo plus OAD arm once off treatment.</p> <p>Maintenance transitions in the placebo plus OAD arm once were based on the average of 3rd- and 4th-line treatment outcomes from the STAR*D study.</p> <p>Transition probabilities for MDE to response or remission, and for response or remission to MDE in patients who failed their initial treatment in the model were based on data from patients in their 4th line of treatment in the STAR*D study.</p> <p>The probability of eligible patients receiving esketamine retreatment (1.48% per cycle) was derived from a calibration exercise with a target of 22% of patients in the esketamine plus OAD arm receiving retreatment over the model time horizon; based on 2 US claims database studies (Karkare 2021; Teeple 2021).</p> <p>Transition probabilities in patients receiving esketamine retreatment were based on the assumption that patients who previously achieved response/remission would achieve response/remission with retreatment, with an adjustment for a reduction in efficacy.</p> <p>Esketamine treatment discontinuation for any cause was applied in the continuation, maintenance, and recovery phases (week 5 onwards), based on an exponential distribution fit to all-cause discontinuations in SUSTAIN-1. The maximum treatment duration with esketamine was 12 months, with the exception of a proportion of patients requiring additional treatment (█%, based on an analysis of esketamine early access program data).</p> <p>Adverse events in the model were based on the incidence of adverse events from the TRANSFORM-2 trial.</p> <p>Age-specific all-cause mortality was modelled based on Australian Bureau of Statistics life tables for males and females (2020-2022; updated). No additional mortality risk associated with TRD was assumed.</p>
Utility values	<p>Unchanged from the July 2023 model.</p> <p>Patient-level EQ-5D-5L data from baseline and day 28 of the TRANSFORM-2 and TRANSFORM-3 trials were transformed into health state utilities using the UK value set; weighted by the proportion of the Australian population aged <65 and ≥65 years. The impact of using the Australian EQ-5D-5L value set was not assessed.</p> <p>Adverse event disutilities derived from a number of published sources, weighted by the incidence of adverse events in the TRANSFORM-2 trial; were applied during induction and maintenance treatment (including esketamine treatment).</p>

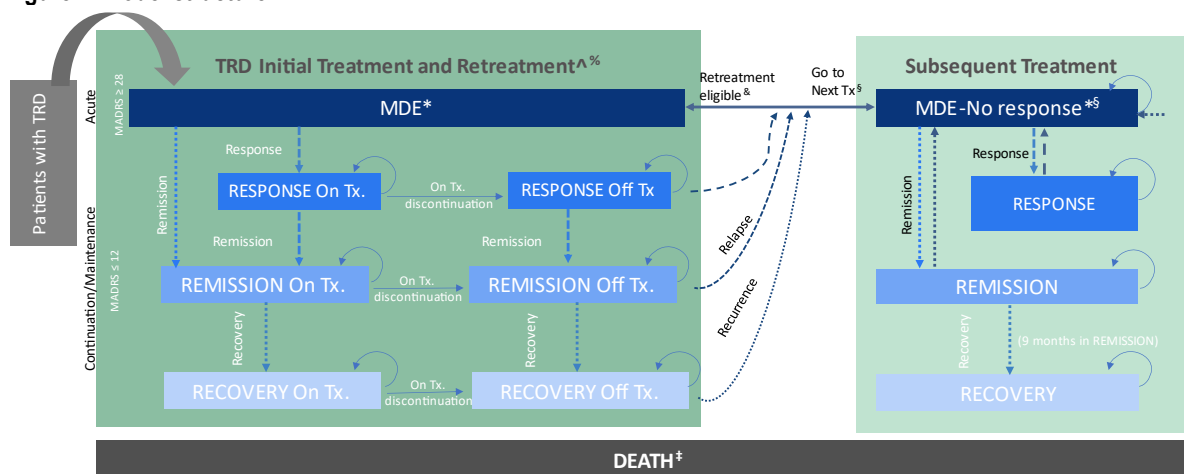
Component	Summary
Costs	<p>Esketamine drug costs were updated, based on the revised effective DPMQ, with a weighted public/private split (20/80). Mean dose and frequency of administration were based on the TRANSFORM-2 and TRANSFORM-3 trials, weighted by the proportion of patients aged <65 and ≥65 years for the induction period; and the SUSTAIN-1 trial for maintenance periods.</p> <p>Oral antidepressant drug costs were updated, based on the February 2024 PBS Schedule, with dosage based on product information documents, weighted by utilisation from PBS item reports (December 2022 to November 2023).</p> <p>Esketamine administration/monitoring costs were updated, based on the March 2024 MBS item 308 (psychiatrist consultation >75 minutes) as a proxy for esketamine administration and monitoring costs. There were no administration costs for the placebo arm.</p> <p>Health care resource use was revised, based on Australian data (Goldney 2007; previously based on UK data from Denee 2021). Hospitalisation data were adjusted for the risk of hospitalisation in patients with TRD versus non-TRD MDD (Zhang 2018); with the number of days per hospitalisation from a study of patients with TRD admitted to a Melbourne clinic. Hospitalisation (inpatient and outpatient) and emergency department costs were based on NHCDC 2020-2021 data. GP and specialist visit costs were based on the March 2024 MBS (item 23: level B GP consultation; average of items 300, 302, 304, 306, 308: psychiatrist consultations ≤15 to >75 minutes; weighted by MBS item reports July 2022 to June 2023).</p> <p>Adverse event costs were updated. Treatment of increased blood pressure, urinary tract infection, and bladder discomfort/pain included the cost of a GP visit (March 2024 MBS item 23: level B GP consultation) and published DPMQs for antihypertensives or course of antibiotics from February 2024 PBS items.</p>
Software package	Microsoft Excel

Source: Constructed during the evaluation using information in Section 3, pp67-126 of the resubmission.

Abbreviations: DPMQ, dispensed price for maximum quantity; GP, general practitioner; MBS, Medicare Benefits Schedule; MDD, major depressive disorder; MDE, major depressive episode; NHCDC, National Hospital Cost Data Collection; OAD, oral antidepressant; PBS, Pharmaceutical Benefits Scheme; TRD, treatment-resistant depression

6.55 Figure 1 illustrates the structure of the economic model in the resubmission.

Figure 1: Model structure



Source: Figure 3-1, p84 of the resubmission

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MDE, major depressive episode; TRD, treatment-resistant depression; Tx, treatment

‡ Age- and sex-adjusted background mortality.

* Treatment-dependent adverse event rates may be assigned.

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

^ User may provide separate transition probabilities for patients 'on treatment' and 'off treatment'.

% Efficacy rates can vary for initial treatment and retreatment.

& Not all retreatment eligible patients will reinitiate esketamine, and some may reinitiate while on subsequent treatment in the MDE state.

6.56 The July 2023 model structure was amended to include retreatment and allow a proportion of patients to continue treatment beyond the maximum 12 months, in response to PBAC concerns that it was likely that a high proportion of patients would receive more than one course of esketamine treatment over the 5-year time horizon (para 7.1 and 7.12, esketamine PSD, July 2023 PBAC meeting); and that stakeholders considered there needed to be some flexibility regarding the maximum 12-month treatment duration (para 7.4, esketamine PSD, July 2023 PBAC meeting).

6.57 To incorporate these changes, additional tunnel states were included to track patient eligibility for retreatment (previously responded to initial treatment of esketamine, have discontinued treatment for at least 4 months, and experienced a subsequent relapse).

6.58 Key drivers of the model are summarised in Table 13 below.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Applicability of continuation criteria	The criteria for continuing treatment in the economic model was based on estimates of response and remission from the TRANSFORM-2 and TRANSFORM-3 trials (response: $\geq 50\%$ improvement in MADRS score; remission: MADRS total score ≤ 12).	High, favours esketamine
Proportion of patients continuing treatment beyond 12 months	Based on data from the Australian early access program which indicated that ██████ % of patients had received treatment beyond 12 months, applied as a reduction to the proportion of patients in the on-treatment recovery health state (with no adjustment to patients in the on-treatment remission and response health states). Patients who are in response or remission (and the remaining patients in the recovery health state) were assumed to remain on treatment for a variety of reasons.	Moderate, direction unclear

Description	Method/Value	Impact
	<p>The █████% estimate from the early access program included patients who had been in the program for less than 12 months, with insufficient follow-up to meet the ≥12 month treatment criterion, but who contribute to the number of patients included in the analysis. Excluding these patients from the analysis results in a higher proportion of patients continuing treatment (20%).</p> <p>The PSCR noted access program data was used to inform these inputs and argued that the design of the program, where patients do not have restrictions on treatment duration and most patients do not pay for esketamine (but do bear the cost of administration), likely means that in practice, a lower proportion would continue on treatment than in the access program. The Response argued the █████% estimated by removing an index start date less than 12 months from data read-out cannot account for patients who should be excluded based on insufficient follow-up and missing data on a break in supply, therefore represents an overestimate.</p> <p>The ESC considered the proportion of patients continuing beyond 12 months was uncertain, and noted the ICER increases if more patients continue treatment.</p>	
<p>Proportion of patients retreated</p>	<p>The model assumes that 22% of patients are retreated over the 5-year model duration, based on the results of 2 US claims data studies (Karkare 2021, Teeple 2021). The resubmission acknowledged limitations of these studies (limited follow-up, the reasons for discontinuation and whether patients restarting treatment have relapsed and experienced a new major depressive episode are unknown).</p> <p>The evaluation noted the 22% estimate was applied to all patients who initiate esketamine in the model, rather than to patients who have discontinued and become eligible for retreatment (consistent with the estimates from the US studies), overestimating the proportion of patients retreated. The PSCR argued the proportion of patients re-treated with esketamine was based on US real world evidence that indicated 18-22% of patients who discontinued over a 1 year period received a second course of treatment, but further argued this was likely to be an underestimate as the US data covers a 1 year period. The Response acknowledged the re-treatment proportion was applied to all patients who initiate esketamine in the model, however argued this is compensated for by the time period of 5 years over which it is applied in the model versus the real world evidence, meaning the re-treatment rate in the model is lower than what would be required to achieve the same proportion over a shorter time period, and reiterated that a higher level of re-treatment lowers the ICER for esketamine in the model.</p> <p>The economic model is also sensitive to assumptions regarding any reduction in esketamine efficacy associated with retreatment, based on an assumed cumulative 15% relative reduction in efficacy assuming all patients receiving retreatment (who have previously responded to treatment) would otherwise achieve 100% response or remission (see Table 15 below).</p> <p>Overall, there are limited data to inform the proportion of eligible patients likely to receive esketamine retreatment, as well as esketamine outcomes associated with retreatment.</p> <p>The ESC considered the proportion of patients who may be retreated with esketamine to be uncertain, and noted the ICER decreases if more patients receive re-treatment. The ESC also considered the assumption of a cumulative 15% relative reduction in efficacy for re-treatment to be highly uncertain, and the likely magnitude of effectiveness in re-treated patients was unknown.</p>	<p>Moderate, direction unclear</p>
<p>Healthcare resource use and costs</p>	<p>The resubmission used an alternative approach to estimating disease management resource use compared to previous esketamine submissions, to address PBAC</p>	<p>High, favours esketamine.</p>

