New Drug Overview
Spravato (esketamine)

INTRODUCTION

- Major depressive disorder (MDD) is a serious and sometimes life-threatening condition with high rates of morbidity. Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may be hospitalized or attempt or commit suicide. MDD is considered the leading cause of disability worldwide and is associated with increased mortality rates; in the United States, over 16 million people are estimated to have depression *(Food and Drug Administration [FDA] Advisory Committee Spravato briefing document 2019)*.
- Approximately 30 to 40% of patients with MDD fail to respond to first-line treatments, including oral antidepressants (ADs) of all classes and/or psychotherapy. Patients who have failed at least 2 trials of AD treatment are generally considered to have treatment resistant depression (TRD). Relative to other patients with MDD, patients with TRD can experience more severe morbidity, with higher rates of hospitalization, suicidal ideation and behavior, and medical complications *(FDA Advisory Committee Spravato briefing document 2019)*.
- Standard of care measures for TRD include switching to a different AD (same or different class), adding an adjunctive treatment with a different mechanism of action, adding or switching psychotherapy, or procedures such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS). For patients with TRD, there are no compelling data that indicate one class of ADs is superior to others *(FDA Advisory Committee Spravato briefing document 2019, Thase and Connolly 2019)*.
- Spravato (esketamine) nasal spray is the S-enantiomer of racemic ketamine and was FDA approved for the treatment of TRD in March 2019. Like ketamine, esketamine is an N-methyl-D-aspartic acid (NMDA) receptor antagonist. Although ketamine has been investigated as a treatment modality to rapidly relieve TRD, the mechanism by which ketamine and esketamine exert their antidepressant effect is unknown. Currently, ketamine is only indicated for anesthesia *(FDA Web site, Thase and Connolly 2019)*.
- Prior to the approval of esketamine nasal spray, the only medication FDA-approved for TRD was Symbyax (olanzapine and fluoxetine). The only other FDA-approved interventions for TRD are device-related (ECT, TMS, vagus nerve stimulator [VNS]). Additional off-label pharmacological interventions for TRD include ketamine infusion and augmentation with other ADs or antipsychotics, lithium, thyroid hormone, or buspirone *(FDA Advisory Committee Spravato briefing document 2019)*.
- Medispan Class: N-methyl-D-aspartic acid (NMDA) Receptor Antagonist

INDICATIONS

- Esketamine is indicated, in conjunction with an oral AD, for the treatment of TRD in adults *(Spravato prescribing information 2019)*.
  Limitations of Use: Esketamine is not approved as an anesthetic agent. The safety and effectiveness of esketamine as an anesthetic agent have not been established.
- Esketamine is a Schedule III (CIII) controlled substance under the Controlled Substances Act with a potential for abuse and misuse.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The clinical trial development program for esketamine in TRD consisted of 3 unpublished, Phase 3, short-term, double-blind (DB), randomized studies (fixed dose [TRANSFORM-1], flexible dose [TRANSFORM-2], and flexible dose in patients ≥ 65 years of age [TRANSFORM-3]); 1 unpublished, long-term, DB, withdrawal, maintenance of effect study (SUSTAIN-1); and 1 unpublished, open-label, long-term safety study (SUSTAIN-2) *(FDA Advisory Committee Spravato briefing document 2019)*.

- As criteria for inclusion for all of the clinical trials, patients had failed at least 2 prior AD trials for the current episode of depression, and baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores, a 10-item instrument with total score ranging from 0 to 60 with a higher score indicating more severe depression, were required to be ≥ 28.
- Rather than randomizing severely ill patients to placebo alone, each study involved the addition of a new AD (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) at the same time that either esketamine or placebo was initiated. This ensured that all patients were receiving some form of active treatment.

