

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211243Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
DIVISION OF PSYCHIATRY PRODUCTS

NDA/BLA #s: NDA 211243
Products: SPRAVATO (esketamine hydrochloride)
APPLICANT: JANSSEN PHARMACEUTICALS INC
FROM: Marc Stone, M.D., Deputy Director for Safety
DATE: *see DARRTS date stamp*

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for SPRAVATO to ensure that the benefits of the drug outweigh the risks of misuse, abuse, and potential serious adverse outcomes from sedation, and dissociation. In reaching this determination, we considered the following:

- A. The estimated number of patients in the United States with treatment-resistant depression (TRD) is 17.5 million in the United States (US). This estimate is based on World Health Organization. Depression and other common mental disorders. Global health estimates. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.
- B. Treatment-resistant depression is particularly difficult to treat and is associated with high morbidity and mortality. Patients with TRD are more likely to have lower remission rates, pronounced functional impairment, a substantially lower quality of life, higher suicide rates, and to incur higher medical and mental healthcare costs compared with patients with non-treatment-resistant major depressive disorder (MDD).

- C. Application for NDA includes five pivotal Phase 3 studies in TRD: three short-term studies, one randomized withdrawal, maintenance of effect study; and one long-term safety study. In addition, supportive data from a Phase 2 dose response study in adults with TRD; and a Phase 2 proof-of-concept study in the related condition of MDD with imminent risk for suicide. Data from the Phase 3 studies demonstrate that treatment with esketamine nasal spray plus a newly initiated oral antidepressant compared to placebo nasal spray plus a newly initiated antidepressant was associated with a rapid reduction of depressive symptoms and a delayed time to relapse of symptoms of depression.
- D. SPRAVATO, is the S-enantiomer of racemic ketamine, is being approved as a nasal spray formulation for the treatment of patients with TRD with chronic dosing for maintenance either weekly or every other week.
- E. SPRAVATO, poses serious risks of misuse, abuse and serious adverse outcomes from sedation and dissociation.
- F. SPRAVATO is not a new molecular entity.

The elements of the REMS will be elements to assure safe use (including pharmacies, practitioners, or health care settings that dispense the drug are specially certified, the drug is dispensed to patients only in certain health care settings, the drug is dispensed to patients with evidence or other documentation of safe-use conditions, each patient using the drug is subject to certain monitoring, and each patient using the drug is enrolled in a registry), an implementation system, and a timetable for submission of assessments of the REMS.

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/s/

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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
PDUFA Goal Date	March 4, 2019
OSE RCM #	2018-1874
Reviewer Name(s)	Somya Dunn, MD
Team Leader	Selena Ready, Pharm.D, DRISK
Division Director	Cynthia LaCivita, Pharm.D, DRISK
Review Completion Date	March 4, 2019
Subject	Evaluation of Need for a REMS
Established Name	Esketamine nasal spray
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation(s)	28 mg esketamine solution drug-device combination for intranasal (IN) administration
Dosing Regimen	Two treatment sessions/week: Starting Day 1 dose of 56 mg Subsequent doses: 56 mg or 84 mg Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary for Spravato, esketamine nasal spray, single entity drug-device combination product, to ensure the benefits outweigh its risks. Janssen Pharmaceuticals, Inc (Applicant) submitted a New Drug Application (NDA) 211243 with the proposed indication for treatment-resistant depression (TRD) in adults. Esketamine is the S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

The risks associated with esketamine are consistent with ketamine, such as misuse, abuse, sedation and dissociation. The Agency is particularly concerned about misuse, abuse and adverse outcomes that may result from the sedation and/or dissociation. DRISK has determined that a REMS with ETASU is needed to ensure the benefits of esketamine nasal spray outweigh its risks of misuse, abuse, and serious adverse outcomes from sedation and dissociation. The Spravato REMS will ensure that healthcare settings and pharmacies are certified and do not dispense Spravato directly to patients for home use. The healthcare setting will certify that a healthcare provider will be present to monitor the patient for at least two hours after self-administering their dose, the patient is counseled on the risks and the need for monitoring, and enrolled into the registry. The patient registry will aid in the collection of serious adverse events related to the REMS risks to help characterize and monitor the safe use of the drug.

The Applicant's amended REMS submission received March 4, 2019 has included all the necessary changes communicated on February 1, 2019, February 26, 2019, February 28, 2019, and March 3, 2019. DRISK is recommending approval of the Spravato REMS.

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure the benefits outweigh its risks for Spravato, a single entity drug-device combination product with esketamine. Janssen Pharmaceuticals, Inc (Applicant) submitted a New Drug Application (NDA) 211243 for Spravato proposed for treatment-resistant depression. This application is under review in the Division of Psychiatry Products (DPP). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Esketamine is not a new molecular entity¹ and is the S-enantiomer of ketamine, an N-methyl-D-aspartate glutamate (NMDA) receptor antagonist that enhances glutamine release in the brain. Spravato is a drug-device combination of esketamine for intranasal (IN) administration. The esketamine drug

¹ Section 505-1(a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

product is a clear and colorless solution of esketamine HCl in water at a concentration of (b) (4) mg/mL and an esketamine base equivalent concentration of (b) (4) mg/mL. The device is a nasal spray solution with one formulation containing 28-mg designed to be a single-use nasal spray device.