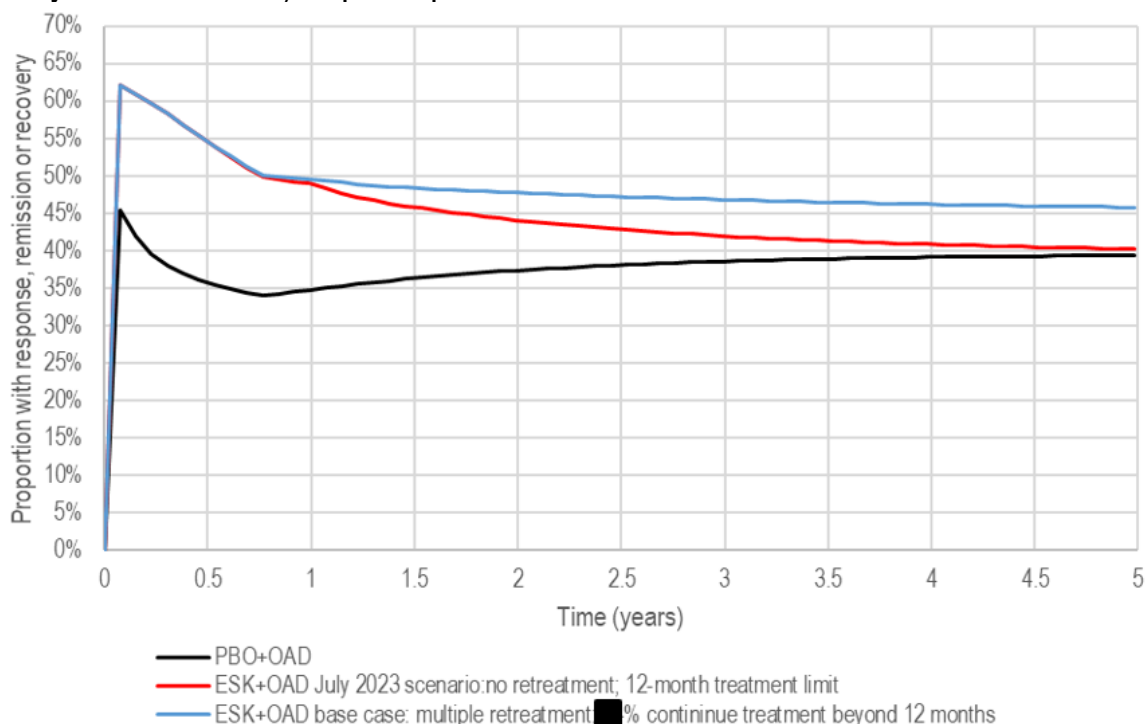
Description	Method/Value	Impact
	<p>concerns with the applicability of the health care resource use source data, a UK retrospective chart review study (Denee 2021).</p> <p>Based on the revised estimates, patients in the esketamine plus OAD arm are hospitalised for 31.2 days compared with 37.6 days for patients in the placebo plus OAD arm over the 5-year model duration. Esketamine plus OAD is associated with a reduction of 6.43 hospitalised days (compared to a reduction of 9.00 days based on Denee 2021).</p> <p>However, the applicability of the resource use estimates to current clinical practice is unclear, given the estimates were based on older Australian data in patients with MDD from the 2004 South Australian Health Omnibus Survey (Goldney 2007); with estimates of hospitalisation further adjusted to account for differences in resource use between patients with non-TRD MDD and TRD (an incidence rate ratio of 1.9) based on survey data from the US and Europe (Zhang 2018, available as an abstract only); with the length of stay per hospitalisation (21 days) based on a post hoc analysis of inpatients with TRD from a single Melbourne clinic.</p> <p>The ESC considered the revised sources for health care resource use were more reasonable than previous submissions as they were based on Australian data, however considered they remained uncertain given the age of the South Australian study and limitations of the data to inform the length of stay per hospitalisation. The ESC noted the ICER is sensitive to these inputs.</p>	
Costs of administration and monitoring	<p>The cost associated with administration and monitoring of esketamine was based on a psychiatrist consultation (MBS item 308 – psychiatrist consultation >75 minutes, \$238.15) as a proxy cost. However, it is unclear whether this is an appropriate proxy for post-administration monitoring, which the resubmission claimed would last 1–2 hours, with supervision predominantly by nurses. The ESC previously considered it was unclear what the likely true cost of administration and monitoring would be in practice, and noted the ICER was moderately sensitive to the assumed cost (para 6.65, esketamine PSD, July 2023 PBAC meeting).</p>	Moderate, unclear direction.
Circumstances of use	<p>Esketamine frequency of administration and dose in the maintenance phases can vary, and in the model was based on use in the clinical trials. It is unlikely that usage in the clinical trials will be replicated in clinical practice. More or less frequent use than was observed in the trials will impact the cost-effectiveness of esketamine.</p>	Moderate, unclear direction.

Source: Constructed during the evaluation

Abbreviations: ICER, incremental cost-effectiveness ratio; MBS, Medicare Benefits Schedule; MDD, major depressive disorder; OAD, oral antidepressant; TRD, treatment resistant depression

- 6.59 The evaluation noted the cost-effectiveness of esketamine was primarily based on the circumstances of use and response criteria in the key trials, which may not be applicable to the proposed PBS population given the broad and subjective nature of the proposed restrictions. The ESC and PBAC noted that, as discussed in paragraph 3.10, the intention was for the proposed restrictions to reflect the population of patients included in the economic model.
- 6.60 Figure 2 compares the proportion of patients in the response, remission or recovery health states in the esketamine plus OAD base case (allowing retreatment and a proportion of patients to continue treatment beyond 12 months); the esketamine plus OAD July 2023 model scenario (with no retreatment and a limit of 12 months treatment) and the placebo plus OAD treatment arm, over the model time horizon.

Figure 2: Proportion of patients achieving response, remission or recovery for esketamine plus OAD (base case and July 2023 model scenario) and placebo plus OAD



Source: Constructed during the evaluation using 'Attachment 3.4 - Esketamine TRD CE Retreatment model' spreadsheet

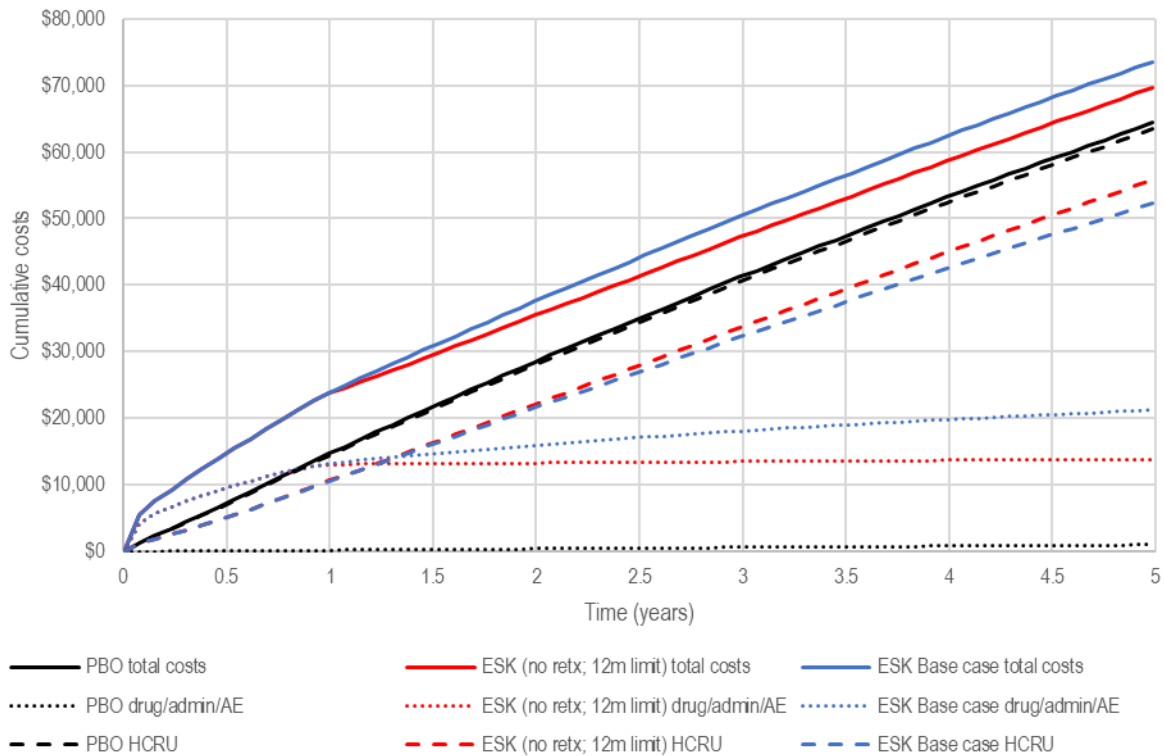
Abbreviations: ESK, esketamine; OAD, oral antidepressant; PBO, placebo

Note: There are minor differences between the esketamine plus OAD July 2023 scenario and placebo plus OAD arm compared with the July 2023 model, due to the current model updating the Australian life tables used to estimate mortality

6.61 The base case model in the resubmission generates a larger difference in the proportion of patients in the response, remission and recovery health states between treatment arms, consistent with the inclusion of esketamine treatment beyond 12 months for a proportion of patients and allowing esketamine retreatment. The esketamine plus OAD arm for the current model base case starts to diverge from the esketamine July 2023 model scenario from cycle 8 (at approximately 7 months), after a proportion of patients become eligible for retreatment from cycle 7.

6.62 Figure 3 summarises the cumulative costs associated with the esketamine plus OAD base case (allowing retreatment and a proportion of patients to continue treatment beyond 12 months); the esketamine plus OAD July 2023 model scenario (with no retreatment and a limit of 12 months treatment) and the placebo plus OAD treatment arm, over the model time horizon.

Figure 3: Cumulative costs for esketamine plus OAD (base case and July 2023 model scenario) and placebo plus OAD



Source: Constructed during the evaluation using 'Attachment 3.4 - Esketamine TRD CE Retreatment model' spreadsheet
 Abbreviations: admin, administration; AE, adverse event; ESK, esketamine plus OAD; HCRU, health care resource use; 12m, 12 months; no retx, no retreatment; OAD, oral antidepressant; PBO, placebo plus OAD

6.63 The base case esketamine plus OAD scenario, including retreatment and allowing a proportion of patients to continue treatment beyond the 12 month limit, results in an increase in drug, administration and adverse event costs and a reduction in health care resource use, compared with the esketamine plus OAD scenario based on the July 2023 submission (no retreatment and treatment limited to 12 months). Both esketamine plus OAD scenarios are associated with higher drug, administration and adverse event costs, but lower health care resource use costs compared to placebo plus OAD.

6.64 The results of the stepped economic evaluation from the July 2023 base case to the current model base case are summarised in Table 14 below.

