Spravato™ (esketamine) – New drug approval

- On March 5, 2019, the FDA announced the approval of Janssen and J&J's Spravato (esketamine), in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.
  - Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.
  - Spravato is a Schedule III controlled substance.
  - Spravato is only available through a restricted program called the Spravato REMS. Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are also certified in the program.

- Patients with major depressive disorder (MDD) who, despite trying at least two antidepressant treatments given at adequate doses for an adequate duration in the current episode, have not responded to treatment are considered to have TRD. It is estimated that approximately one-third of U.S. adults with MDD have TRD.

- Spravato, the S-enantiomer of racemic ketamine, is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The exact mechanism by which esketamine exerts its antidepressant effect is unknown.
  - Ketamine is available as an injection and is approved as an anesthetic agent.

- The efficacy of Spravato was established in a 4-week study in 223 adult patients with TRD. Patients were randomized to receive twice weekly doses of intranasal Spravato or intranasal placebo. All patients also received open-label concomitant treatment with a newly initiated daily oral AD. The primary efficacy measure was change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase.
  - Spravato demonstrated statistical superiority on the primary efficacy measure vs. placebo (least-squares mean difference: -4.0; 95% CI: -7.3, -0.6).

- The efficacy of Spravato was also established in a long-term, maintenance-of-effect study in adults. Patients in this study were responders in one of two short-term controlled studies or in an open-label direct-enrollment study in an initial 4-week phase. After at least 16 initial weeks of treatment with Spravato and an oral AD, stable remitters and stable responders were randomized separately to continue intranasal treatment with Spravato or switch to placebo nasal spray, in both cases with continuation of their oral AD. The primary study endpoint was time to relapse in the stable remitter group.
  - Patients in stable remission who continued treatment with Spravato plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus an oral AD (Hazard Ratio [HR]: 0.49; 95% CI: 0.29, 0.84).
  - Time to relapse was also significantly delayed in the stable responder population (HR: 0.30; 95% CI: 0.16, 0.55).

- In addition, two studies were conducted to assess the effects of Spravato on driving skills; one study in 25 adult patients with MDD and one study in 23 healthy patients. On-road driving performance was assessed by the mean standard deviation of the lateral position (SDLP), a measure of driving impairment.
  - The effects of a single 84-mg dose of Spravato on next day driving and the effect of repeated administration of 84 mg of Spravato on same-day driving performance were evaluated in MDD patients. For the single dose treatment phase, an ethanol-containing beverage was used as a

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positive control. The SDLP after administration with Spravato was similar to placebo in the next day and repeated administration phases.
  - The effect of a single 84-mg dose of Spravato on driving in healthy patients was evaluated in a cross-over study with mirtazapine 30 mg as a positive control. The SDLP 8 hours after Spravato nasal spray administration was similar to placebo.

- Spravato carries a boxed warning for sedation, dissociation, abuse and misuse, and suicidal thoughts and behaviors.

- Spravato is contraindicated in patients with aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation, intracerebral hemorrhage, and hypersensitivity to esketamine, ketamine, or any of the excipients.

- Other warnings and precautions of Spravato include increased blood pressure, cognitive impairment, impaired ability to drive and operate machinery, ulcerative or interstitial cystitis, and embryo-fetal toxicity.

- The most common adverse reactions (≥ 5% and at least twice that of placebo plus oral AD) with Spravato use were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.

- Spravato should be administered intranasally under the supervision of a healthcare provider and the recommended dose of Spravato is as follows:

Treatment phase	Dosing frequency	Adult dose
Induction Phase	*Weeks 1 to 4:* Administered twice per week	Day 1 starting dose: 56 mg Subsequent doses: 56 or 84 mg
Maintenance phase	*Weeks 5 to 8:* Administer once weekly	56 mg or 84 mg
	Week 9 and after: Administer every 2 weeks or once weekly*	56 mg or 84 mg

* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response

  - Spravato should be administered in conjunction with an oral AD.
  - Blood pressure should be assessed prior to dosing with Spravato. After dosing, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted.
  - During and after Spravato administration at each treatment session, patients should be observed for at least 2 hours until the patient is safe to leave.

- Janssen plans to make Spravato available by the end of the month to certified treatment centers in accordance with the REMS. Spravato will be made available as an aqueous solution of esketamine in a vial within a nasal spray device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine.