

Medical Policy



Title: Esketamine Nasal Spray for Depression

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are adults and diagnosed with treatment-resistant depression 	Interventions of interest are: <ul style="list-style-type: none"> Esketamine 	Comparators of interest are: <ul style="list-style-type: none"> Standard medical management (pharmacotherapy, psychotherapy and/or somatic therapy) 	Relevant outcomes include: <ul style="list-style-type: none"> Change in disease status Quality of life Treatment-related mortality Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are adults and diagnosed with major depressive disorder with acute suicidal ideation or behavior 	Interventions of interest are: <ul style="list-style-type: none"> Esketamine 	Comparators of interest are: <ul style="list-style-type: none"> Standard medical management (pharmacotherapy, psychotherapy and/or somatic therapy) 	Relevant outcomes include: <ul style="list-style-type: none"> Change in disease status Quality of life Treatment-related mortality Treatment-related morbidity

DESCRIPTION

Esketamine is the S-isomer of racemic ketamine. Esketamine targets the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor in nerve cells. However, the mechanism by which esketamine exerts its antidepressant effect is unknown. It is currently approved for patients with treatment-resistant depression or major depressive disorder with acute suicidal ideation or behavior. Treatment-resistant depression is chronic depression that does not improve despite the adequate use of multiple antidepressants. The poor response to multiple antidepressants limits additional treatment options. Patients with major depressive disorder who have active suicidal ideation with intent constitute a psychiatric emergency as the time between the onset of suicidal ideation and suicide attempt is often very short. While standard antidepressants effectively treat depressive symptomatology, including suicidal ideation, these agents require 4 to 6 weeks to exert their full effect, limiting their utility in crisis situations.

OBJECTIVE

The objective of this evidence review is to assess whether treatment with esketamine improves the net health outcome in patients with treatment-resistant depression or major depressive disorder with acute suicidal ideation or behavior.

BACKGROUND

Treatment-Resistant Depression

Patients with either major depressive disorder or bipolar disorder can manifest depressive episodes (Table 1). Patients whose depressive disorder does not respond satisfactorily to adequate treatment have harder-to-treat depression, generally referred to as treatment-resistant depression.¹ Overall, approximately 1 in 3 patients with depression are considered treatment-resistant.² While there is no standardized definition of treatment-resistant depression, a generally accepted definition is failure of 2 or more antidepressant treatment attempts with an adequate dose and duration.³ The majority of systematic reviews and guidelines or consensus statements report that the commonly used definitions were based on treatment of patients whose depression failed to respond (a decrease in depressive severity of at least half) or did not go into remission (complete recovery as measured by a score on a depressive severity instrument below a threshold) following 2 or more treatment attempts of an adequate dose and duration. Experts do not agree on how to define adequate dose and adequate duration, although the minimum duration cited is typically 4 weeks.

Lack of consensus on the definition of treatment-resistant depression limit the ability of systematic reviewers or other experts to synthesize information and generalize treatment-resistant depression findings to the array of patient populations encountered in daily practice. According to the Technology Assessment by the Agency for Healthcare Research and Quality (AHRQ) on defining treatment-resistant depression in the Medicare population, the lack of a clear definition for treatment-resistant depression has made translating research findings or systematic reviews into clinical practice guidelines challenging and inconsistent. As a result, guideline definitions of treatment-resistant depression differ, agreement on what constitutes prior treatment adequacy is lacking, and recommended “next step” interventions can diverge.³

According to the AHRQ Report, there are no validated, standard diagnostic tools for treatment-resistant depression. Diagnosis of a major depressive episode or bipolar disorder can be made through a standard clinical evaluation using the Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD), or through a structured clinical assessment tool. Subsequently, treatment history may be elicited by a clinical interview (e.g., the number of prior pharmacologic attempts of adequate dose and duration that did not produce remission) or administering a structured, staging tool (Antidepressant Treatment Response Questionnaire, Thase Rush Staging Model, Massachusetts General Hospital Staging Model, or the Maudsley Staging Model) to confirm treatment resistance. No preferred approach exists and careful history has not been compared directly with a structured tool.³

Table 1. Diagnostic Criteria for a Major Depressive Episode

	Criteria (Meet A through E)
A	Five or more symptoms for 2 weeks (1 of which must be either depressed mood or anhedonia): <ol style="list-style-type: none"> 1. Depressed mood most of the day nearly every day 2. Anhedonia most of the day nearly every day 3. Significant weight loss or gain 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive guilt 8. Diminished ability to think or concentrate; indecisiveness 9. Recurrent thoughts of death; suicidal ideation or attempt
B	Symptoms cause clinically significant distress or functional impairment
C	The episode is not attributable to the physiological effects of a substance or another medical condition
D	The episode is not better explained by a psychotic illness
E	There has never been a manic or hypomanic episode

Adapted from the Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed., American Psychiatric Association, 2013.⁴

Major Depressive Disorder and Suicidal Ideation/Behavior

In a community survey conducted in 21 countries with over 100,000 individuals by the World Health Organization, the 12-month prevalence of suicidal ideation (thoughts) was approximately 2%,⁵ and the lifetime prevalence was 9%.⁶ Approximately 12.3 million US adults have had serious thoughts of suicide in the past year, and Hispanic or Latino adults are more likely than

White or Asian adults to have attempted suicide within this timeframe.⁷ Psychiatric illness is strongly associated with risk of suicide,⁸ and major depressive disorder is the psychiatric diagnosis most commonly associated with suicide.⁹ The reported prevalence of suicidal ideation in adult patients with major depressive disorder is as high as 60%, and the lifetime incidence of attempted suicide in this population ranges between 10% and 20%.^{10,11} Further, the lifetime risk of completed suicide has been estimated to be 3.4% in this population.¹²

Patients with major depressive disorder who have active suicidal ideation with intent constitute a psychiatric emergency as the time between the onset of suicidal ideation and suicide attempt is often very short.¹³ These patients are often hospitalized to protect them from self-harm, although the benefits of hospitalization are often temporary. Moreover, while standard antidepressants effectively treat depressive symptomatology, including suicidal ideation,¹⁴ they require 4 to 6 weeks to exert their full effect,^{15,16} limiting their utility in crisis situations.

Current Treatment

Prior to the approval of esketamine, olanzapine-fluoxetine combination was the only U.S. Food and Drug Administration (FDA)-approved drug for treatment-resistant depression. The strategy for managing treatment-resistant depression generally involves modifying current antidepressant therapy or augmenting existing therapies with non-antidepressant medications (such as atypical antipsychotics).^{17,2} Modification strategies include use of higher doses, switching to a new antidepressant, or adding on to an existing therapy. The adequate duration of antidepressant therapy is usually a minimum of 6 weeks. An additional 4 to 6 weeks may be required for patients who show a partial response.¹⁸

Patients with long-standing treatment-resistant depression who do not benefit from treatment modification or augmentation strategies are referred to as having refractory depression. For these patients, other strategies such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, or vagus nerve stimulation techniques have been used with limited success.^{19,20} Depression-focused psychotherapy may be added to pharmacotherapy, but is generally not considered stand-alone therapy for refractory depression. Off-label treatments include: drugs from multiple classes (antipsychotics, lithium, thyroid hormone, ketamine), often in combination with antidepressants.

REGULATORY STATUS

On March 6, 2019, esketamine (Spravato) nasal spray was approved by the FDA for the treatment of treatment-resistant depression in adults.

On July 31, 2020, esketamine (Spravato) nasal spray received an approval for a supplemental indication for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior.

POLICY

- A. Esketamine nasal spray may be considered **medically necessary** if all of the following conditions are met:

Initial Authorization for 28 Days

1. Individual is 18 years of age or older
2. Individual meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode (See Table 1) by a structured clinical interview for DSM-5 disorders.
3. Individual current depressive episode is moderate or severe based on either of the following:
 - a. Montgomery-Asberg Depression Rating Scale (MADRS) \geq 28 (see policy guidelines) **OR**
 - b. Hamilton Rating Scale for Depression (HAM-D) score \geq 17 (see policy guidelines)
4. Individual has tried and had an inadequate response to 2 antidepressant agents from 2 different antidepressant classes (i.e. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, or mirtazapine). An adequate trial of an antidepressant is defined by BOTH of the following:
 - a. The trial length was at least 6 weeks at generally accepted doses or of sufficient duration as determined by the treating physician at the generally accepted doses; **AND**
 - b. Individual was \geq 80% adherent to the agent during the trial
5. Individual is to receive esketamine nasal spray in conjunction with an oral antidepressant.
6. Individual does not have a current substance use disorder unless in remission (complete abstinence for a month)
7. Individual does NOT have any U.S. Food and Drug Administration (FDA) labeled contraindications to the requested agent and esketamine nasal spray is intended to be used consistently with the FDA approved label (see policy guidelines) including meeting Spravato Risk Evaluation and Mitigation Strategy (REMS) program requirements (see policy guidelines).
8. The prescriber is a specialist in the area of the individual's diagnosis (e.g. psychiatrist) or the prescriber has consulted with a specialist in the area of the individual's diagnosis.

Reauthorization for UP TO 1 Year

- B. Esketamine nasal spray may be reauthorized for up to 1 year if all of the following conditions are met:
1. Individual has had improvement in depression symptoms as evaluated with an appropriate depression rating scale (e.g. Patient Health Questionnaire -9, Clinically Useful Depression Outcome Scale, Quick Inventory of Depressive Symptomatology-Self Report 16 Item, MADRS, HAM-D).
 2. Individual is to receive esketamine nasal spray in conjunction with an oral antidepressant.
 3. Individual does not have a current substance use disorder
 4. Individual does NOT develop any FDA labeled contraindications to the requested agent and esketamine nasal spray is intended to be used consistently with the FDA

approved label (see policy guidelines) including meeting Spravato REMS program requirements (see policy guidelines).

Major Depressive Disorder with Acute Suicidal Ideation or Behavior

- C. Esketamine nasal spray may be considered **medically necessary** for a treatment period of 28 days if all of the following conditions are met:
1. Individual is 18 years of age or older
 2. Individual meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode (See Table 1) by a structured clinical interview for DSM-5 disorders.
 3. Individual current depressive episode is moderate or severe based on either of the following scales:
 - a. Montgomery-Asberg Depression Rating Scale (MADRS) \geq 28 (see policy guidelines) **OR**
 - b. Hamilton Rating Scale for Depression (HAM-D) score \geq 17 (see policy guidelines)
 4. Individual is currently hospitalized and is at a imminent risk for suicide as documented by:
 - a. Individual response to a structured assessment for suicidal ideation indicative of imminent risk of suicide (see policy guidelines) **AND**
 - b. Confirmation of imminent risk of suicide by clinical assessment by a mental health professional/psychiatrist (see policy guidelines)
 5. Individual is to receive esketamine nasal spray in conjunction with standard-of-care treatment based on clinical judgment and practice guidelines that may be comprised of oral antidepressant(s), an atypical antipsychotic, or a mood stabilizer.
 6. Individual does NOT have any Food and Drug Administration (FDA) labeled contraindications to the requested agent and esketamine nasal spray is intended to be used consistently with the FDA approved label (see policy guidelines) including meeting Spravato Risk Evaluation and Mitigation Strategy (REMS) program requirements (see policy guidelines).
 7. The prescriber is a specialist in the area of the individual's diagnosis (e.g. psychiatrist) or the prescriber has consulted with a specialist in the area of the individual's diagnosis.
- D. Esketamine nasal spray is considered **experimental/ investigational** in all other situations.

POLICY GUIDELINES

- A. A treatment session for use of esketamine nasal spray must ensure the following:
1. Treatment is administered under the direct supervision of a healthcare provider.
 2. Blood pressure is assessed before and after treatment to ensure safety in accordance with the U.S. Food and Drug Administration label.
 3. Individual receiving treatment should be advised to avoid food for at least 2 hours before administration and to avoid drinking liquids at least 30 minutes prior to administration.
 4. Individual receiving treatment should be advised to avoid use of nasal corticosteroid or nasal decongestant 1 hour prior to treatment.

5. Individual is monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the individual is considered clinically stable and ready to leave the healthcare setting.
- B. For treatment-resistant depression, the recommended adult dosage of esketamine nasal spray during the induction and maintenance phases are as follows:
1. Induction phase (weeks 1-4): Administer twice per week with day 1 starting dose at 56 mg and subsequent doses at 56 mg or 84 mg. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.
 2. Maintenance phase (weeks 5-8): Administer once weekly doses at 56 mg or 84 mg. Starting week 9 and after, administer every 2 weeks or once weekly doses at 56 mg or 84 mg. Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.
- C. For the treatment of adults with major depressive disorder with acute suicidal ideation or behavior, the recommended adult dosage of esketamine nasal spray is 84 mg twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. The use of esketamine nasal spray beyond 4 weeks has not been systematically evaluated.
- D. Esketamine nasal spray is contraindicated in individuals with the following conditions:
1. Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation.
 2. Intracerebral hemorrhage.
 3. Hypersensitivity to esketamine, ketamine, or any of the excipients.
- E. Esketamine nasal spray has a boxed warning because of 1) risk for sedation and dissociation after administration 2) potential for abuse and misuse. In order to mitigate these risks, it is available only through a restricted program called the SPRAVATO REMS. The essential features of this program include
1. Esketamine nasal spray is only dispensed and administered to individuals in a medically supervised healthcare setting that monitors these individuals.
 2. Pharmacies and healthcare settings that dispense esketamine nasal spray are certified.
 3. Ensuring that each individual is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring.
 4. Enrollment of all individuals in a registry to further characterize the risks and support safe use
- F. **Montgomery–Asberg Depression Rating Scale (MADRS)**
1. The MADRS is commonly used to evaluate the efficacy of antidepressant by assessing the severity of depression. It contains 10 items and the total score ranges from 0 to 60. The following cut-offs were proposed to classify the level of depression severity:
 - a. 0-6: No depression (absence of symptoms)
 - b. 7-19: Mild depression
 - c. 20-34: Moderate depression
 - d. 35-60: Severe depression

G. Hamilton Rating Scale for Depression (HAM-D)

1. The HAM-D is a 17-item rating scale to determine the severity level of depression in a individual before, during, and after treatment. The total score ranges from 0 to 52, with the score corresponding to the following classifications:
 - a. 0-7: No depression (normal)
 - b. 8-16: Mild depression
 - c. 17-23: Moderate depression
 - d. ≥24: Severe depression

H. Tools for Assessment of Suicidal Ideation/Behavior

There are multiple tools used for assessment of suicidal ideation and behavior. The eligibility criteria in the clinical trials of esketamine required that the individuals respond affirmatively to questions B3 ("Think about suicide [killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?") on the Mini-International Neuropsychiatric Interview instrument. Other scales that are commonly used to assess suicidal ideation include the Beck Scale for Suicide Ideation (SSI) and the Columbia-Suicide Severity Rating Scale (C-SSRS). SSI is a 19 item clinician-administered scale querying, among other things, the individual's wish to die, wish to live, and the duration and intensity of thoughts of suicide. Each item is rated on a 3-point scale from 0 to 2, with a total score ranging from 0 to 38. The SSI can be administered at initial evaluation and subsequently repeated to assess improvement. C-SSRS characterizes current thoughts of suicide and past suicidal behaviors. It features a clinician-administered initial evaluation form, a "since last visit" version, and a self-report form. It can be used in many settings, including medical, inpatient, and outpatient behavioral health.