Table 14: Results of the stepped economic evaluation from the July 2023 base case to the current model base case

Step and component	Esketamine + OAD	Placebo + OAD	Increment
Step 0: July 2023 base case			
Costs	\$ <i>1</i>	\$100,328	\$ <i>1</i>
QALYs	2.7323	2.5916	0.1407
Incremental cost/QALY gained			\$<i>1</i>
Step 1: Correcting the number of cycles of esketamine treatment (previously 14 cycles) to 13 cycles; 5% annual discount rate applied as an annual rate rather than a per (4-week) cycle rate			
Costs	\$ <i>8</i>	\$102,940	\$ <i>1</i>
QALYs	2.8016	2.6593	0.1423
Incremental cost/QALY gained			\$<i>2</i>
Step 2: Unit costs updated to the most recent MBS/PBS Schedules and NHCDC data; market share data used to calculate weighted average drug costs updated; ABS life tables updated from 2019-2021 to 2020-2022 data			
Costs	\$ <i>1</i>	\$100,260	\$ <i>1</i>
QALYs	2.8014	2.6591	0.1423
Incremental cost/QALY gained			\$<i>1</i>
Step 3: Retreatment with esketamine introduced based on the same efficacy as the initial treatment			
Costs	\$ <i>1</i>	\$100,260	\$ <i>1</i>
QALYs	2.8594	2.6591	0.2003
Incremental cost/QALY gained			\$<i>2</i>
Step 4: Reduction in efficacy associated with retreatment introduced			
Costs	\$ <i>1</i>	\$100,260	\$ <i>1</i>
QALYs	2.8531	2.6591	0.1940
Incremental cost/QALY gained			\$<i>2</i>
Step 5: Allowance for a proportion of patients to receive esketamine treatment beyond 12 months			
Costs	\$ <i>1</i>	\$100,260	\$ <i>1</i>
QALYs	2.8641	2.6591	0.2050
Incremental cost/QALY gained			\$<i>3</i>
Step 6: Rates of health care resource use based on Australian data (previously based on UK data)			
Costs	\$ <i>1</i>	\$64,405	\$ <i>1</i>
QALYs	2.8641	2.6591	0.2050
Incremental cost/QALY gained			\$<i>4</i>
Step 7: Reduction in the effective price of esketamine (AEMP per 28 mg device reduced from \$<i>1</i> to \$<i>1</i>)			
Costs	\$ <i>1</i>	\$64,405	\$ <i>1</i>
QALYs	2.8641	2.6591	0.2050
Incremental cost/QALY gained (base case)			\$<i>3</i>

Source: Table 3-32, p113 of the resubmission; 'Attachment 3.4 Esketamine TRD CE Retreatment model' spreadsheet

Abbreviations: AEMP, approved ex-manufacturer price; MBS, Medicare Benefits Schedule; OAD, oral antidepressant; PBS, Pharmaceutical Benefits Scheme; NHCDC, National Hospital Cost Data Collection; QALY, quality adjusted life year

Note: Some values in Table 3-32 of the resubmission could not be verified during the evaluation; values calculated during the evaluation are indicated in italics.

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$15,000 to < \$25,000

³ \$35,000 to < \$45,000

⁴ \$55,000 to < \$75,000

6.65 Based on the resubmission's economic model, treatment with esketamine nasal spray plus a newly initiated oral antidepressant versus treatment with a newly initiated oral antidepressant alone in patients with TRD is associated with an incremental cost per QALY gained of \$35,000 to < \$45,000. This compares to an incremental cost per QALY gained of \$25,000 to < \$35,000 in the July 2023 resubmission.

6.66 Incorporating retreatment and reducing the effective price of esketamine (which reduced the ICER); and allowing a proportion of patients to continue treatment beyond 12 months and using Australian data to inform health care resource use (which increased the ICER) had the largest impacts on the stepped economic evaluation. The incorporation of retreatment in the model improves the cost-effectiveness of esketamine due to the increased proportion of patients who subsequently achieve remission with retreatment, and the associated reduction in disease management costs, which offset the additional drug and administration costs of esketamine retreatment.

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

- Additional drug, administration and adverse event costs of \$**|**; based on an average duration of treatment of 9.56 months (7.89 months of which was for initial treatment).
- An additional 0.53 years (6.3 months) free from major depressive disorder, which would save \$11,902 in disease management costs, and be associated with improved quality of life.

6.68 The results of key sensitivity analyses are summarised in Table 15 below.

Table 15: Results of key sensitivity analyses

	Incremental cost (\$)	Incremental QALYs	ICER	% change in ICER
Base case		0.2050	1	-
Discount rate (base case: 5%)				
0%		0.2203	1	-%
3.5%		0.2093	1	-%
Time horizon (base case: 5 years)				
1 year		0.0705	2	+%
3 years		0.1545	3	+%
7 years		0.2437	1	-%
10 years		0.2913	4	-%
Probabilities of remission and response in induction phase (base case: remission 46.5% ESK+OAD vs 26.8% OAD; response 15.6% ESK+OAD vs 18.5% OAD from TRANSFORM-2 and TRANSFORM-3 weighted average)				
Increase ESK+OAD probabilities by 20%		0.2680	4	-%
Decrease ESK+OAD probabilities by 20%		0.1420	3	+%
Increase OAD probabilities by 20%		0.1811	3	+%
Decrease OAD probabilities by 20%		0.2289	4	-%
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)		0.1847	3	+%
STAR*D probabilities adjusted to 4-weekly estimates based on time to response (8.3 weeks)/remission (7.4 weeks)		0.1650	3	+%
Subsequent treatment loss of response, relapse from remission and recurrence from recovery (base case: recovery to MDE 3.6% per cycle; remission to MDE 12.8%/cycle; response to MDE 22.8%/cycle)				
Increase probabilities by 20%		0.2214	1	-%

	Incremental cost (\$)	Incremental QALYs	ICER	% change in ICER
Decrease probabilities by 20%		0.1851	5	+%
Proportion of patients remaining on esketamine beyond 12 months (base case: % , based on EAP data)				
0%		0.1940	4	-%
% (EAP data adjusted to exclude patients with <12 months of follow-up)		0.2095	5	+%
21.5% (Teepie 2021)		0.2104	5	+%
23.9% (Karkare 2021)		0.2118	3	+%
No limit (the 29.4% of patients remaining on treatment at 12 months continue treatment)		0.2164	3	+%
Proportion of patients receiving esketamine retreatment (base case: 22% of initiating patients over 5 years (equivalent to 1.48% of eligible patients per cycle); no limit on number of retreatment episodes)				
No retreatment		0.1551	3	+%
6.36% of initiating patients, based on the Australian early access program		0.1693	5	+%
All eligible patients receive retreatment in the cycle they become eligible		0.4631	6	-%
22% of patients eligible for retreatment over 5 years		0.1696	5	+%
Patients receive only 1 additional episode of retreatment (19.9% of patients retreated)		0.2019	1	+%
Efficacy of esketamine retreatment (base case: 7.8% relative reduction in efficacy applied sequentially, yielding a cumulative efficacy reduction of 15% in most patients; otherwise assumed to have a 100% response/remission rate)				
No reduction in efficacy for retreatment; assuming all patients previously responding/achieving remission achieve response/remission again		0.2114	1	-%
A 31.0% relative reduction in efficacy (efficacy reduction of 52% for the majority of patient pathways); based on a threshold analysis of the reduction required for the ICER to be \$50,000.		0.1878	5	+%
Retreatment efficacy for remission and response during the induction phase based on the SUSTAIN-3 subgroup analysis (Castro 2023) ^a		0.1958	5	+%
Initial treatment transition probabilities used (incorporating responders and non-responders)		0.1887	5	+%
Health state utility values (base case: trial-based estimates using the UK value set: MDE 0.4316; response 0.7664; remission 0.8606; recovery 0.8606)				
MDE utility increased by 20%		0.1626	3	+%
MDE utility decreased by 20%		0.2474	1	-%
Recovery utility increased to 1.0		0.2567	1	-%
Recovery utility decreased by 20%		0.1413	3	+%
Health state utilities from TRANSFORM-2 using Canadian value set		0.1829	5	+%
Esketamine utilisation and costs (base case: trial-based circumstances of use)				
All patients receive once weekly dosing during maintenance weeks 9+		0.2050	3	+%
All patients receive once fortnightly dosing during maintenance weeks 9+		0.2050	4	-%
Esketamine administration and monitoring costs (base case: \$238.15 per administration, based on MBS item 308; psychiatrist consultation >75 minutes)				
Increase costs by 50%		0.2050	3	+%
Decrease costs by 50%		0.2050	6	-%

	Incremental cost (\$)	Incremental QALYs	ICER	% change in ICER
Health care resource use (base case: Goldney 2007 MDD excess utilisation; hospitalisation rate adjusted for risk in TRD versus non-TRD patients (Zhang 2018) and multiplied by LOS from post hoc analysis of Melbourne clinic data; hospitalisation days 0.94 per cycle)				
Denee 2021 UK data as per previous submissions		0.2050	⁶	-1%
Hospitalisation costs based on AR-DRG episode of care (U63A; Major affective disorders, major complexity; \$22,305); with rate of hospitalisation as per base case (Goldney 2007 estimate adjusted for TRD versus non-TRD based on Zhang 2018)		0.2050	³	+1%
Hospitalisation costs based on AR-DRG episode of care (weighted average of U63A/B; Major affective disorders, major/minor complexity) with LOS adjustment for TRD versus non-TRD based on Zhang 2018 (2.4 versus 1.5 days=1.6); with rate of hospitalisation as per base case		0.2050	³	+1%
Hospitalisation days based on post hoc analysis of Melbourne clinic data based on 3-year hospitalisation rate and LOS (2.32 days per cycle)		0.2050	Esketamine dominant	-
Hospitalisation days based on post hoc analysis of Melbourne clinic data based on 10-year hospitalisation rate and LOS (1.13 days per cycle)		0.2050	⁴	-1%

Source: Table 3-37, and Figure 3-6, p125 of the resubmission; 'Attachment 3.4 Esketamine TRD CE Retreatment model' spreadsheet
 Abbreviations: AE, adverse event; AIHW, Australian Institute of Health and Welfare; AR-DRG, Australian refined diagnosis related group; EAP, early access program; ICER, incremental cost-effectiveness ratio; LOS, length of stay; MDE, major depressive episode; NICE, National Institute for Health and Care Excellence; QALY, quality adjusted life year; TRD, treatment-resistant depression

Note: A number of sensitivity analyses affect the proportion of patients retreated over the model time horizon (e.g. response rates, the proportion of patients remaining on esketamine beyond 12 months). Consistent with the approach presented in the resubmission, these sensitivity analyses were conducted based on 1.48% of eligible patients being retreated each cycle; estimates were not recalibrated so that the total proportion of patients treated over the model time horizon remained at 22%.

^a Retreatment efficacy for remission (60.9%) and response (12.5% = 73.4%-60.9%) during the induction phase based on the SUSTAIN-3 subgroup analysis of patients receiving a second esketamine induction following relapse on placebo plus OAD (Castro 2023)

The redacted values correspond to the following ranges:

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

6.69 The economic model was most sensitive to the time horizon, the probability of achieving remission or response at treatment induction, the proportion of patients remaining on esketamine treatment beyond 12 months, the proportion of patients retreated with esketamine, the effectiveness of the subsequent treatment mix based on the STAR*D study, the esketamine dosing schedule in the maintenance period (weekly/fortnightly), esketamine administration and monitoring costs, estimates of inpatient hospitalisation days associated with TRD (and associated cost), and health state utility values.

6.70 Due to limitations of the model structure, it was not possible to assess the impact of the requirement for a 4-month treatment gap prior to retreatment. The PSCR however

acknowledged the 4-month treatment gap parameter could not be varied in the model, but argued this was consistent with the MBS listing of rTMS and that given re-treatment requires relapse in addition to a treatment break, any change would likely have a small effect on the re-treatment rate.

- 6.71 The ESC noted the economic model was sensitive to a number of inputs which are associated with significant uncertainty, as outlined in Table 13.
- 6.72 The ESC noted that MSAC had previously considered eTMS to be largely cost-effective because the ICER in the respecified base case and sensitivity analyses remained less than \$50,000 per QALY¹. The Pre-PBAC Response argued the evidence base for rTMS was of lower quality than for esketamine as there were no direct comparative trials of efficacy or safety compared with OADs and further argued other factors, such as the risk sharing arrangement (RSA) proposal for esketamine, provide certainty compared to the consideration of rTMS.
- 6.73 The ESC noted a number of plausible sensitivity analyses for esketamine resulted in ICERs above \$45,000 to < \$55,000 per QALY including:
- Applying hospitalisation episode of care per cycle (rather than nights per cycle) to calculate health resource costs (ICER \$55,000 to < \$75,000 per QALY);
 - Assuming ■% (rather than ■%) of patients remain on treatment for longer than 12 months (ICER \$45,000 to < \$55,000 per QALY); and
 - Assuming 22% of patients eligible for retreatment over 5 years (rather than 22% of initiating patients over 5 years) (ICER \$45,000 to < \$55,000 per QALY).
- 6.74 The ESC noted that plausible multivariate analyses would result in ICERs over \$95,000 to < \$115,000 per QALY.
- 6.75 The Pre-PBAC Response argued the direction of the impact of uncertainties raised by the ESC (Table 13 and Table 15 refer) were unclear and stated the sensitivity analyses range from esketamine being dominant over OADs, up to \$55,000 to < \$75,000 per QALY. The pre-PBAC response argued that while there may be concern that the ICER is higher than the resubmission base case, it may also be possible that the ICER is lower. The Response also argued it was important to note that esketamine provided value to patients and society beyond that captured in the economic model.

Drug cost/patient

- 6.76 The estimated drug cost per patient for esketamine applied in the economic model and the financial estimates is summarised in the table below.

Table 16: Esketamine drug cost per patient

	Economic model	Financial estimates
INITIAL TREATMENT		
Patients on initial treatment for less than 12 months (█% of patients)		
- Duration of treatment	18.0 weeks ^a	22.95 weeks ^f
- Cost of treatment	\$ ^b	\$ ^g
Patients on initial treatment for at least 12 months (█% of patients)		
- Duration of treatment	130.3 weeks ^c	136.14 weeks ^h
- Cost of treatment	\$ ^b	\$ ^g
RETREATMENT		
- Proportion of patients receiving retreatment	22% over 5 years	61% over 6 years ⁱ
Receiving retreatment for less than 12 months (█% of patients)		
- Duration of treatment	27.1 weeks ^d	19.51 weeks ^j
- Cost of treatment	\$ ^b	\$ ^g
Receiving retreatment for at least 12 months (█% of patients)		
- Duration of treatment	83.6 weeks ^e	115.72 weeks ^j
- Cost of treatment	\$ ^b	\$ ^g
TOTAL		
Average cost per patient (including initial treatment and retreatment)	\$^b	\$^k

Source: Constructed during the evaluation based on 'Attachment 3.4 – Esketamine TRD CE Retreatment model' spreadsheet; and 'Attachment 4.1 Esketamine UCM March 2024' spreadsheet

Note: The private hospital/community access DPMQs in the resubmission were incorrectly calculated and were not corrected in the economic model and financial implications.

^a Based on the proportion of patients in on-treatment health states for initial treatment over the first year (13 cycles) of the economic model, adjusted to remove patients who continued treatment beyond 12 months (█%).

^b Based on output of the economic model.

^c Based on the proportion of patients in on-treatment health states for initial treatment from cycle 14 of the economic model; adjusted for the proportion of patients who continued treatment beyond 12 months (█%); plus 52 weeks of treatment in the first year (13 cycles).

^d Based on the proportion of patients in on-treatment health states for retreatment treatment over the first year (13 cycles) of the economic model, adjusted to remove patients who continued treatment beyond 12 months (█%); adjusted for the proportion of patients receiving retreatment (22%).

^e Based on the proportion of patients in on-treatment health states for retreatment from cycle 14 of the economic model; adjusted for the proportion of patients who continued treatment beyond 12 months (█%); plus 52 weeks of treatment in the first year (13 cycles); adjusted for the proportion of patients receiving retreatment (█%).

^f Stated to be based on output from the economic model. The resubmission's estimate differed from that derived from the economic model (22.78 weeks; average duration of treatment in the first 12 months of the model) and did not adjust for the proportion of patients who received treatment for beyond 12 months.

^g Based on the number of scripts (initial, week 1-4; continuing, week 5-8; continuing, week 9+) derived from the duration of treatment, multiplied by the corresponding adherence rate and esketamine cost per script (see Table 17 below).

^h Based on output from the economic model, adjusted for the proportion of patients who continued treatment from cycle 14 of the economic model (13.04%) rather than the █% of patients who received treatment for at least 12 months (the difference is due to a proportion of patients dying or discontinuing treatment between cycles 13 and 14).

ⁱ The proportion of patients initiating esketamine treatment in Year 1 who are retreated over the 6-year utilisation and cost model; calculated using a cohort approach, for consistency with the economic model.

^j Assumed to be █% of the duration of treatment used for initial treatment.

^k Weighted average based on the proportions of patients in each category and costs of treatment for each patient category.

Estimated PBS usage & financial implications

6.77 The resubmission was not considered by DUSC. The resubmission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of esketamine for TRD. Key changes in the financial model in the resubmission include:

- Extrapolation of DUSC PBS 100% sample analysis to the years of listing covered by the current resubmission (2025-2030).
- Addition of a 1% year on year growth rate for patients in the psychiatry setting.
- Reduction in number of grandfathered patients.
- Reduced uptake rates (average reduction of 3% across 6 years of listing compared to the July 2023 resubmission, to address concerns about likely barriers to access).
- Proportion of patients retreated with esketamine derived from trial-based estimates of response/remission and subsequent relapse, with 100% of patients who relapse after responding to esketamine previously assumed to be retreated, mostly in the same year of treatment initiation or in the year following.
- Proportion of patients treated beyond 12 months, derived from the sponsor’s early access program.
- Average duration of therapy estimated separately by subgroups, derived from the resubmission’s economic model (up to 12 months or beyond 12 months treatment; initial, retreatment or grandfathered patients).
- Revising the effective AEMP of esketamine nasal spray from \$| to \$| per 28 mg device.

6.78 Table 17 summarises the key inputs for the financial estimates.

Table 17: Key inputs for financial estimates

Data	Source	Comment
Eligible population		
Number of adult patients meeting criteria for TRD	DUSC PBS 100% sample analysis. Patients who had inadequate responses to ≥2 antidepressants in the current MDD episode and started a new treatment (switching to a new antidepressant, adding on an augmentation agent or another antidepressant). A logarithmic function was applied to the 100% PBS trend data from 2019 to 2021 to extrapolate growth of TRD (compound growth rate of 2.6% per year; 59,446 patients in Year 1).	Unchanged from the 2023 resubmission.
Prescription setting	100% PBS sample analysis. The PBS 100% patient line combination data show an average 19.1% of all patient initiations from 2019 to 2021 occurred in the psychiatry setting. The resubmission assumed an additional 1% per year would initiate treatment with psychiatrists given a likely increase in referral rates over time (20.1% in Year 1 to 25.1% in Year 6).	The data source was unchanged from the July 2023 resubmission. The approach was reasonable, however the addition of an annual increase in patients treated by psychiatrists was an assumption and is therefore uncertain.
Grandfathered patients	Estimated < 500 patients enrolled in the sponsor’s early access program (updated from 500 to < 5,000 patients in the July 2023 resubmission – < 500 patients have since ceased treatment with esketamine).	Grandfathered patients were excluded from the submission’s estimates of uptake, which was appropriate. This approach excluded grandfathered patients from calculations of retreatment estimates.

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Data	Source	Comment
Treatment utilisation		
Uptake rates	Sponsor assumption. Uptake rates applied to initial treatment only vary with line of therapy and increase over time (average ██████% in Year 1 to ██████% in Year 6). The uptake rate for grandfathered patients was assumed to be 100%.	The current resubmission assumed uptake of esketamine would be higher in Years 1 and 2 but lower in later years than assumed in the July 2023 resubmission. While the resubmission attempted to address PBAC concerns around uptake of esketamine in the context of likely barriers to access, compared to July 2023, uptake remained high.
Proportion of patients who retreat with esketamine in subsequent episodes of TRD	Patients who are responders/remitters to their initial course of esketamine (62.07%) based on TRANSFORM-2 and TRANSFORM-3 trial data, and who have subsequently relapsed into MDE/TRD, based on the SUSTAIN-1 Kaplan Meier curve of the combined Stable Remitter and Stable Responder population, are eligible for retreatment. The 35% risk of relapse at 36 weeks was converted to an annual relapse rate (50.56%). 100% of these patients are assumed to be retreated with esketamine.	The approach to retreatment was an updated approach compared to the July 2023 resubmission. 31% of all patients treated in Year 1 are retreated patients, increasing to 57% in Year 6. The risk of relapse is also applied to patients in years subsequent to treatment initiation (i.e. Year 1 patients who have not relapsed in Year 1, may relapse in Year 2, and so on). Relapse rates may not reflect treatment status – the risk of relapse (based on rates in esketamine-treated patients) is applied to patients over 6 years, while the majority of patients are treated with esketamine for less than 12 months, therefore the same risk of relapse has been applied to patients both on and off treatment with esketamine, which may underestimate the proportion of patients who are re-treated (as relapse rates may be higher in patients who are not on esketamine treatment). DUSC has previously considered the applicability of the trial-based estimates to Australian clinical practice is unclear (para 6.68, esketamine PSD, July 2022 PBAC meeting). The assumption that all eligible patients would receive retreatment was uncertain and was inconsistent with the economic model.
Distribution of patients seeking retreatment	Sponsor assumption (50% retreated in year of relapse, 45% in second year, 5% in third year).	Updated approach compared to the July 2023 resubmission. The estimates were based on assumptions and are therefore uncertain.
Dose distribution	The split between the 28 mg dose and the 56 mg/84 mg doses was derived from the proportion of patients aged 18-64 years, and 65 years and over in the DUSC dataset (92.4%, and 7.6% respectively). The split between the 56 mg and 84 mg doses for initial treatment was derived from the TRANSFORM-2 trial four-week initial treatment period, and for continuing treatment from the SUSTAIN-1 maintenance phase.	Unchanged from the July 2023 resubmission. The dose split used to define the elderly population, based on the population split in the DUSC 100% PBS dataset, differed from the population split used in the economic model (based on ABS population projections; 17.1% aged 65 years or older). The PBAC has previously considered that differences between the clinical trial settings and Australian clinical practice may result in differences in dose distribution, frequency and adherence (Table 18, esketamine PSD, July 2023 PBAC meeting).

Data	Source	Comment
Dose frequency	Derived from the proportion of patients maintained on either weekly (40%) or fortnightly (60%) dosing in the SUSTAIN-1 trial.	Unchanged from the July 2023 resubmission. Dose frequency in clinical practice may differ from that observed in the clinical trial setting.
Proportion of use up to or beyond 12 months	Distribution of patients by duration of therapy from supply data from sponsor's EAP. All patients (initial, retreatment and grandfathered) are split using these proportions (<12 months: █%; 12+ months: █%)	The resubmission argued that, as the majority of patients enrolled in the EAP do not pay for treatment and there is no restriction on treatment duration, the proportion of patients supplied with esketamine for more than 12 months (█%) represents an upper bound on what would be expected in the Australian setting. However, the analysis included a number of patients with limited follow-up (entered the EAP within 12 months of the analysis) who could not meet the ≥12-month criterion, potentially underestimating the proportion of patients continuing treatment beyond 12 months in clinical practice.
Duration of treatment	Average duration derived from the proportion of patients on treatment over time in the economic model (which incorporates the proportion of patients responding at 4 weeks and continuing treatment). Estimated separately for patients treated up to 12 months (average duration 22.95 weeks [5.3 months]), and those treated beyond 12 months (average duration 136.14 weeks (or 31.42 months). Treatment duration for retreated patients was assumed to be 85% of initial treatment duration; and Grandfathered treatment was assumed to be 4 weeks less than the initial treatment duration, as the 4-week induction phase was assumed to occur prior to PBS listing of esketamine.	The estimated duration of treatment for patients receiving treatment for up to 12 months included the patients who received treatment beyond 12 months, therefore overestimating the duration of treatment for patients with less than 12 months of treatment. The PBAC considered the approach used in the resubmission to calculate duration of treatment was reasonable. Retreatment and grandfathered treatment durations were assumptions and therefore uncertain.
Adherence	92.5% for initial treatment, and 73.8% for continuing treatment. Derived from TRANSFORM-2 (initial treatment) and SUSTAIN-1 (maintenance) trial data.	Unchanged from the July 2023 resubmission. Differences between the clinical trial setting and Australian clinical practice may result in differences in adherence.

Source: Section 4.2.; Section 4.3of the resubmission; 'Attachment 4.1 Esketamine UCM March 2024' Excel workbook

Abbreviations: AEMP, approved ex-manufacturer price; EAP, early access program; GP, general practitioner; MDD, major depressive disorder; TRD, treatment-resistant depression.

6.79 Table 18 presents the derivation of the estimated number of patients that would be treated with esketamine on the PBS/RPBS for TRD.

Table 18: Estimated utilisation of esketamine

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patient numbers						
Number of TRD patients in third line setting and over ^a	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ²
% patients initiated in the psychiatry setting (19.1%, with 1% year on year growth applied)	█ ³ %	█ ³ %	█ ³ %	█ ³ %	█ ³ %	█ ³ %
Number of patients initiated in psychiatry setting	█ ^{3b}	█ ³	█ ³	█ ³	█ ³	█ ³
Average uptake of esketamine across all lines, excluding retreatment	█ ⁴ %	█ ⁴ %	█ ⁴ %	█ ⁴ %	█ ⁴ %	█ ⁴ %
Patients – initial treatment	█ ⁴	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Responders/remitters to initial esketamine (62.07%)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Retreated patients (50.56% relapse after responding/remitting, 100% of these patients are retreated) ^c	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Patients – retreatment (50% retreated in year of relapse, 45% after 1 year and 5% after 2 years)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Total esketamine treated patients	█ ^{4 d}	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ³

Source: Table 4-3 Table 4-4; of the resubmission

^a Based on the 100% PBS sample estimated to have TRD based on prior antidepressant scripts, with a logarithmic function applied to extrapolate growth rate per annum.

^b Excluding < 500 grandfathered patients in Year 1 of listing, for whom uptake was calculated separately and assumed to be 100%

^c Patients who did not relapse in year 1 of treatment remain at risk of relapse in subsequent years (i.e. 50.56% of patients in Year 1 relapse, of the remaining 49.44% of patients, 50.56% relapse in their second year, and so on).

^d Including < 500 grandfathered patients.

The redacted values correspond to the following ranges:

¹ 50,000 to < 60,000

² 60,000 to < 70,000

³ 10,000 to < 20,000

⁴ 500 to < 5,000

⁵ 5,000 to < 10,000

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

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Initial treatment (including grandfathered patients)	1	1	2	2	2	2
Patients receiving retreatment	1	1	1	1	1	1
Total patients treated with esketamine (including grandfathered patients)	1	2	2	2	2	3
Total patients treated with esketamine (July 2023)	1	1	2	2	2	2
Total scripts	3	4	5	6	6	6
Total scripts (July 2023)	4	4	5	6	6	7
Net cost to the PBS/RPBS	8	9	10	11	12	12
Net PBS/RPBS costs (July 2023)	9	10	12	13	13	14

Source: Table 4-3 Table 4-4, p139; Table 4-8, Table 4-11, of the resubmission; 'Attachment 4.1 Esketamine UCM March 2024' spreadsheet. Note: The private hospital/community access DPMQs in the resubmission were incorrectly calculated and were not corrected in the financial implications.

The redacted values correspond to the following ranges:

- ¹ 50,000 to < 60,000
- ² 60,000 to < 70,000
- ³ 10,000 to < 20,000
- ¹ 500 to < 5,000
- ² 5,000 to < 10,000
- ³ 20,000 to < 30,000
- ⁴ 20,000 to < 30,000
- ⁵ 30,000 to < 40,000
- ⁶ 40,000 to < 50,000
- ⁷ 50,000 to < 60,000
- ⁸ \$20 million to < \$30 million
- ⁹ \$30 million to < \$40 million
- ¹⁰ \$40 million to < \$50 million
- ¹¹ \$50 million to < \$60 million
- ¹² \$60 million to < \$70 million
- ¹³ \$70 million to < \$80 million
- ¹⁴ \$80 million to < \$90 million

6.81 The estimated net cost to the PBS/RPBS of listing esketamine based on the proposed effective price was \$20 million to < \$30 million in Year 1 of listing, increasing to \$60 million to < \$70 million in Year 6, an estimated net cost of \$200 million to < \$300 million in the first 6 years of listing. In the July 2023 resubmission, the estimated net cost to the PBS/RPBS based on the proposed effective price was \$30 million to < \$40 million in Year 1 of listing, increasing to \$80 million to < \$90 million in Year 6, an estimated net cost of \$300 million to < \$400 million over the first 6 years of listing. The current resubmission incorporated more initial and retreated patients compared to the July 2023 resubmission, as well as a proportion of patients with treatment duration beyond 12 months. However the reduced effective price for esketamine, and a reduction in the average treatment duration for most patients, resulted in a lower overall net cost to the PBS/RPBS in the current submission.

6.82 The ESC noted the script 'duration (periods)' (Column L) on the 3a.Scripts – proposed worksheet was incorrectly completed for a number of rows. The ESC considered that because the 2.d Patients – DTG worksheet had been used to calculate the patient years of treatment from Week 5, the 'duration (periods)' column should reflect a total

of 52 weeks of treatment across the Week 5 - 8 and Week 9+ rows. The pre-PBAC response noted that correcting this error reduced the net cost to the PBS/ RPBS by 0.6%. The PBAC noted the model appropriately assumed 4.02 scripts would be required for fortnightly dosing (i.e., half the scripts required for weekly dosing); however, the number of packs per script should remain as 4 (rather than 2 as used in the model).

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

- The PBAC previously considered the uptake of esketamine in new patients was likely overestimated (26% in Year 1 to 45% in Year 6; para 7.15, esketamine PSD, July 2023 PBAC meeting). The current resubmission reduced uptake estimates by an average of 3% over the first 6 years of listing (31% in Year 1 to 39% in Year 6), with a small increase in uptake in the first two years. The pre-PBAC response revised uptake to 29% in Year 1 to 37% in Year 6.
- The approach to retreatment was an updated approach compared to July 2023 resubmission. Retreated patients as a proportion of all treated patients increases from 31% in Year 1 to 57% in Year 6 because the risk of relapse is also applied to patients in years subsequent to treatment initiation (i.e. Year 1 patients who have not relapsed in Year 1, may relapse in Year 2, and so on). Relapse rates may not reflect treatment status – the risk of relapse is applied to patients over 6 years, while the majority of patients are treated for less than 12 months. The assumption that all patients eligible for retreatment would receive it was uncertain.
- The proportion of patients continuing treatment beyond 12 months, based on data from the sponsor's early access program, was uncertain. The analysis included a number of patients with limited follow-up (entered the EAP within 12 months of the analysis) who could not meet the ≥ 12 month criterion, potentially underestimating the proportion of patients continuing treatment beyond 12 months in clinical practice. The PSCR argued that the proportion continuing treatment beyond 12 months (1%) was the best available estimate.
- The average duration of esketamine treatment, used to estimate the number of scripts per patient, was based on inputs and assumptions in the resubmission's economic model, which may have been incorrectly calculated (for example, the estimated duration of treatment for patients receiving treatment for up to 12 months included the patients who received treatment beyond 12 months duration of treatment which is likely to overestimate treatment duration). The PBAC considered the approach used in the resubmission to calculate duration of treatment was reasonable; however, the duration of treatment in clinical practice remained highly uncertain.
- DUSC previously considered the applicability of trial-based estimates of adherence, persistence and dose distribution to Australian clinical practice is

unclear; that difficulty in accessing supervised administration, the burden of appointments for administration and the inability to drive for the rest of the day following treatment may impact adherence; and that there is significant risk of use outside the proposed restriction in patients with conditions other than TRD (para 6.68, esketamine PSD, July 2022 PBAC meeting).

- 6.84 The PSCR noted that in comparing the proportion of patients retreated across the economic and financial models, the evaluation stated that 61.2% of patients are retreated in the financial model. The PSCR considered that the retreatment rate in the financial model is 41% across 5 years, based on 10,000 to < 20,000 patients retreated with esketamine divided by 20,000 to < 30,000 patients initially treated with esketamine (compared to 22% over 5 years in the economic model). The PSCR stated the economic model retreatment assumptions are more conservative, and likely an underestimate and that, given higher retreatment rates result in lower ICERs, it is not unreasonable for the financial model to assume a higher retreatment rate than the economic model. The PSCR stated any uncertainty would be addressed through the proposed RSA. The ESC noted 61.2% was not presented as the total proportion of retreated patients; it was the proportion of patients (500 to < 5,000/500 to < 5,000) who initiate treatment in Year 1 and are retreated once over the 6 year time horizon of the financial model. This estimate was included in the evaluation to compare with the cohort in the economic model, in which 22% of the initial cohort receive retreatment over the 5 year model time horizon.
- 6.85 The ESC advised there remained substantial uncertainties with the utilisation and financial estimates due to the uptake of esketamine, the extent of use for more than 12 months and re-treatment rates being uncertain. The ESC noted the PSCR stated that while there were uncertainties with the financial estimates, the proposed RSA mitigates the financial risks to the PBS. The ESC noted the risks (such as extent of use beyond 12 months) can only be managed through an RSA if the utilisation estimates have not been overestimated.

Quality Use of Medicines

- 6.86 The resubmission did not present an updated quality use of medicines strategy, stating that the July 2023 resubmission outlined the strategy in detail that is currently in place for patients accessing esketamine through the EAP, the Department of Veterans' Affairs and through state-based workers compensation schemes. The PBAC has previously considered that the sponsor 'has developed an appropriate QUM strategy and accompanying activities for esketamine' (para 6.76, esketamine PSD, July 2023 PBAC meeting).
- 6.87 There is no funding mechanism to cover the administration and monitoring required for esketamine. The submission stated that this may be absorbed by public hospitals or private clinics making special funding arrangements or may be, in part or in whole, passed on to patients. The submission stated that the sponsor recognises that this may

result in inequities in treatment access as some patients will be required to pay out-of-pocket, which they may not be able to afford.

- 6.88 The ESC noted likely access issues with esketamine relating to the lack of funding (and hence patient out of pocket costs) for administration and post-administration monitoring, and health system constraints in terms of access to psychiatrists, particularly in rural and remote areas.