- The evidence in support of esketamine's effectiveness primarily derives from the positive results of TRANSFORM-2 and SUSTAIN-1. The other studies failed to achieve statistical significance for their primary endpoints, although results were numerically better for the esketamine groups compared to placebo *(FDA Advisory Committee Spravato briefing document 2019)*.
- TRANSFORM-2 was a short-term, DB, placebo-controlled (PC), parallel-group (PG), multi-center (MC), flexible-dose, randomized controlled trial (RCT). Adults (ages 18 to 64) with TRD and experiencing moderate to severe symptomatology were randomized to intranasal esketamine 56 mg twice weekly for 4 weeks + a newly initiated oral AD daily (n = 114), or intranasal placebo + a newly initiated oral AD daily (n = 109). Patients could be titrated to esketamine 84 mg based on efficacy and tolerability. The primary endpoint was change from baseline (CFB) of the MADRS total score at Day 28 *(FDA Advisory Committee Spravato briefing document 2019).*
  - Patients treated with esketamine had statistically significantly greater improvement in depressive symptoms, as measured by the MADRS CFB at Day 28 vs placebo (see Table 1). The first key secondary endpoint, MADRS sustained response starting Day 2 through Day 28, was not statistically significantly different between the esketamine and placebo groups.
  - Although not statistically evaluated, the percentage of patients categorized as responders (≥ 50% MADRS reduction from baseline) and the percentage of patients achieving remission (MADRS score ≤ 12) were also reported (see Table 1).

Table 1. TRANSFORM-2 MADRS endpoints

Endpoint	Esketamine + oral AD n = 114	Placebo + oral AD n = 109
Baseline MADRS total score (SD)	37.0 (5.7)	37.3 (5.7)
LS mean CFB (SE) at Day 28	-19.8 (1.3)	-15.8 (1.2)
LS mean difference from placebo (SE) at Day 28 (1-sided p-value)	-4.0 (1.7) (p = 0.010)	N/A
MADRS sustained response starting Day 2	8% (p = 0.161)*	5%
	Esketamine + oral AD n = 101	**Placebo + oral AD n = 100**
MADRS responders at Day 28, n (%)	70 (69%)	52 (52%)
MADRS remitters at Day 28, n (%)	53 (53%)	31 (31%)

Abbreviations: LS = least squares, SD = standard deviation, SE = standard error
*Due to a fixed testing sequence, this was the only secondary endpoint that could be formally tested.

- SUSTAIN-1 was a DB, MC, randomized withdrawal trial in which patients were enrolled via transfer entry from the short-term trials (TRANSFORM-1 or TRANSFORM-2) (n = 268) or direct entry (n = 437). Patients received esketamine + an oral AD during an open-label optimization phase. At the end of the optimization phase, patients in stable remission and patients with stable response were randomized to continue esketamine + oral AD or to continue the oral AD but switch to placebo nasal spray for the variable duration maintenance phase. The primary endpoint was time to relapse, defined as MADRS total score ≥ 22 for 2 consecutive assessments, hospitalization for worsening depression, suicide attempt or completion, or any other clinically relevant event suggestive of relapse, among stable remitters during the maintenance phase *(FDA Advisory Committee Spravato briefing document 2019).*
  - For the primary endpoint, among stable remitters, 26.7% of patients in the esketamine + AD group and 45.3% of patients in the placebo + AD group experienced a relapse event during the maintenance phase. The median time to relapse was not estimable (NE) for the esketamine + AD groups, as the 50% relapse rate was not reached based on Kaplan-Meier estimates. The median time to relapse was 273.0 days (95% confidence interval [CI], 97.0 to NE) for the placebo + AD group. Esketamine + AD statistically significantly delayed relapse compared to placebo + AD (p = 0.003). The risk of relapse decreased by 51% in the esketamine + AD group compared to placebo + AD (estimated hazard ratio [HR], 0.49; 95% CI, 0.29 to 0.84).
  - Among stable responders, 25.8% of patients in the esketamine + AD group and 57.6% of patients in the placebo + AD group experienced relapse. The median time to relapse was 635 days (95% CI, 264 to 635) for the esketamine +

AD group and 88.0 days (95% CI, 46 to 196) for the placebo + AD group. Esketamine + AD significantly delayed relapse ($p < 0.001$) and decreased the risk of relapse by 70% (HR, 0.30; 95% CI, 0.16 to 0.55).