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RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 30, 2024.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can

generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

ESKETAMINE

Clinical Context and Therapy Purpose

The purpose of esketamine in adults who have treatment-resistant depression or major depressive disorder with acute suicidal ideation or behavior is to provide a treatment option that is an improvement on or an alternative to existing therapies. Potential benefits of this therapy may include the following:

- A fast-acting treatment to “jump start” recovery;
- A durable treatment that keeps them well over time;
- A novel mechanism of action or approach that may allow successful treatment of many individuals for whom other available treatments have failed.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with a diagnosis of treatment-resistant depression or major depressive disorder with acute suicidal ideation or behavior. In this context,

- Treatment-resistant depression is defined as failure of 2 or more antidepressant treatment attempts with adequate dose and duration.
- Major depressive disorder is defined as an individual meeting DSM-5 diagnostic criteria (See Table 1) without psychotic features.
- Current suicidal ideation with intent is defined by a confirmed “Yes” response to Question B3 [Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (i.e., about killing yourself)?] AND Question B10 [Intend to act on thoughts of killing yourself?] obtained from the Mini-International Neuropsychiatric Interview. Note: the response to B3 must refer to the present, whereas the response to B10 may reflect the past 24 hours.

Interventions

The therapy being considered is esketamine, which is a non-selective, non-competitive N-methyl-D-aspartate receptor antagonist. The exact mechanism by which esketamine exerts an antidepressant effect is unknown. Esketamine is administered as a nasal spray in a medically-supervised setting because of the risk of sedation and dissociation.

Comparators

The relevant comparators are standard medical management (pharmacotherapy, psychotherapy, and/or somatic therapy). Available treatments have significant adverse reactions: weight gain and extrapyramidal symptoms (combination olanzapine and fluoxetine); risks of general anesthesia and memory loss (electroconvulsive therapy); surgical intervention and infection (vagus nerve stimulator). Transcranial magnetic stimulation has fewer risks relative to these other interventions but may be less effective.

Outcomes

The general outcomes of interest are change in disease status, functional outcomes, quality of life, treatment-related mortality, and treatment-related morbidity. See Table 2 for the description and relevance of the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Rating Scale for Depression (HAM-D). While pivotal trials that established short-term efficacy for other U.S. Food and Drug Administration (FDA)-approved antidepressants typically lasted at least 6 weeks, the acute-term esketamine trials were designed for only 4 weeks with the objective to demonstrate treatment effects in a shorter period of time. Event driven randomized withdrawal trials are required to demonstrate durability of effect in maintenance treatment.

Table 2. Health Outcome Measures Relevant to Treatment-Resistant Depression, Major Depressive Disorder, Suicidal Ideation, and Suicidal Behavior

Outcome	Description	Scale	Clinically Meaningful Difference
MADRS	<ul style="list-style-type: none"> Physician scored Rates presence and severity of depression Symptom domains include sadness; pessimism; inability to feel; suicidality 	<ul style="list-style-type: none"> Contains 10 items (scored from 0 to 6) with higher scores indicating more severe depression No validated cut-off score but generally 0 to 6 normal (no depression); 7 to 19 mild depression; 20 to 34 moderate depression; 35 to 59 severe depression; 60 or greater very severe depression²¹, 	<ul style="list-style-type: none"> No consensus to define remission. Thresholds for remission have ranged from 6 to 12 in trials. One literature review reported that the mean weighted MADRS score for remission was 4.0 (95% CI: 3.5-4.5) based on 10 studies.²² The definition of remission was a complete absence of clinically significant symptoms of depression. As per FDA, for drugs that have been approved to treat MDD as monotherapy or adjunctive treatment, treatment differences were typically closer to 3 or 4 points in MADRS scores. The observed treatment

Outcome	Description	Scale	Clinically Meaningful Difference
			differences in esketamine studies were in that range. ^{23,}
HAM-D	<ul style="list-style-type: none"> • Physician scored • Rates presence and severity of depression • Used in a number of registration studies of approved oral antidepressants • Symptom domains include sadness; pessimism; inability to feel; suicidality 	<ul style="list-style-type: none"> • There are 2 versions: 17 or 25 items; 17 items is more common • Each item scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression • Scores range from 0 to 48 • Scores as low as 17 are associated with moderate depression and those at or above 24 are associated with severe depression^{24,} 	<ul style="list-style-type: none"> • Remission is defined as total score of 7 or less. But 2 or less has been suggested as optimal. • Response to treatment is defined as a 50% reduction from baseline scores.
SIBAT	<ul style="list-style-type: none"> • Contains both patient- and clinician-reported modules and can be assessed by patient or rated by the physician • Includes assessments of <ul style="list-style-type: none"> ○ Severity of Suicidality (CGI-SS-r) ○ Imminent Suicide Risk (CGI-SR-I) ○ Frequency of Suicidal Thinking (FoST)^{25,} 	<ul style="list-style-type: none"> • CGI-SS-r: rated from 0 (normal, not at all suicidal) to 6 (among the most extremely suicidal patients) • CGI-SR-I: rates best clinical judgment of participant's imminent risk for suicide within the next 7 days. Scale indicates: 0 (No imminent suicide risk), 1 (Minimal imminent), 2 (Mild imminent), 3 (Moderate imminent), 4 (Marked imminent), 5 (Severely imminent), 6 (Extreme imminent). • FoST: describes the clinician determined estimate of the frequency of the participant's suicidal thinking. Scored on a 6-point Likert scale: 0 (Never), 1 (Rarely), 2 (Sometimes), 3 (Often), 4 (Most of the time), 5 (All of the time).^{25,} 	<ul style="list-style-type: none"> • No literature was identified for a consensus definition for a clinically meaningful change in scores

CGI-SR-I: Clinical Global Impression of Imminent Suicide Risk Scale, CGI-SS-r: Clinical Global Impression of Severity of Suicidality-Revised, CI: confidence interval; FDA: U.S. Food and Drug Administration; FoST: Frequency of Suicidal Thinking, HAM-D: Hamilton Rating Scale for Depression, MADRS: Montgomery-Asberg Depression Rating Scale, MDD: major depressive disorder; SIBAT: Suicide Ideation and Behavior Assessment Tool.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Treatment-Resistant Depression

Esketamine received a breakthrough therapy designation based on preliminary evidence that it could provide an advantage over existing therapy for treatment-resistant depression by providing rapid relief of depressive symptoms.²³ The clinical development program for esketamine is summarized in Table 3. The clinical development program comprises of 3 RCTs in acute (4-week) settings (TRANSFORM-1, -2 and -3), 1 randomized withdrawal study in a long-term (16-week) setting (SUSTAIN-1), and 2 open-label, long-term safety studies (SUSTAIN-2 and SUSTAIN-3). Information summarized here was obtained primarily from FDA documents^{21,23}, as well as peer reviewed publications.^{26,27,28,29,30,31,32}

Table 3. Summary of the Clinical Development Program for Esketamine in Treatment-Resistant Depression

	Phase	N	Esketamine Dose	Design and Objective	Treatment Phase and Duration	Outcome
PIVOTAL TRIALS						
TRANSFORM-2 (NCT02418585) ³⁰ ,	3	223	Flexible dose esketamine 56 or 84 mg	DB RCT (Efficacy and safety in adults 18 to 64 years)	4-week prospective observation phase + 4-weeks RCT + 24-week follow-up	<ul style="list-style-type: none"> • MADRS change • Clinical remission • Clinical response
SUSTAIN-1 (NCT02493868) ²⁷ ,	3	297	Flexible dose esketamine 56 or 84 mg	Open label single arm (Assess relapse prevention in those who attain stable remission or	16-week open-label induction phase + 48-week (variable) randomized maintenance phase + 2-week follow-up	<ul style="list-style-type: none"> • Relapse

	Phase	N	Esketamine Dose	Design and Objective	Treatment Phase and Duration	Outcome
				response with esketamine)		
SUPPORTING TRIALS						
TRANSFORM-1 (NCT02417064) ^{28,}	3	342	Fixed dose esketamine 56 or 84 mg	DB RCT (Efficacy and safety in adults 18 to 64 years)	4-week prospective observation phase + 4-weeks RCT + 24-week follow-up	<ul style="list-style-type: none"> • MADRS change • Clinical remission • Clinical response
TRANSFORM-3 (NCT02422186) ^{29,}	3	138	Flexible dose esketamine 28, 56, or 84 mg	DB RCT (Efficacy and safety in adults 65 years or older)	4-week prospective observation phase + 4-week double-blind induction phase + 2-week follow-up	<ul style="list-style-type: none"> • MADRS change • Clinical remission • Clinical response
SUSTAIN-2 (NCT02497287) ^{31,}	3	802	Flexible dose esketamine 28, 56, or 84 mg	Open label (Long-term efficacy and safety)	4-week screening phase + 4-week induction phase + up to 48-week optimization/maintenance phase + 4-week follow-up	<ul style="list-style-type: none"> • MADRS change • Clinical remission • Clinical response • Safety
SUSTAIN-3 (NCT02782104) ^{32,}	3	1148	Flexible dose esketamine 28, 56, or 84 mg	Open label (Long-term efficacy and safety)	4-week induction + variable duration optimization/maintenance	<ul style="list-style-type: none"> • MADRS change • Clinical remission • Clinical response • Safety

DB: double-blind; MADRS: Montgomery-Asberg Depression Rating Scale; NCT: national clinical trial; RCT: randomized controlled trial.

Pivotal Trials

The primary evidence for the approval of esketamine was comprised of a flexible-dose trial in adults younger than 65 years of age (TRANSFORM-2) and a randomized withdrawal study (SUSTAIN-1). The pivotal trial characteristics and results are summarized in Table 4 and 5, respectively. Across studies, demographic and baseline disease characteristics of patients randomized to esketamine and placebo nasal spray groups were similar. Patients in all of these studies had failed trials of at least 2 prior antidepressant drugs and had more severe symptoms on average than patients entering antidepressant studies for previously FDA-approved drugs including trials for olanzapine plus fluoxetine for treatment-resistant depression. All patients in phase 3 studies initiated a new daily oral antidepressant (open-label duloxetine, escitalopram, sertraline, or venlafaxine extended-release) at the time of randomization to esketamine or placebo.

In the TRANSFORM-2 trial, the primary endpoint was change in MADRS total score from baseline to week 4. Secondary endpoints were onset of clinical response by day 2 and sustained response through week 4, change in functioning and disability, and change in patient-reported depressive symptoms. The trial met the primary endpoint with a 4-point difference (95% confidence interval [CI], -7.3 to 0.6) in least square (LS) mean difference of MADRS score in favor of esketamine. Assessment of time course of response in the MADRS score showed that a treatment difference between esketamine versus placebo was observed at 24 hours (data not shown). The drug-placebo difference in MADRS change from baseline remained consistent through the end of week 4 with no further separation between groups after day 2. At the end of week 4, 67% of the patients randomized to esketamine were receiving 84 mg twice weekly. Jamieson et al (2023) published health-related quality of life data from TRANSFORM-2.³³ The European Quality of Life Group, Five Dimension, Five Level (EQ-5D-5L) scale identified lower impairment at 28 days with esketamine compared with placebo groups including: mobility (10.6% vs 25.0%), self-care (13.5% vs 32.0%), usual activities (51.9% vs 72.0%), pain/discomfort (35.6% vs 54.0%), and anxiety/depression (69.2% vs 78.0%). Sheehan Disability Scale (SDS) scores were also improved with esketamine compared with placebo (-13.6 vs -9.4).

In the SUSTAIN-1 trial, the primary objective was to assess durability of treatment effect by assessing how long patients who received at least 16 initial weeks of treatment with esketamine and achieved remission or stable response were able to delay relapse of depressive symptoms after being randomized to withdrawal or continuation of esketamine. Background antidepressant therapy was continued in both treatment arms. Stable remission was defined as a MADRS total score ≤ 12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRS total score reduction $\geq 50\%$ for the last 2 weeks of optimization and not in remission. The primary endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score ≥ 22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse. Results showed time to relapse was significantly delayed if patients continued esketamine versus being switched to placebo among stable remitters (not estimable vs 273 days; hazard ratio [HR]=0.49) as well as responders (635 days vs 88 days; HR=0.30).

Adverse events were appropriately monitored, with specific assessments for adverse events of special interest that included sedation, dissociation, and increases in blood pressure (data not shown). The time course of these events closely followed the pharmacokinetic profile of esketamine, and their incidence was dose-related. These events are monitorable, and most occurred within the first 2 hours following drug administration.²³

While no major limitations in study relevance or study design and conduct were noted, concerns related to the possibility of unblinding and limited generalizability of trial results to the intended population of use are noteworthy. Esketamine is known to result in dissociative effects and therefore there were concerns that blinded patients would be able to discern whether they were receiving active treatment or not. To minimize the potential of unblinding, investigators incorporated design elements in the study protocols to enhance blinding. For example, centralized, blinded, remote raters were used in all phase 3 studies. A bittering agent was also added to placebo to enhance the blind. Regarding the generalizability of the results, a lack of racial/ethnic diversity and enrollment of patients with less severe depression were the main concerns. More than 90% of patients enrolled in the trials were Caucasians while it is known that

depression is also common among other racial and ethnic minorities.³⁴ While esketamine is likely to be used for patients with chronic, severe depression, who have failed multiple other therapies, only 36% to 40% of studied patients had failed 3 or more therapies in the current depressive episode. Lastly, more robust data are needed to determine how esketamine compares with other therapies for treatment-resistant depression as there are no head-to-head trials comparing esketamine with standard of care prior to its approval.

Table 4. Summary of Characteristics of Key Randomized Trials of Esketamine in Treatment-Resistant Depression

Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Active	Comparator
TRANSFORM-2 ^{23,21,30,}	US and global	50	2015-2017	<p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Ages 18 to 64 years • Major depressive disorder (DSM-5) • IDS-C30 \geq 34 • Failed 1 to 5 oral ADs based on MGH-ATRQ • MADRS \geq 28 <p><i>Patient characteristics</i></p> <ul style="list-style-type: none"> • Current episode duration (yrs.): 2.2 • MADRS mean: 37 • Past failures of \geq 3 ADs: 36% 	Esketamine plus oral AD (n= 109)	Placebo plus oral AD (n=114)
SUSTAIN-1 ^{27,}	US and global	160	2015-2018	<p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Participants from TRANSFORM-1 and -2 who achieved stable remission or stable response^a <p><i>Patient characteristics</i></p> <ul style="list-style-type: none"> • Current episode duration (yrs.): NR • Stable remitters (59% of enrolled), 	Esketamine plus oral AD (n=152)	Placebo plus oral AD (n=145)

Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Active	Comparator
				MADRS mean: 37.5 <ul style="list-style-type: none"> Stable responders (41% of enrolled), MADRS mean: 39.5 		

^a Stable remission was defined as achieving MADRS ≤ 12 for at least 3 out of the last 4 weeks of the 12-week optimization phase of receiving esketamine, while stable response was defined as achieving $\geq 50\%$ reduction in MADRS total score from baseline in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.

AD: antidepressant; DSM: Diagnostic and Statistical Manual of Mental Disorders; IDS-C30: Inventory of Depressive Symptomatology-Clinician; MADRS: Montgomery-Asberg Depression Rating Scale; MGH-ATRQ: Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire; NR: not reported.