Financial Management – Risk Sharing Arrangements

- 6.89 To address concerns of uncertainty in the utilisation of esketamine, including the number of patients eligible for and expected to receive initial therapy and retreatment, the resubmission proposed a risk-sharing arrangement consisting of annual subsidisation caps set at the estimated annual Commonwealth Payment (net cost) of esketamine nasal spray at the requested effective prices.
- 6.90 The total value of the subsidisation cap over the 5-year period represents a [REDACTED] % reduction from that proposed in the July 2023 resubmission. In addition, the resubmission proposed a reimbursement of [REDACTED] % for any potential use above specified subsidisation caps (increased from [REDACTED] % in the July 2023 resubmission and [REDACTED] % in the July 2022 resubmission). The proposed subsidisation caps were set according to the estimated financial impacts over the first five years of listing.
- 6.91 The resubmission acknowledged the consideration by the PBAC at the July 2022 meeting that a [REDACTED] % rebate for any potential use over subsidisation caps would provide greater certainty around the high proposed cost to government (para 7.14, esketamine PSD; July 2022 PBAC meeting). The current resubmission reiterated an inability to offer [REDACTED] % rebates, arguing that: the proposed financial impact is more certain than in previous resubmissions due to use of the 100% PBS sample to identify eligible patients; there has been a reduction in the proposed costs to government; a revised approach was taken to estimating retreated patients; tight controls exist around the use of esketamine (Schedule 8) requiring the ability to monitor and provide correct model of care; and a robust QUM program is in place which ensures that only those patients appropriate for esketamine will receive it.
- 6.92 Table 20 presents the subsidisation caps proposed in the resubmission.

Table 20: Proposed risk-sharing arrangement subsidisation caps

	Year 1	Year 2	Year 3	Year 4	Year 5
Value of subsidisation caps	1	2	3	4	5
Number of scripts in subsidisation caps	6	7	8	9	9
Number of devices in subsidisation caps	10	11	12	13	13
July 2023 subsidisation caps ^a	2	3	5	14	14

Source: Table 4-20 of the resubmission.

^a The July 2023 resubmission proposed a rebate of █ % for any potential use above the subsidisation cap.

The redacted values correspond to the following ranges:

¹ \$20 million to < \$30 million

² 30 million to < \$40 million

³ \$40 million to < \$50 million

⁴ \$50 million to < \$60 million

⁵ \$60 million to < \$70 million

⁶ 10,000 to < 20,000

⁷ 20,000 to < 30,000

⁸ 30,000 to < 40,000

⁹ 40,000 to < 50,000

¹⁰ 100,000 to < 200,000

¹¹ 200,000 to < 300,000

¹² 300,000 to < 400,000

¹³ 400,000 to < 500,000

¹⁴ \$70 million to < \$80 million

⁵ \$90 million to < \$100 million

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of esketamine for the treatment of treatment-resistant depression (TRD) in patients who have failed two or more prior oral anti-depressant drugs (OADs). The PBAC reiterated its previous consideration that, based on the available clinical evidence, esketamine was likely to be effective for some patients. The PBAC noted the economic model in the resubmission included provision for treatment beyond 12 months and retreatment (as requested in July 2023), and while it considered there were substantial uncertainties with the effectiveness of esketamine and the extent of use in these settings, esketamine was overall likely to be cost-effective at the price proposed in the resubmission. The PBAC deferred the item to enable the restriction criteria to be refined and the utilisation estimates to be revised.

7.2 The PBAC noted the input from healthcare professionals and individuals supported the listing of esketamine and described it as an effective and well-tolerated treatment, with patients who respond experiencing a rapid and life-changing impact on symptoms and quality of life. The Committee recalled the input from clinicians and individuals in previous considerations of esketamine described similar benefits from esketamine treatment. The PBAC also acknowledged the input from the RANZCP, which noted the College has a clinical memorandum on the use of ketamine/ esketamine in practice and highlighted that affordability is a part of ensuring patients have access to evidence-based treatments.

7.3 The PBAC reaffirmed its previously expressed view that there is a moderate to high

clinical need for additional treatment options for TRD.

- 7.4 The PBAC recalled that in its consideration of esketamine in July 2023 that treatment was limited to a maximum of 12 months and retreatment was not addressed in the requested listing. The Committee considered that flexibility regarding treatment duration and allowing retreatment would need to be addressed in a resubmission (paragraphs 7.4, 7.7, 7.8 and 7.16, esketamine PSD, July 2023). The Committee acknowledged the resubmission was focussed on how to incorporate these treatment settings into the restrictions and exploring the impact of these on the cost effectiveness and utilisation estimates.
- 7.5 The PBAC recalled its previous consideration that that the nominated comparator of a newly initiated OAD alone was reasonable (paragraph 7.9, esketamine PSD, July 2023).
- 7.6 The PBAC noted the current resubmission presented additional information from the open label extension study SUSTAIN-3, two real-world studies of US claims databases (Teeples 2021 and Karkare 2021) and the Sponsor's Australian Early Access Program (EAP). The PBAC noted this information was used primarily to inform inputs to the economic model and utilisation estimates with regards to the use of esketamine beyond 12 months and in retreatment settings. The Committee recalled it had previously considered the clinical claim of superior comparative effectiveness compared to newly initiated OAD alone may be reasonable, but the magnitude and clinical importance of the observed benefits were uncertain. The PBAC noted the randomised controlled trial evidence underpinning this claim was unchanged and the additional information provided did not further inform the magnitude or clinical importance of the treatment effect of esketamine. Further, the PBAC considered the additional information provided only limited data for the clinical effectiveness or safety of esketamine in the retreatment or long-term treatment settings.
- 7.7 The PBAC recalled it had previously considered the claim of inferior comparative safety was reasonable. The PBAC noted an updated Periodic Benefit-Risk Evaluation Report (PBRER) was provided with the resubmission, which did not raise any new safety concerns associated with esketamine.
- 7.8 The PBAC noted the resubmission revised the economic model to include treatment beyond 12 months and retreatment (after a treatment break of at least 4 months), and also included the use of Australian healthcare resource use (rather than a UK dataset) and a revised ex-manufacturer price per esketamine nasal spray device (\$|, compared to \$| in July 2023). The PBAC noted inclusion of retreatment and the lower cost of esketamine reduced the ICER (Step 3 and Step 7 in Table 14), and allowing use beyond 12 months and using Australian healthcare resource use increased the ICER (Step 5 and Step 6 in Table 14). The PBAC noted the base case economic model in the resubmission resulted in an incremental cost effectiveness ratio (ICER) of \$35,000 to < \$45,000 per quality adjusted life year (QALY). The PBAC noted the model was sensitive to a number of inputs and assumptions including the probability of remission

and response, proportion of patients treated for longer than 12 months, proportion of patients retreated, effectiveness of retreatment, utilities, and utilisation (including dose and frequency).

- 7.9 The PBAC considered that, on balance, while there remained limitations and uncertainties with the economic model, acknowledging there is unlikely to be further data forthcoming to address the uncertainties and noting the moderate to high clinical need, esketamine was likely to be cost-effective at the price proposed in the resubmission.
- 7.10 With regards to the utilisation estimates:
- The PBAC noted an error was identified in the estimates regarding fortnightly dosing as outlined in paragraph 6.82.
 - The PBAC recalled it had previously noted a number of aspects of treatment, including access to psychiatrists, access to accredited treatment centres, patient reluctance given the monitoring requirements and nature of the treatment and out of pocket costs may limit the uptake of esketamine (paragraph 7.15, esketamine PSD, July 2023 PBAC meeting). The PBAC noted the resubmission assumed 31% uptake in eligible patients in Year 1, increasing to 39% in Year 6, which was amended to 29% in Year 1 and 37% in Year 6 in the pre-PBAC response. The PBAC considered the likely uptake of esketamine in the pre-PBAC response remained overestimated, particularly in the first few years.
 - The PBAC considered the estimate that $\frac{1}{2}$ % of patients being treated longer than 12 months was highly uncertain.
 - The PBAC considered the approach to determining the number of patients who would be retreated was not well supported and was inconsistent with the approach used in the economic model. The PBAC noted the economic model assumed 22% of patients that initiated treatment with esketamine would be retreated over the 5 year time horizon of the model. The utilisation estimates assumed 61% of patients who initiated treatment with esketamine in Year 1 would be retreated over 6 years.
 - The PBAC noted the sponsor stated any uncertainties with the utilisation estimates could be mitigated with an RSA; however, the PBAC agreed with the ESC that the risk is only managed if the utilisation estimates have not been overestimated.
- 7.11 The PBAC noted the resubmission's arguments that a managed access program for esketamine is not feasible or practical, however also noted there are limited data to inform the appropriate use of esketamine in clinical practice, especially over the longer-term. As such, the PBAC considered the restriction criteria need to be structured in a manner that allows the use of esketamine on the PBS to be monitored. The PBAC considered the parameters to be monitored should include the number of patients initiating treatment, treatment duration, extent of retreatment, dose and

frequency.

- 7.12 The PBAC noted five separate restrictions were requested (as outlined in paragraph 3.1) and considered it may be reasonable to consolidate criteria and have one for initial induction (weeks 1-4), one for continuing treatment (week 5 onwards) and retreatment induction (weeks 1-4), but noted that additional consideration is required to ensure the criteria allow for monitoring as discussed in paragraph 7.11. Additionally, the PBAC noted a number of outstanding issues related to the proposed restriction as outlined in Section 3 that need to be resolved.
- 7.13 The PBAC requested revised utilisation estimates to address the issues raised in paragraph 7.10 and for an appropriate set of restriction criteria to be developed (as discussed in paragraphs 7.11 and 7.12).

Outcome:

Deferred

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.

Addendum to the July 2024 PBAC PSD:

4.01 ESKETAMINE, Nasal spray solution 28 mg in 0.2 mL (2 actuations) Spravato[®], Janssen-Cilag Pty Ltd.

9 Purpose of submission

- 9.1 At its July 2024 meeting, the PBAC deferred making a recommendation for the listing of esketamine for the treatment of treatment-resistant depression (TRD) in patients who have failed two or more prior oral antidepressant drugs (OADs) to enable the restriction criteria to be refined and the utilisation estimates to be revised.

10 Requested listing

- 10.1 Between the July 2024 and December 2024 meetings, the Department consulted with the Royal Australian and New Zealand College of Psychiatrists (RANZCP) on the restrictions for esketamine. Based on this advice, changes were made to the proposed restrictions, including:
- A reduction from five distinct restrictions to three, for (i) induction treatment, (ii) non-induction treatment and (iii) transition from non-PBS treatment;
 - Amending the indication from ‘major depressive disorder’ to ‘treatment resistant major depression’;
 - Remove the requirements for the two prior OADs to be from different pharmacological classes and for patients to be undergoing concomitant treatment with an OAD;
 - Remove the criterion describing 8 doses over a period of 4 weeks;
 - Remove the age restriction, noting this is outlined in the TGA Product Information and there may be very rare instances where flexibility for clinical decision-making may be warranted;
 - Amend the treatment criteria to require that prescribing be completed by the treating psychiatrist and that the patient must be undergoing supervision at an accredited treatment centre for the administration of esketamine;
 - Remove the prescribing instruction defining ‘inadequately responsive’ to prior treatment/therapy; and
 - Add a new prescribing instruction outlining the following for patients re-initiating treatment:

- At least a four-week gap from last treatment course to re-initiation of treatment;
- Evidence documented in patient records, using a structured rating scale, of a significant clinical therapeutic benefit of the prior course of treatment with esketamine; and
- Evidence of a relapse in depression documented in the patient records using a structured rating scale.

10.2 The revised restrictions proposed by the Secretariat are presented below.

Induction treatment

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty (effective)	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESKETAMINE					
esketamine 28 mg/0.2 mL x1 nasal spray device 28mg	S85: \$ () S100 Public: \$ () S100 Private: \$ ()	8	8	0	Spravato
esketamine 28 mg/0.2 mL x2 nasal spray device 56mg	S85: \$ () S100 Public: \$ () S100 Private: \$ ()	8	16	0	
esketamine 28 mg/0.2 mL x3 nasal spray device 84mg	S85: \$ () S100 Public: \$ () S100 Private: \$ ()	8	24	0	
Category / Program: TBD either: GENERAL - General Schedule (Code GE) Section 100 – Highly Specialised Drugs Program (Public and Private Hospitals)					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum quantity or number of units will be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Restriction Summary <i>New1 / Treatment of Concept: New1A</i>					
Episodicity: N/A					
Severity: Treatment resistant					
Condition: Major depression					
Indication: Treatment resistant major depression					
Treatment Phase: Induction treatment					
Clinical criteria					
The condition must have been inadequately responsive to at least two oral anti-depressant drug therapies					
AND					
Treatment criteria					
Must be treated by a psychiatrist, where all prescribing must be completed by the treating psychiatrist					
AND					
Treatment criteria					

Patient must be undergoing supervision at an accredited treatment centre for the administration of esketamine
<p>Prescribing Instructions: The following must apply if reinitiating treatment: (i) at least four-week gap from last treatment course to re-initiation of treatment; and (ii) evidence, documented in the patient’s medical record using a structured rating scale, of significant clinical therapeutic benefit of the prior course of treatment with esketamine; and (iii) evidence, documented in the patient’s medical record using a structured rating scale, of a relapse in depression</p>

Non-induction treatment

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty (effective)	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESKETAMINE					
esketamine 28 mg/0.2 mL x1 nasal spray device 28mg	S85: \$ () S100 Public: \$ () S100 Private: \$ ()	4	4	5	Spravato
esketamine 28 mg/0.2 mL x2 nasal spray device 56mg	S85: \$ () S100 Public: \$ () S100 Private: \$ ()	4	8	5	
esketamine 28 mg/0.2 mL x3 nasal spray device 84mg	S85: \$ () S100 Public: \$ () S100 Private: \$ ()	4	12	5	
Restriction Summary New3 / Treatment of Concept: New3A					
Category / Program: TBD either: GENERAL - General Schedule (Code GE) Section 100 – Highly Specialised Drugs Program (Public and Private Hospitals)					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum quantity or number of units will be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Episodicity: N/A					
Severity: Treatment resistant					
Condition: Major depression					
Indication: Treatment resistant major depression					
Treatment Phase: Non-induction treatment					
Clinical criteria					
The treatment must be to continue existing PBS-subsidised treatment for treatment resistant major depression					
AND					
Clinical criteria					
The treatment must not exceed each of: (i) an administered dose beyond 84 mg, (ii) a quantity of drug, after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceed a quantity sufficient to treat the patient for 24 weeks					
AND					
Clinical criteria					

Patient must have demonstrated adequate response to treatment with esketamine after the 4-week induction and every 6 months thereafter as evaluated by a structured clinical rating scale (evidence of scores and justification of demonstration of response must be retained in the patient's medical records)
AND
Treatment criteria
Must be treated by a psychiatrist, where all prescribing must be completed by the treating psychiatrist
AND
Treatment criteria
Patient must be undergoing supervision at an accredited treatment centre for the administration of esketamine
Restriction Summary New3 / Treatment of Concept: New3A
Episodicity: N/A
Severity: Treatment resistant
Condition: Major depression
Indication: Treatment resistant major depression
Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' arrangement
Clinical criteria
Patient must have received non-PBS treatment with this drug for this condition prior to <listing date>
AND
Clinical criteria
The condition must have been inadequately responsive to at least two anti-depressant drug therapies prior to commencing treatment with this drug for this condition
AND
Clinical criteria
The treatment must not exceed each of: (i) an administered dose beyond 84 mg, (ii) a quantity of drug, after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceed a quantity sufficient to treat the patient for 24 weeks
AND
Clinical criteria
Patient must have demonstrated adequate response to treatment with esketamine after the 4-week induction and every 6 months thereafter as evaluated by a structured clinical rating scale (evidence of scores and justification of demonstration of response must be retained in the patient's medical records)
AND
Treatment criteria
Must be treated by a psychiatrist, where prescribing must also be completed by the treating psychiatrist
AND
Treatment criteria
Patient must be undergoing supervision at an accredited treatment centre for the administration of esketamine
Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' or the 'Extended continuing treatment' criteria.
Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

10.3 The Pre-PBAC Response agreed with the proposed changes compared to the July 2024 submission, however stated that removing the age restriction would have an impact on the utilisation and financial impact (discussed further below).

- 10.4 The Pre-PBAC Response argued that with respect to whether the listing should be in the General Schedule or Section 100 Highly Specialised Drugs, that the context of the submission history and how the Sponsor anticipated esketamine would be used in practice was relevant. Specifically the Response stated the Sponsor anticipated that most prescribing would be in the private hospital setting, which justified the request for listing in Section 100 in earlier submissions, however for the duration they have been supplying esketamine outside the PBS through an early access program and the private market (since 2021), the majority of supply has been provided through community pharmacies, and anticipates less than 10% of prescribing will be through hospitals on the PBS. Therefore, the Response indicated a preference for a listing on the General Schedule, as that reflects the current way esketamine is primarily being dispensed.

For more detail on PBAC's view, see Section 12 PBAC outcome.

11 Estimated PBS usage & financial implications

- 11.1 Between the July and December 2024 meetings, the Sponsor provided revised utilisation and financial estimates. A summary of how the Sponsor addressed the outstanding financial issues is presented in the table below.

Table 21: How the additional information has addressed the issues raised in the July 2024 PSD

PBAC PSD, July 2024, paragraph 7.10	Comments
The PBAC noted an error was identified in the estimates regarding fortnightly dosing as outlined in paragraph 6.82. i.e. the model appropriately assumed 4.02 scripts would be required for fortnightly dosing (i.e., half the scripts required for weekly dosing); however, the number of packs per script should remain as 4 (rather than 2 as used in the model).	The proposal has revised the number of devices to 4 for the 28 mg dose, 8 for the 58 mg dose and 12 for the 84 mg dose.
The PBAC recalled it had previously noted a number of aspects of treatment, including access to psychiatrists, access to accredited treatment centres, patient reluctance given the monitoring requirements and nature of the treatment and out of pocket costs may limit the uptake of esketamine (paragraph 7.15, esketamine PSD, July 2023 PBAC meeting). The PBAC noted the resubmission assumed 31% uptake in eligible patients in Year 1, increasing to 39% in Year 6, which was amended to 29% in Year 1 and 37% in Year 6 in the pre-PBAC response. The PBAC considered the likely uptake of esketamine in the pre-PBAC response remained overestimated, particularly in the first few years.	The proposal has reduced the treatment uptake rates in Years 1 and 2 by five percentage points (see Table 22).
The PBAC considered the estimate that █% of patients being treated longer than 12 months was highly uncertain.	The proposal did not revise this assumption
<p>The PBAC considered the approach to determining the number of patients who would be retreated was not well supported and was inconsistent with the approach used in the economic model. The PBAC noted the economic model assumed 22% of patients that initiated treatment with esketamine would be retreated over the 5-year time horizon of the model. The utilisation estimates assumed 61% of patients who initiated treatment with esketamine in Year 1 would be retreated over 6 years.</p> <p>The PBAC noted the sponsor stated any uncertainties with the utilisation estimates could be mitigated with an RSA; however, the PBAC agreed with the ESC that the risk is only managed if the utilisation estimates have not been overestimated.</p>	<p>The proposal reduced the re-treatment rate from 61.2% to 44.5%.</p> <p>This was achieved by reducing the uptake of retreatment over the forward estimates from 100% to 73%. Applying 73% to the assumption for patients who respond or are in remission (62.07%) results in 44.5% of patients who initiated treatment with esketamine in Year 1 being retreated over the period of the forward estimates. The Pre-PBAC Response stated this change was made pragmatically to address PBAC concerns and argued this was a significant change from the July 2024 resubmission which assumed all eligible patients would be retreated.</p>

Source: Prepared by the Secretariat

11.2 Uptake rates in the July 2024 resubmission, July 2024 pre-PBAC response and December 2024 proposal are summarised in the table below. The proposal stated that in response to PBAC concerns that uptake was overestimated in the first two years, uptake has been reduced by 5 percentage points in Years 1 and 2 compared to the financial estimates provided in the pre-PBAC response for the July 2024 PBAC meeting. In Year 3 and beyond, the sponsor has maintained the same uptake rates as the pre-PBAC response of the July 2024 submission. In summary, the proposal stated that there is now sufficient experience, awareness, and exposure to esketamine existing within the Australian prescribing community to be confident that the proposed uptake rate is not an overestimate.

Table 22: Uptake rates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
July 2024 resubmission	31%	35%	37%	38%	39%	39%
July 2024 pre-PBAC response	29%	35%	35%	36%	37%	37%
December 2024 proposal	24%	30%	35%	36%	37%	37%

Source: Table 2, December 2024 proposal

11.3 The estimated PBS usage and financial implications is presented in the table below. The net cost of listing esketamine on the PBS is estimated to be \$200 million to < \$300 million over 6 years.

Table 23: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
December 2024						
Number of TRD patients in third line setting and over	¹	²	²	²	²	²
Initial treatment (including grandfathered patients)	³	³	³	⁴	⁴	⁴
Patients receiving retreatment	⁵	³	³	³	³	³
Total patients treated with esketamine (including grandfathered patients)	³	³	⁴	⁴	⁴	⁴
Total scripts	⁶	⁷	⁷	⁸	⁸	⁹
Net cost to the PBS/RPBS	\$¹⁹	\$¹¹	\$¹²	\$¹³	\$¹⁴	\$¹⁴
July 2024						
Initial treatment (including grandfathered patients)	³	³	⁴	⁴	⁴	⁴
Patients receiving retreatment	⁴	⁴	⁴	⁴	⁴	⁴
Total patients treated with esketamine (including grandfathered patients)	³	⁴	⁴	⁴	⁴	⁶
Total scripts	⁶	⁷	⁸	⁹	⁹	⁹
Net cost to the PBS/RPBS (previous submissions)						
July 2024	\$¹⁰	\$¹¹	\$¹²	\$¹³	\$¹⁴	\$¹⁴
July 2023	\$¹¹	\$¹²	\$¹⁴	\$¹⁵	\$¹⁵	\$¹⁶
July 2022	\$¹¹	\$¹⁴	\$¹⁷	\$¹⁸	\$¹⁸	\$¹⁸
July 2021	\$¹¹	\$¹⁴	\$¹⁸	\$¹⁸	\$¹⁸	\$¹⁸

Source: July 2024 PSD, December 2024 proposal

The redacted values correspond to the following ranges:

- ¹ 50,000 to < 60,000
- ² 60,000 to < 70,000
- ³ 500 to < 5,000
- ⁴ 5,000 to < 10,000
- ⁵ < 500
- ⁶ 10,000 to < 20,000
- ⁷ 20,000 to < 30,000
- ⁸ 30,000 to < 40,000
- ⁹ 40,000 to < 50,000
- ¹⁰ \$20 million to < \$30 million
- ¹¹ \$30 million to < \$40 million
- ¹² \$40 million to < \$50 million
- ¹³ \$50 million to < \$60 million
- ¹⁴ \$60 million to < \$70 million
- ¹⁵ \$70 million to < \$80 million
- ¹⁶ \$80 million to < \$90 million
- ¹⁷ \$90 million to < \$100 million
- ¹⁸ \$100 million to < \$200 million
- ¹⁹ \$10 million to < \$20 million

11.4 The Secretariat noted the financial estimates were based on DUSC data from 2021 and using an updated DUSC analysis (2022 and 2023 data) to estimate the number of patients that would be eligible reduced the net cost of listing esketamine on the PBS is estimated to \$200 million < \$300 million over 6 years (Table 24).

Table 24: Estimated use and financial implications using an updated DUSC analysis

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Using updated DUSC analysis						
Number of TRD patients in third line setting and over	¹	¹	¹	²	²	²
Initial treatment (including grandfathered patients)	³	³	³	⁴	⁴	⁴
Patients receiving retreatment	⁵	³	³	³	³	³
Total patients treated with esketamine (including grandfathered patients)	³	³	⁴	⁴	⁴	⁴
Total scripts	⁶	⁶	⁷	⁸	⁸	⁸
Net cost to the PBS/RPBS	\$ ⁹	\$ ¹⁰	\$ ¹¹	\$ ¹²	\$ ¹²	\$ ¹³

TRD = treatment-resistant depression

The redacted values correspond to the following ranges:

¹ 50,000 to < 60,000

² 60,000 to < 70,000

³ 500 to < 5,000

⁴ 5,000 to < 10,000

⁵ < 500

⁶ 10,000 to < 20,000

⁷ 20,000 to < 30,000

⁸ 30,000 to < 40,000

⁹ \$10 million to < \$20 million

¹⁰ \$30 million to < \$40 million

¹¹ \$40 million to < \$50 million

¹² \$50 million to < \$60 million

¹³ \$60 million to < \$70 million

11.5 The Pre-PBAC Response acknowledged the updated DUSC analysis, however argued using the 100% PBS dataset does not account for patients treated with non-PBS subsidised OADs, and therefore likely does not capture the entire eligible population. In addition, the Response further argued that, if an age agnostic listing of esketamine were supported, that the DUSC analysis would further underestimate the eligible treatment population (as the DUSC analysis excluded patients under 18 years of age). On that basis, the Sponsor argued the estimates in their proposal were pragmatically the most reasonable basis for the estimates. The PBAC considered the number of patients under 18 years of age likely to be treated with esketamine was very small.

For more detail on PBAC’s view, see section 12 PBAC outcome.

12 Financial Management – Risk Sharing Arrangement

12.1 Consistent with the July 2024 PSD, the sponsor proposed a risk sharing arrangement for esketamine, with expenditure caps based on the net cost to government (as outlined in Table 19) and a rebate of |% for any expenditure above the caps. This

proposal reiterated the sponsor is unable to offer a $\frac{1}{2}$ % rebate for use beyond the expenditure caps.

For more detail on PBAC's view, see section 12 PBAC outcome.

13 PBAC Outcome

- 13.1 The PBAC recommended the General Schedule and Section 100 (Highly Specialised Drugs Program – Public and Private Hospitals), authority required (telephone/online) listings of esketamine for treatment-resistant major depression in patients who have failed at least two prior oral anti-depressant drugs (OADs). In making this recommendation, the PBAC considered the additional changes to the restriction and financial estimates had adequately addressed its concerns raised at the July 2024 meeting. The PBAC noted consultation with the Royal Australian and New Zealand College of Psychiatrists (RANZCP) led to a revised restriction that resulted in a more practical wording that supports use in the intended population. The PBAC considered the revised financial estimates provided a more reasonable basis for Risk Sharing Arrangement expenditure caps. The PBAC reiterated its previous consideration that, given the uncertainty with how esketamine would be used in practice (particularly in terms of use beyond 12 months and the extent of retreatment), it was appropriate for utilisation to be monitored following the listing.
- 13.2 The PBAC considered listing in both the General Schedule and Section 100 (Highly Specialised Drugs Program – Public and Private Hospitals) would provide appropriate access for patients across the different treatment settings. The PBAC noted the pre-PBAC response stated that most supply to date has been via community pharmacies (paragraph 10.4) but the PBAC considered the use in hospital clinics may increase over time.
- 13.3 With respect to the wording of the restrictions, the PBAC noted the Secretariat consulted with the RANZCP and formulated a revised set of restrictions that is more practical and usable in practice. Overall, the PBAC considered the proposed restrictions to be reasonable and noted the Sponsor had agreed with the proposed revisions in its pre-PBAC response. The PBAC noted the proposed restriction included the treatment criterion “Patient must be undergoing supervision at an accredited treatment centre for the administration of esketamine”. The PBAC noted accreditation of clinics is being done as part of the TGA approved Risk Management Plan (RMP), and considered the restriction wording proposed by the Secretariat to acknowledge this requirement was reasonable. The PBAC noted the accreditation process is managed by the Sponsor and that prospective treatment centres would need to liaise with them to become a treatment centre and considered, with broader accessibility to esketamine via the PBS, that it was important this requirement and information on how to commence the process was readily accessible to interested healthcare providers.
- 13.4 The PBAC noted the revised financial estimates reduced uptake in the first two years

- of listing by five percentage points and reduced the retreatment rate over the forward estimates from $\frac{1}{2}\%$ to $\frac{1}{4}\%$ (Table 21). The PBAC noted updated DUSC data was available that reduced the estimated cost over 6 years (paragraph 11.4) and further noted the arguments presented in the pre-PBAC response for not using the updated DUSC data (paragraph 11.5). Noting the inherent uncertainty in the likely number of treated patients, the PBAC considered that, on balance, the estimated number of treated patients and financial estimates provided in the proposal (Table 23) were reasonable.
- 13.5 The PBAC considered the revised financial estimates provided an acceptable basis for expenditure caps in the Risk Sharing Arrangement and an $\frac{1}{2}\%$ rebate for use over the caps was reasonable.
- 13.6 The PBAC considered that given the uncertainty as to how esketamine would be used in practice, it was appropriate for its utilisation to be closely monitored by the DUSC following listing. The PBAC advised that, at a minimum, the number of patients treated with esketamine, treatment duration, extent of retreatment and use in patients under 18 years of age should be monitored.
- 13.7 The PBAC advised that esketamine should not be treated as interchangeable with any other drugs.
- 13.8 The PBAC advised that esketamine not suitable for prescribing by nurse practitioners, as the listing is restricted to psychiatrists.
- 13.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for esketamine:
- While esketamine was likely to be effective for some patients, it is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative therapies, and the magnitude of benefit remains uncertain based on the available information.
 - The treatment is not expected to address a high and urgent unmet clinical need, as alternative interventions for TRD are available (including non-pharmacological interventions).
 - It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 13.10 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

14 Recommended listing

14.1 Add new item:

Induction treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESKETAMINE					
esketamine 28 mg/0.2 mL x1 nasal spray device 28mg	NEW	8	8	0	Spravato
esketamine 28 mg/0.2 mL x2 nasal spray device 56mg	NEW	8	16	0	
esketamine 28 mg/0.2 mL x3 nasal spray device 84mg	NEW	8	24	0	
Category / Program: GENERAL - General Schedule (Code GE) Section 100 – Highly Specialised Drugs Program (Public and Private Hospitals)					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum quantity or number of units will be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Episodicity: N/A					
Severity: Treatment resistant					
Condition: Major depression					
Indication: Treatment resistant major depression					
Treatment Phase: Induction treatment					
Clinical criteria					
The condition must have been inadequately responsive to at least two oral anti-depressant drug therapies					
AND					
Treatment criteria					
Must be treated by a psychiatrist, where prescribing must also be completed by the treating psychiatrist					
AND					
Treatment criteria					
Patient must be undergoing supervision at an accredited treatment centre for the administration of esketamine					
Prescribing Instructions: The following must apply if reinitiating treatment: (i) at least four-week gap from last treatment course to re-initiation of treatment; and (ii) evidence, documented in the patient's medical record using a structured rating scale, of significant clinical therapeutic benefit of the prior course of treatment with esketamine; and (iii) evidence, documented in the patient's medical record using a structured rating scale, of a relapse in depression					

Non-induction treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ESKETAMINE					
esketamine 28 mg/0.2 mL x1 nasal spray device 28mg	NEW	4	4	5	Spravato
esketamine 28 mg/0.2 mL x2 nasal spray device 56mg	NEW	4	8	5	
esketamine 28 mg/0.2 mL x3 nasal spray device 84mg	NEW	4	12	5	
Category / Program: GENERAL - General Schedule (Code GE) Section 100 – Highly Specialised Drugs Program (Public and Private Hospitals)					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increases in the maximum quantity or units will be authorised					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Episodicity: N/A					
Severity: Treatment resistant					
Condition: Major depression					
Indication: Treatment resistant major depression					
Treatment Phase: Non-induction treatment					
Clinical criteria					
The treatment must be to continue existing PBS-subsidised treatment for this indication					
AND					
Clinical criteria					
The treatment must not exceed each of: (i) an administered dose beyond 84 mg, (ii) a quantity of drug, after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceed a quantity sufficient to treat the patient for 24 weeks					
AND					
Clinical criteria					
Patient must have demonstrated adequate response to treatment with esketamine after the 4-week induction and every 6 months thereafter as evaluated by a structured clinical rating scale (evidence of scores and justification of demonstration of response must be retained in the patient's medical records)					
AND					
Treatment criteria					
Must be treated by a psychiatrist, where prescribing must also be completed by the treating psychiatrist					
AND					
Treatment criteria					
Patient must be undergoing supervision at an accredited treatment centre for the administration of esketamine					
Episodicity: N/A					

Severity: Treatment resistant
Condition: Major depression
Indication: Treatment resistant major depression
Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' arrangement
Clinical criteria
Patient must have received non-PBS treatment with this drug for this indication prior to <listing date>
AND
Clinical criteria
The condition must have been inadequately responsive to at least two anti-depressant drug therapies prior to commencing of treatment with this drug for this condition
AND
Clinical criteria
The treatment must not exceed each of: (i) an administered dose beyond 84 mg, (ii) a quantity of drug, after accounting for repeat prescriptions plus different pack sizes where prescribed, that would exceed a quantity sufficient to treat the patient for 24 weeks
AND
Clinical criteria
Patient must have demonstrated adequate response to treatment with esketamine after the 4-week induction and every 6 months thereafter as evaluated by a structured clinical rating scale (evidence of scores and justification of demonstration of response must be retained in the patient's medical records)
AND
Treatment criteria
Must be treated by a psychiatrist, where prescribing must also be completed by the treating psychiatrist
AND
Treatment criteria
Patient must be undergoing supervision at an accredited treatment centre for the administration of esketamine
Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Non-induction ' treatment' criteria.
Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

This restriction may be subject to further review. Should there be any changes made to the restriction, the sponsor will be informed.

15 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.

16 Sponsor's Comment

The sponsor had no comment.