CLINICAL GUIDELINES

- For the treatment of MDD, guidelines from the American Psychiatric Association (APA) (2010) and the Veterans Affairs (VA)/Department of Defense (DoD) (2016) state that the effectiveness of AD medications is generally considered comparable between and within classes; therefore, the initial selection of an AD should be based on anticipated adverse effects (AEs), pharmacological properties of the medication, and additional individualized factors such as medication response in prior depressive episodes, cost, and patient preference *(APA 2010, VA/DoD 2016)*.
  - Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion are considered optimal first-line choices for most patients.
  - For patients demonstrating partial or no response to initial maximized pharmacotherapy, a switch to another monotherapy (medication from the same or different class or psychotherapy) or augmentation with a second medication is recommended.
  - For patients who do not adequately respond to medication therapy, ECT should be considered.
  - The VA/DoD guidelines currently recommend against the use of ketamine infusion outside of a research setting due to the limited information on its safety and duration of effect.

SAFETY SUMMARY

- Esketamine is contraindicated in patients with aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation and intracerebral hemorrhage.
- Esketamine has a boxed warning for sedation; dissociation; abuse and misuse; and suicidal thoughts and behaviors. Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, esketamine is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).
  - The goal of the esketamine REMS is to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by esketamine administration, and abuse and misuse of esketamine by:
    - Ensuring that esketamine is only dispensed to and administered in medically supervised healthcare settings that provide patient monitoring; patients must be monitored for at least 2 hours after administration of esketamine.
    - Ensuring that pharmacies and healthcare settings that dispense esketamine are certified.
    - Ensuring that each patient is informed about serious adverse outcomes from dissociation and sedation and the need for monitoring.
    - Enrollment of all patients in the REMS (registry) to further characterize the risks and support safe use.
- Additional warnings for esketamine include cognitive impairment, impaired ability to drive and operate machinery, and embryo-fetal toxicity.
- The most commonly observed AEs (incidence ≥ 5% and at least twice that of placebo + oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.

DOSING AND ADMINISTRATION

- Esketamine is intended for patient administration under the direct observation of a healthcare provider. Esketamine must never be dispensed directly to a patient for home use.

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Spravato (esketamine)	Nasal spray	Nasal	Induction Phase (Weeks 1 to 4): twice weekly Maintenance Phase: once weekly to every 2 weeks	• During and after esketamine administration at each treatment session, the patient must be observed for at least 2 hours until the patient is safe to leave.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• If baseline blood pressure is elevated (eg, > 140 mmHg systolic, > 90 mmHg diastolic), the risks of short-term increases in blood pressure and benefit of esketamine treatment should be considered.

See the current prescribing information for full details

CONCLUSION

- MDD, estimated to affect more than 16 million adults in the US, is a serious condition resulting in high rates of disability and morbidity. Comparatively, patients considered to have TRD can experience more severe morbidity, with higher rates of hospitalization, suicidal behavior, and medical complications. Guideline-recommended treatment includes switching ADs, augmenting with other ADs or antipsychotic medications, psychotherapy, and/or procedures such as ECT.
- Esketamine, an NMDA receptor antagonist, is indicated for TRD in adult patients in conjunction with an oral AD. In the 3 short-term, Phase 3, TRANSFORM trials, esketamine + AD demonstrated efficacy in decreasing MADRS score vs placebo + AD, although only TRANSFORM-2 resulted in statistical significance. In SUSTAIN-1, a long-term maintenance withdrawal trial, esketamine + AD statistically significantly delayed relapse vs placebo + AD in patients who had achieved stable remission or response while receiving esketamine + an oral AD.
- Due to safety concerns regarding sedation, dissociation, and risk of abuse and misuse, esketamine has a REMS program that mandates certification of dispensing pharmacies and administration settings, patient registry enrollment, and patient monitoring. Esketamine may only be administered in a healthcare setting under direct supervision by a healthcare provider.
- Esketamine provides an important treatment option with a different mechanism of action for patients with TRD who have exhausted appropriate oral ADs. However, esketamine carries the risk of serious AEs, an intensive REMS program, and strict administration and monitoring requirements. Safety, efficacy, and discontinuation data for long-term maintenance use of esketamine are currently limited.

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