Table 5. Summary of Results from Key Randomized Trials of Esketamine in Treatment-Resistant Depression

Study	Change in MADRS (SD)	Clinical Response	Clinical Remission
TRANSFORM-2 ^{30,21,}	223	223	223
Esketamine	-20.8 (-23.3 to -18.4)	69%	53%
Placebo	-16.8 (-19.3 to -14.4)	52%	31%
Difference (95% CI)	- 4.0 (-7.3, -0.6); p=.010	-	-
	Relapse (%)	Median Time to Relapse (days)	
SUSTAIN-1 ^{27,21,}	297	297	
Among stable remitters, n	176	176	
Esketamine	27%	NE	
Placebo	45%	273 (97 to NE)	
HR (95% CI)	-	0.49 ^a (0.3 to 0.8); p=.003 ^b	
Among stable responders	121	121	
Esketamine	26%	Median: 635 (265 to 635)	
Placebo	58%	Median: 88 (46 to 196)	
HR (95% CI)	-	0.30 ^a (0.16 to 0.55); p<.001	

CI: confidence interval; HR: hazard ratio; MADRS: Montgomery-Asberg Depression Rating Scale; NE: not estimable; SD: standard deviation.

^a Compares esketamine arm to placebo arm.

^b p-value adjusted for interim analysis that included a sample size re-estimation

Supportive Evidence

Supporting trials include TRANSFORM-1 and -3 and SUSTAIN-2. Trial characteristics and results are summarized in Table 6 and 7, respectively.

TRANSFORM-1 was a fixed-dose study in adults younger than 65 years of age. The study was conducted at 96 sites worldwide with 42 sites in the United States. Subjects were randomized at a 1:1:1 ratio to either 56 mg esketamine, 84 mg esketamine, or placebo. The prespecified analysis plan dictated that efficacy of the 84-mg dose would be evaluated first, followed by evaluation of the 56-mg dose. The primary endpoint of change from baseline to day 28 in mean MADRS total score showed no statistically significant difference between the 84 mg esketamine dose versus placebo, the 56 mg dose as well as other secondary endpoints were not formally evaluated.

TRANSFORM-3 was a flexible-dose study in patients ≥ 65 years of age. The sample size in the geriatric study was only about half of that in the successful flexible-dose study. The study included flexible doses ranging from 28 to 84 mg; the effect of esketamine in the combined dose group was not statistically superior to placebo. However, the magnitude of the treatment effect (3.6-point improvement on the MADRS) is in the range of effects observed in other antidepressant studies, as well as other phase 3 studies in the esketamine development program. Unlike other studies where separation of clinical response was apparent within 2 days of treatment and treatment effect remained constant throughout, in this trial, the treatment difference with esketamine was only apparent towards the end of the study with no separation of MADRS scores early. The reason for this anomaly remains unexplained.

SUSTAIN-2 was an open-label, long-term study of esketamine nasal spray focused on safety. Common treatment-emergent adverse events included dizziness (32.9%), dissociation (27.6%), nausea (25.1%), and headache (24.9%); 76 patients discontinued esketamine therapy due to adverse events. Serious treatment-emergent adverse events occurred in 55 patients. Of these, 5 events in 4 patients were considered to be drug-related by the investigator: suicidal ideation (n=1), suicide attempt (n=1), anxiety and delusions (both in 1 patient), and delirium (n=1). Most treatment-emergent adverse events occurred on dosing days, were mild or moderate in intensity, and resolved in the same day. Overall, the nature of adverse events reported was consistent with the known safety profile of esketamine.

SUSTAIN-3 was an additional open-label, long-term safety study of esketamine completed in December 2022.³² Interim data (cutoff December 2020) has been published with a mean esketamine exposure duration of 31.5 months. The most common treatment-emergent adverse events during optimization/maintenance included headache (33.2%), dizziness (30.8%), nausea (29.9%), dissociation (23.2%), nasopharyngitis (22.6%), and somnolence (22.2%). Severe dissociation events occurred during induction, but resolved within 90 minutes of dosing.

Table 6. Summary of Characteristics of Supporting Trials of Esketamine in Treatment-Resistant Depression

Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Active	Comparator
TRANSFORM-1 ²⁸ ,	US and global	91	2015 - 2018	<p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Ages 18 to 64 years • Major depressive disorder (DSM-5) • IDS-C30 \geq31 • Failed 1 to 5 oral ADs based on MGH-ATRQ • MADRS \geq28 <p><i>Patient characteristics</i></p> <ul style="list-style-type: none"> • Current episode duration (yrs.): 3.9 • MADRS mean: 37.5 • Past failures of \geq 3ADs: 40% 	Esketamine plus oral ADs (n=229)	Placebo plus oral ADs (n=113)
TRANSFORM-3 ²⁹ ,	US and global	70	2015 - 2017	<p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Same as above except age \geq65 <p><i>Patient characteristics</i></p> <ul style="list-style-type: none"> • Current episode duration (yrs.): 4.1 • MADRS mean: 35 • Past failures of \geq 3ADs: 39% 	Esketamine plus oral AD (n= 72)	Placebo plus oral AD (n=66)
SUSTAIN-2 ³¹ ,	US and global	114	2015 - 2017	<p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Patients entered the study either directly (age \geq18 years) or after completing the double-blind induction phase of a randomized, 4-week, efficacy study (age \geq65 years) • Transferred-entry patients who were responders in the short-term study joined in the optimization/maintenance phase while nonresponders joined in the induction phase • Major depressive disorder (DSM-5) 	<p>Induction phase: self-administered esketamine twice weekly for 4 weeks as a flexible dose regimen starting at 28 mg (\geq65 years) or 56 mg (<65 years)</p> <p>Adjustments for subsequent doses (<65 years: 56 or 84 mg; \geq65 years: 28, 56, or 84 mg) were allowed based on efficacy and tolerability</p> <p>Direct-entry patients simultaneously initiated a new oral AD and transferred</p>	NA - open label long-term study

Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Active	Comparator
				<ul style="list-style-type: none"> • Nonresponse to ≥ 2 ADs • MADRS ≥ 22 at screening <p><i>Patient characteristics</i></p> <ul style="list-style-type: none"> • History of suicidal ideation in the prior 6 months: 26.9% • MADRS mean: 31.4 • Past failures of ≥ 3 ADs: 39.9% • Family history of depression: 43.1% • Mean age: 52.2 years • 62.6% women; 85.5% White 	<p>nonresponders continued the oral AD in the short-term study</p> <p>Optimization/maintenance phase: responders from the induction phase were given esketamine once weekly (same dose) and continued on oral AD treatment; transferred entry responders started a flexible dosing regimen at 28 mg (week 5) with potential up-titration (56 or 84 mg) through week 8 and continued on oral AD treatment</p>	
SUSTAIN-3 ^{32,}	US and global	59	2016 - 2022	<p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Patients from a phase 3 parent study who had confirmed benefit were enrolled into either a 4-week induction or the optimization/maintenance based on their status from the original study 	<p>Induction phase: self-administered esketamine twice weekly for 4 weeks as a flexible dose regimen starting at 28 mg (≥ 65 years) or 56 mg (< 65 years)</p> <p>Optimization/maintenance phase: individualized interval dosing based on CGI-S algorithm</p>	NA - open label long-term study

^a Stable remission was defined as achieving MADRS ≤ 12 for at least 3 out of the last 4 weeks of the 12-week optimization phase of receiving esketamine, while stable response was defined as achieving $\geq 50\%$ reduction in MADRS total score from baseline in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.

AD: antidepressant; DSM: Diagnostic and Statistical Manual of Mental Disorders; CGI-S: clinical global impression - severity; IDS-C30: Inventory of Depressive Symptomatology-Clinician; MADRS: Montgomery-Asberg Depression Rating Scale; MGH-ATRQ: Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire; NA: not applicable.

Table 7. Summary of Results from Supporting Trials of Esketamine in Treatment-Resistant Depression

Study	Change in MADRS (SD)	Clinical Response	Clinical Remission
TRANSFORM-1 ²⁸ ,	342	342	342
Esketamine 84 mg	-18.2 (-20.9 to -15.6)	53%	39%
Esketamine 56 mg	-18.9 (-21.4 to -16.4)	54%	36%
Placebo	-14.9 (-17.4 to -12.4)	39%	31%
Difference (95% CI) Esketamine 84 mg Esketamine 56 mg	-3.2 (-6.9, 0.5); p=.088 -4.1 (-7.7, -0.6); p=.027	a	a
TRANSFORM-3 ²⁹ ,	137	123	123
Esketamine	-10.1 (-13.1 to -7.1)	27%	17.5%
Placebo	-6.3 (-9.4 to -3.6)	13.3%	6.7%
Difference (95% CI)	-3.6 (-7.2, 0.07); p=.059	a	a
SUSTAIN-2 ³¹ ,	Induction phase (n=779) Optimization/maintenance phase (n=603)		
Esketamine	Induction baseline to endpoint: -16.4 (8.76) Optimization/maintenance to endpoint: 0.3 (8.12)	Induction phase: 78.4% Optimization/maintenance phase: 76.5%	Induction phase: 47.2% Optimization/maintenance phase: 58.2%
SUSTAIN-3 ³² ,	Induction phase (n=458) Optimization/maintenance phase (n=690)		
	Induction baseline to endpoint: -12.8 (9.73) Optimization/maintenance to endpoint: 1.1 (9.93)	Induction phase: 49.2% at end of induction Optimization/maintenance phase: NR	Induction phase: 35.6% Optimization/maintenance phase: 46.1%

^a As per U.S. Food and Drug Administration, none of the results on the prespecified key secondary endpoints (only designated in TRANSFORM-1 and TRANSFORM-2) were statistically significant after controlling for type I error based on the prespecified statistical analysis plan.
CI: confidence interval; MADRS: Montgomery-Asberg Depression Rating Scale; SD: standard deviation.

Section Summary

The evidence for use of esketamine for treatment resistant depression consists of 4 RCTs (TRANSFORM-1, -2 and -3 and SUSTAIN-1) with placebo comparators that enrolled more than

700 patients across studies and open label, long-term studies with a focus on safety (SUSTAIN-2 and SUSTAIN-3). Of the 4 RCTs, TRANSFORM-2 and SUSTAIN-1 were the basis for FDA approval. While both trials used the flexible esketamine dosing, the objective of TRANSFORM-2 was to assess short-term (4 week) efficacy of esketamine while SUSTAIN-1 aimed to assess durability of efficacy over the long-term (event-driven study with no fixed duration). Results of TRANSFORM-2 showed that the trial met the primary endpoint with a 4 point difference (95% CI -7.3 to 0.6) in LS mean difference of the MADRS total score in favor of esketamine. As per the FDA, statistically significant response results on the MADRS can likely be considered clinically meaningful. The magnitude of treatment effect observed in TRANSFORM-2 was within the range observed in clinical trials for other approved antidepressants currently on the market. Assessment of time course of response showed that the treatment effect was apparent at 24 hours and remained fairly consistent through the end of 4 weeks with no further separation between groups after day 2. Results of the SUSTAIN trial showed that patients who received at least 16 initial weeks of treatment with esketamine and achieved clinical remission or response were less likely to relapse if they continued esketamine versus being switched to placebo (HR= 0.49 for remitters and HR=0.30 for responders, respectively). TRANSFORM-1 (a fixed-dose study) and TRANSFORM-3 (a flexible-dose study in patients ≥ 65 years of age) were negative. Safety data from the long-term SUSTAIN-2 and interim results of SUSTAIN-3 studies revealed treatment-emergent adverse events consistent with the known safety profile of esketamine. While no major limitations in study relevance or study design and conduct were noted in the RCTs, concerns related to the possibility of unblinding and limited generalizability of trial results to the intended population of use are noteworthy.

Major Depressive Disorder with Acute Suicidal Ideation or Behavior

The clinical development program for esketamine is summarized in Table 8 and comprises of 2 identical RCTs in an acute (4-week) setting (ASPIRE-1 and 2). The pivotal trial characteristics and results are summarized in Table 9 and 10, respectively. Across both studies, demographic and baseline disease characteristics of patients randomized to esketamine and placebo nasal spray groups were similar. Both studies enrolled adults with moderate-to-severe major depressive disorder (MADRS total score >28) who had active suicidal ideation and intent and were treated with esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks. A one time dose reduction to 56 mg was allowed for patients unable to tolerate the 84 mg dose after the first dose. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant as determined by the investigator. After completion of the 4-week treatment period with esketamine/placebo, study follow-up continued through day 90.

The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after the first dose. The secondary efficacy measure was the change in the Clinical Global Impression of Suicidal Severity - Revised (CGI-SS-r) score at 24 hours after the first dose. In both studies, esketamine plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo. On average, the difference in LS mean change in total MADRS score from baseline to 24 hours was a 3.8 and 3.9 point improvement in ASPIRE-1 and -2, respectively. Further, between 4 hours after the first dose and day 25, both esketamine and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through day 25 according to the prescribing label. In both studies, treatment with esketamine did not demonstrate superiority compared to placebo nasal spray in improving CGI-SS-r. The CGI-SS-r is a 1 item, clinician-rated assessment used to rate

the current severity of a patient's suicidal ideation and behavior. Among other endpoints, the proportion of patients who achieved remission was higher among esketamine-treated patients versus placebo at 24 hours after the first dose as well as on day 25 (Table 10). Adverse events were appropriately monitored, with specific assessments for adverse events of special interest that included sedation, dissociation, and increases in blood pressure (data not shown). The time course of these events closely followed the pharmacokinetic profile of esketamine, and their incidence was dose-related. These events are monitorable, and most occurred within the first 2 hours following drug administration.³⁵

While no major limitations in study relevance or study design and conduct were noted, concerns related to the possibility of unblinding and limited generalizability of trial results to the intended population of use are noteworthy. Esketamine is known to result in dissociative effects and therefore there were concerns that blinded patients would be able to discern whether they were receiving active treatment or not. To minimize the potential of unblinding, investigators incorporated design elements in the study protocols to enhance blinding. For example, efficacy and safety assessments were performed by different raters. A bittering agent was also added to placebo to enhance the blind. Regarding the generalizability of the results, the lack of racial/ethnic diversity and enrollment of patients with less severe depression were the main concerns. More than 70% of patients enrolled in the trials were Caucasians while it is known that depression is also common among other racial and ethnic minorities.³⁴ Lastly, the effectiveness of esketamine in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated in the ASPIRE-1 and -2 studies. Both studies were not powered to detect a statistically significant difference between suicidal ideation and/or suicides. Patients in both the esketamine and placebo group experienced a rapid reduction in the severity of their suicidality, the difference between treatment groups was not statistically significant. This may be due to the substantial impact of inpatient psychiatric hospitalization in diffusing the acute suicidal crisis. Further, comprehensive standard-of-care was enhanced by twice-weekly study visits with extensive clinical contact and permitted benzodiazepine use, all of which may have contributed to the rapid reduction of suicidality in both treatment groups.

Table 8. Summary of the Clinical Development Program for Esketamine in Major Depressive Disorder with Acute Suicidal Ideation or Behavior

	Phase	N	Esketamine Dose	Design & Objective	Treatment phase and duration	Outcome
PIVOTAL TRIALS						
ASPIRE I (NCT03039192) ^{36,35}	3	224	Flexible dose (initiated at 84 mg but could be reduced to 56 mg after 4 weeks)	DB RCT (Efficacy and safety in adults 18 to 64 years)	<ul style="list-style-type: none"> 24- to 48-hr screening period to assess eligibility 4-week double-blind treatment phase 	<ul style="list-style-type: none"> MADRS change SIBAT change

	Phase	N	Esketamine Dose	Design & Objective	Treatment phase and duration	Outcome
					<ul style="list-style-type: none"> 9-week post-treatment follow-up 	
ASPIRE II (NCT03097133) ^{37,35,}	3	227	Flexible dose (initiated at 84 mg but could be reduced to 56 mg after 4 weeks)	DB RCT (Efficacy and safety in adults 18 to 64 years)	<ul style="list-style-type: none"> Same as above 	<ul style="list-style-type: none"> Same as above

DB: double-blind; NCT: national clinical trial; MADRS: Montgomery-Asberg Depression Rating Scale; RCT: randomized controlled trial; SIBAT: Suicide Ideation and Behavior Assessment Tool.

Table 9. Summary of Characteristics of Key Randomized Trials of Esketamine in Major Depressive Disorder with Acute Suicidal Ideation or Behavior

Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Active	Comparator
ASPIRE I (NCT03039192) ^{36,35,}	US, Europe, Asia, and South Africa	50	2017-2018	<p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> Ages 18 to 64 years Major depressive disorder (DSM-5) Patients respond affirmatively to MINI questions B3 ("Think about suicide [killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?") within 24 hours of randomization In clinical need of acute psychiatric hospitalization 	Esketamine plus standard of care AD (n=112)	Placebo plus standard of care AD (n=112)

Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Active	Comparator
				due to imminent suicide risk <ul style="list-style-type: none"> MADRS ≥ 28 on predose day 1 <i>Patient characteristics</i> <ul style="list-style-type: none"> Mean age: 41 years MADRS total scores, mean: 41 Prior suicide attempt: 60% Suicide attempt in the last month: 28% 		
ASPIRE II (NCT03097133) ^{37,35,}	US and global	160	2017-2019	<i>Inclusion criteria</i> <ul style="list-style-type: none"> Same as above <i>Patient characteristics</i> <ul style="list-style-type: none"> Mean age: 41 years MADRS total scores, mean: 40 Prior suicide attempt: 66% Suicide attempt in the last month: 26% 	Esketamine plus oral AD (n=114)	Placebo plus standard of care AD (n=113)

AD: antidepressant; DSM: Diagnostic and Statistical Manual of Mental Disorders; MADRS: Montgomery-Asberg Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview.

Table 10. Summary of Results from Key Randomized Trials of Esketamine in Major Depressive Disorder with Acute Suicidal Ideation or Behavior

Study	MADRS Scores (Primary Endpoint)	Remission (MADRS Total Score ≤ 12), %	CGI-SS-r Score (Primary Secondary Endpoint) ^a
ASPIRE I (NCT03039192) ^{36,35,}	N=223	N=223	N=223
Esketamine ^b	Baseline: 41.3 ($\pm 5.87^c$) LS mean change 24	24 h post first dose: 19% Day 25, 4 h post dose: 54%	Not reported

Study	MADRS Scores (Primary Endpoint)	Remission (MADRS Total Score ≤12), %	CGI-SS-r Score (Primary Secondary Endpoint) ^a
	h post first dose: -15.9 (±1.04 ^d)		
Placebo ^b	Baseline Score: 41.0 (±6.29 ^c) LS mean change 24 h post first dose: -12.0 (±1.02 ^d)	24 h post first dose: 9% Day 25, 4 h post dose: 38%	Not reported
Difference	LS Difference (95% CI): -3.8 (-6.56 to -1.09)	24 h post first dose: 9.8% (0.87 to 18.77) Day 25, 4 h post dose: 16.1 (3.20 to 28.94)	24 h post first dose: -0.26 (-0.59 to 0.08)
ASPIRE II (NCT03097133) ^{37,35,}	N=226	N=226	N=223
Esketamine ^b	Baseline Score: 39.4 (±5.21 ^c) LS mean change : -16.0 (±1.02 ^d)	24 h post first dose: 22% Day 25, 4 h post dose: 47%	Not reported
Placebo ^b	Baseline Score: 39.9 (±5.76 ^c) LS mean change : -12.2 (1±1.05 ^d)	24 h post first dose: 11% Day 25, 4 h post dose: 37%	Not reported
Difference	LS difference (95% CI): -3.9 (-6.60 to -1.11)	24 h post first dose: 11.3% (1.83 to 20.80) Day 25, 4 h post dose: 10.2% (-2.58 to 22.98)	24 h post first dose: -0.14 (-0.48 to 0.19)

CGI-SS-r= Clinical Global Impression-Severity of Suicidality-revised; CI=confidence interval; LS=least-squares; MADRS=Montgomery-Asberg Depression Rating Scale.

^a The CGI-SS-r is a 1 item, clinician-rated assessment used to rate the current severity of a patient's suicidal ideation and behavior. Scores on the CGI-SS-r range from 0 to 6, with higher scores indicating more severe suicidal ideation and behavior.

^b Treatment included an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (antidepressant monotherapy or antidepressant monotherapy plus augmentation therapy).

^c standard deviation.

^d standard error.

Section Summary

The evidence for use of esketamine for treatment of adults with major depressive disorder with acute suicidal ideation or behavior consists of 2 RCTs (ASPIRE-1 and -2) with placebo comparators that enrolled 449 patients. The 2 identical RCTs enrolled adults with moderate-to-severe major depressive disorder who had active suicidal ideation and intent with the primary objective to assess short-term (24-hour after the first dose) efficacy of esketamine. Results showed that both trials met the primary endpoint with approximately a 4 point difference in LS mean difference of MADRS total score in favor of esketamine. As per the FDA, statistically significant response results on the MADRS can likely be considered clinically meaningful. The magnitude of treatment effect was within the range observed in clinical trials for other approved

antidepressants currently on the market. Assessment of time course of response showed that the treatment effect was apparent at 24 hours and remained fairly consistent through day 25 with no further separation between groups after day 2. While no major limitations in study relevance or study design and conduct were noted, concerns related to the possibility of unblinding and limited generalizability of trial results to the intended population of use are noteworthy.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Physicians

The American College of Physicians published a living clinical guideline for the acute phase of major depressive disorder in 2023, which was most recently updated in July 2024.³⁸ They recommend either cognitive behavioral therapy or a second-generation antidepressant or both for patients with acute moderate or severe major depressive disorder. There are no recommendations relevant to esketamine.

American Psychiatric Association

The American Psychiatric Association issued clinical practice guidelines for major depressive disorder in 2010 with no subsequent updates.³⁹ These are considered legacy practice guidelines and can no longer be assumed to be current.

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review (ICER) published a final Report on the comparative clinical effectiveness and value of esketamine for treatment-resistant depression on June 20, 2019.² The Report concludes the following on the strength of evidence that esketamine improves outcomes in patients with treatment-resistant depression- "Evidence provides moderate certainty that the addition of esketamine to a newly initiated antidepressant has comparable or better net health benefit, with a small (but non-zero) chance of net harm, compared with newly initiated antidepressant alone. There was insufficient evidence to judge the net health benefit of esketamine versus ketamine or other therapies for treatment-resistant depression."

U.S. Preventive Services Task Force Recommendations

Not applicable

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Clinical Studies

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT05973851	A Randomised, Controlled Trial to Investigate the Effect of a Four Week Intensified Pharmacological Treatment for Major Depressive Disorder Compared to Treatment as Usual in Subjects Who Had a First-time Treatment Failure on Their First-line Treatment	418	Jun 2026
NCT05554627	VA Aripiprazole vs. Esketamine for Treatment of Depression VAST-D II	940	Nov 2028
NCT04599855	A Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Esketamine Nasal Spray, Administered as Monotherapy, in Adult Participants with Treatment-resistant Depression	450	Feb 2024
NCT04829318	Open-label Long-Term Extension Study for Participants with Treatment-resistant Major Depressive Disorder Who Are Continuing Esketamine Nasal Spray Treatment from Study 54135419TRD3013	183	Jul 2024
<i>Unpublished</i>			
NCT03185819	Study to evaluate the efficacy and safety of 3 fixed doses of intranasal esketamine in addition to comprehensive standard of care for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in pediatric participants assessed to be at imminent risk for suicide	147 (actual)	Mar 2023

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
S0013	Esketamine, nasal spray, 1 mg
G2082	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of <u>up to 56 mg of</u> esketamine nasal self-administration, includes 2 hours post-administration observation
G2083	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of <u>greater than 56 mg</u> esketamine nasal self-administration, includes 2 hours post-administration observation

REVISIONS	
12-02--2021	Policy added to the bcbsks.com web site.
12-13-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section <ul style="list-style-type: none"> ▪ Removed J3490 ▪ Added S0013
	Updated References Section
11-17-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section <ul style="list-style-type: none"> ▪ Removed ICD-10 Codes
	Updated References Section
12-03-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section

REFERENCES

1. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997; 58 Suppl 13: 23-9. PMID 9402916

2. Institute for Clinical and Economic Review, Final Evidence Report. Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value. 2019; https://icer.org/wp-content/uploads/2020/10/ICER_TRD_Final_Evidence_Report_062019.pdf. Accessed August 30, 2024.
3. Gaynes BN, Asher G, Gartlehner G, et al. Definition of Treatment-Resistant Depression in the Medicare Population [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Feb 9. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK526366/>
4. American Psychiatric Association. DSM 5. Diagnostic and statistical manual of mental disorders. American Psychiatric Press Inc, (5th edition). 2013; Washington, DC: American Psychiatric Association.
5. Borges G, Nock MK, Haro Abad JM, et al. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. *J Clin Psychiatry*. Dec 2010; 71(12): 1617-28. PMID 20816034
6. Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry*. Feb 2008; 192(2): 98-105. PMID 18245022
7. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2021 National Survey on Drug Use and Health. NSDUH; <https://www.hhs.gov/about/news/2023/01/04/samhsa-announces-national-survey-drug-use-health-results-detailing-mental-illness-substance-use-levels-2021.html>. Accessed August 30, 2024.
8. Tidemalm D, Långström N, Lichtenstein P, et al. Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. *BMJ*. Nov 18 2008; 337: a2205. PMID 19018040
9. Kessler RC, Berglund P, Borges G, et al. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *JAMA*. May 25 2005; 293(20): 2487-95. PMID 15914749
10. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*. Apr 01 2018; 75(4): 336-346. PMID 29450462
11. Holma KM, Melartin TK, Haukka J, et al. Incidence and predictors of suicide attempts in DSM-IV major depressive disorder: a five-year prospective study. *Am J Psychiatry*. Jul 2010; 167(7): 801-8. PMID 20478879
12. Blair-West GW, Cantor CH, Mellsop GW, et al. Lifetime suicide risk in major depression: sex and age determinants. *J Affect Disord*. Oct 1999; 55(2-3): 171-8. PMID 10628886
13. Deisenhammer EA, Ing CM, Strauss R, et al. The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt?. *J Clin Psychiatry*. Jan 2009; 70(1): 19-24. PMID 19026258
14. Montgomery SA, Dunner DL, Dunbar GC. Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo. *Eur Neuropsychopharmacol*. Mar 1995; 5(1): 5-13. PMID 7613102
15. Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. *Am J Psychiatry*. Jul 2007; 164(7): 1029-34. PMID 17606654

16. Wasserman D, Rihmer Z, Rujescu D, et al. [The European Psychiatric Association (EPA) guidance on suicide treatment and prevention]. *Neuropsychopharmacol Hung*. Jun 2012; 14(2): 113-36. PMID 22710852
17. Ionescu DF, Rosenbaum JF, Alpert JE. Pharmacological approaches to the challenge of treatment-resistant depression. *Dialogues Clin Neurosci*. Jun 2015; 17(2): 111-26. PMID 26246787
18. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer Adherence*. 2012; 6: 369-88. PMID 22654508
19. Papadimitropoulou K, Vossen C, Karabis A, et al. Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis. *Curr Med Res Opin*. Apr 2017; 33(4): 701-711. PMID 28035869
20. Lex H, Ginsburg Y, Sitzmann AF, et al. Quality of life across domains among individuals with treatment-resistant depression. *J Affect Disord*. Jan 15 2019; 243: 401-407. PMID 30268955
21. FDA Briefing Document Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting February 12, 2019. <https://public4.pagefreezer.com/browse/FDA/04-03-2022T19:30/https://www.fda.gov/advisory-committees/february-12-2019-joint-meeting-psychopharmacologic-drugs-advisory-committee-pdac-and-drug-safety-and#event-materials>. Accessed August 30, 2024.
22. Zimmerman M, Chelminski I, Posternak M. A review of studies of the Montgomery-Asberg Depression Rating Scale in controls: implications for the definition of remission in treatment studies of depression. *Int Clin Psychopharmacol*. Jan 2004; 19(1): 1-7. PMID 15101563
23. Center for Drug Evaluation and Research Application Number: 211243Orig1s000 Summary Review https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000SumR.pdf. Accessed August 30, 2024.
24. Zimmerman M, Martinez JH, Young D, et al. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord*. Sep 05 2013; 150(2): 384-8. PMID 23759278
25. Alphs L, Fu D-J, Williamson D, et al. Validation and mapping of the Suicidal Ideation and Behavior Assessment Tool (SIBAT). (abstract W88) *Neuropsychopharmacology*. 2018;43:S427S428.
26. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. Feb 01 2018; 75(2): 139-148. PMID 29282469
27. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. Sep 01 2019; 76(9): 893-903. PMID 31166571
28. Fedgchin M, Trivedi M, Daly EJ, et al. 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*. Oct 01 2019; 22(10): 616-630. PMID 31290965

29. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression-TRANSFORM-3. *Am J Geriatr Psychiatry*. Feb 2020; 28(2): 121-141. PMID 31734084
30. Popova V, Daly EJ, Trivedi M, et al. 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*. Jun 01 2019; 176(6): 428-438. PMID 31109201
31. Wajs E, Aluisio L, Holder R, et al. 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*. Apr 28 2020; 81(3). PMID 32316080
32. Zaki N, Chen LN, Lane R, et al. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. *Neuropsychopharmacology*. Jul 2023; 48(8): 1225-1233. PMID 37173512
33. Jamieson C, Popova V, Daly E, et al. Assessment of health-related quality of life and health status in patients with treatment-resistant depression treated with esketamine nasal spray plus an oral antidepressant. *Health Qual Life Outcomes*. May 08 2023; 21(1): 40. PMID 37158911
34. Dunlop DD, Song J, Lyons JS, et al. Racial/ethnic differences in rates of depression among preretirement adults. *Am J Public Health*. Nov 2003; 93(11): 1945-52. PMID 14600071
35. Janssen Pharmaceuticals, Inc. Prescribing Information Spravato (esketamine) nasal spray. July 2024. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d81a6a79-a74a-44b7-822c-0dfa3036eaed>. Accessed August 30, 2024.
36. Fu DJ, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *J Clin Psychiatry*. May 12 2020; 81(3). PMID 32412700
37. Ionescu DF, Fu DJ, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int J Neuropsychopharmacol*. Jan 20 2021; 24(1): 22-31. PMID 32861217
38. Qaseem A, Owens DK, Etzeandía-Ikobaltzeta I, et al. Nonpharmacologic and Pharmacologic Treatments of Adults in the Acute Phase of Major Depressive Disorder: A Living Clinical Guideline From the American College of Physicians. *Ann Intern Med*. Feb 2023. Updated July 2024. <https://www.acpjournals.org/doi/10.7326/ANNALS-24-00593>. Accessed August 30, 2024.
39. Practice Guideline for the Treatment of Patients With Major Depressive Disorder Third Edition: AMERICAN PSYCHIATRIC ASSOCIATION. 2010; https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed August 30, 2024.

OTHER REFERENCES

1. Blue Cross and Blue Shield of Kansas Behavioral Health Liaison Committee February 2023.