The FDA previously approved ketamine (under NDA 16812 as Ketalar) for use as a rapid-acting general anesthetic in February 1970, administered in solution form for use either intravenously (IV) or intramuscularly (IM). Esketamine is not approved in the U.S. but it has been approved for use as an IV or IM anesthetic in Europe and South America. Neither ketamine or esketamine are approved for any psychiatric indication worldwide. Ketamine has been studied for use in major depressive disorder (MDD) and several other psychiatric indications and it has been reported that ketamine is being prescribed and administered off-label for those indications.²

The Applicant proposes esketamine nasal spray for intranasal use for the treatment of treatment-resistant depression (TRD). TRD is defined as a lack of clinically meaningful improvement in depressive symptoms after treatment with at least two different oral antidepressant medications taken at adequate doses for at least 6 weeks for the current depressive episode.

The proposed dosing regimen for Spravato was initially intranasal twice a week for an initial four-week induction period in addition to a newly initiated oral antidepressant. The Applicant proposed initial dose was 28 to 56 mg at each administration (one or two sprays), this was to be titrated to 84 mg by the second week. The Applicant proposed further treatment on a weekly basis for an additional four-week (b) (4) and then weekly or every other week during an ongoing maintenance phase. However, the dosing regimen that is being considered during the review process is an induction phase with a starting dose of 56 mg as utilization of the 28 mg dose was not found effective. Subsequent doses from week one through four would be 56 mg or 84 mg twice weekly. Then at weeks five to eight, 56 mg or 84 mg once weekly and from week nine and thereafter administer 56 mg or 84 mg every two weeks or once weekly.³

NDA 211243 has been granted FDA Breakthrough Therapy and has a designated priority review.

2.2 DRISK REVIEWS CONTRIBUTING TO THIS ORIGINAL APPLICATION

- Dunn, S. Division of Risk Management Review of the Spravato REMS materials and Supporting Document, submitted to DARRTS February 1, 2019.
- Dunn, S. Division of Risk Management Review of the Spravato REMS materials and Supporting Document, submitted to DARRTS February 25, 2019.

² Kavalali ET, Monteggia LM. Synaptic mechanisms underlying rapid antidepressant action of ketamine. *Am J Psychiatry* 2012;169(11):1150-6.

³ Section 505-1(a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- Dunn, S. Division of Risk Management Review of the Spravato REMS materials and Supporting Document, submitted to DARRTS February 28, 2019.
- Dunn, S. Division of Risk Management Review of the Spravato REMS materials and Supporting Document, submitted to DARRTS March 3, 2019.

2.3 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209819 relevant to this review:

- 11/7/2013: Spravato is granted Breakthrough Therapy.
- 6/28/2018: The Pre-NDA meeting was held and the Applicant was told that although the need for a REMS would be a review issue, the distribution scheme proposed in the pre-meeting package closely resembled a REMS with ETASU and they were encouraged to submit a proposed REMS with their application.
- 9/4/2018: NDA 211243 was submitted and the application included a REMS proposal. The proposal included a restricted distribution with use of specialty distributors and/or specialty pharmacies to ship Spravato directly to sites of care. (b) (4)
- 11/20/2018: FDA sent an Information Request to the Applicant asking them to describe how they plan to implement their distribution scheme and informing them that their REMS should be designed to mitigate identified adverse events or potential adverse events. We communicated that we were concerned about the sedation, dissociation and elevated blood pressure observed in the clinical program and were considering a REMS to mitigate these risks.
- 11/30/2018: The Applicant sent a response (Seq 0023) clarifying the distribution scheme and providing preliminary feedback on the risks identified in their proposal. They communicated that they planned to submit a revised REMS proposal on 12/14/2018 and at that time they would (b) (4).
- 12/14/2018: (b) (4)
 (b) (4)
 (b) (4) The Applicant amended their REMS submission with a proposed a REMS with outpatient healthcare setting certification (Seq 0028). Their proposed goal was:

The goal of the (b) (4) REMS is to mitigate the (b) (4)

(b) (4)

- 1/8/2019: The Agency and Applicant held a teleconference to discuss the upcoming advisory committee meeting where the Agency informed the Applicant that although the REMS was still under review, the Agency proposed REMS would consist of healthcare setting enrollment, patient monitoring and a patient enrollment with registry. The Agency also stated that the REMS would include the risk of sedation due to the concerns of adverse outcomes that could result from sedation.
- 2/1/2019: The Agency provided comments on the Applicant REMS materials. The Applicant was provided with a draft REMS goal and request to design materials to support a REMS program that would include the elements described at the 1/8/2019 meeting.
- 2/12/2019: The Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee was held. The Applicant proposed a REMS program that contained elements similar to what the Agency conveyed to the Applicant on 2/1/2019. The committee voted to approve the drug 14 yes to 2 no and 1 abstained vote. The committee generally believed that their application was adequate efficacy and safety data and that the Agency proposed REMS program would mitigate the risks of misuse, abuse and adverse outcomes from sedation and dissociation. 2/15/2019: The Applicant submitted revised REMS materials to support the REMS they proposed at the PDAC and DSaRM AC (Seq 0040).
- 2/19/2019: The Applicant and Agency had a teleconference to discuss the details of the REMS program, including the timing of the frequency of the Patient Monitoring Form and what information would be captured by the registry.
- 2/26/2019: The Agency provided the Applicant feedback on the materials submitted on 2/19/2019.
- 2/28/2019: The Applicant submitted revised REMS materials in response to Agency feedback on 2/26/19 (Seq 0044).
- 2/28/19: The Agency provided feedback on the revised REMS materials submitted on 2/28/19.
- 3/1/2019: The Applicant amended their submission and submitted materials in response to the 2/28/2019 Agency comments and edits (Seq 0045).
- 3/3/2019: The Agency provided feedback on the revised REMS materials submitted on 3/1/19.
- 3/3/2019: The Applicant amended their submission and submitted materials in response to the Agency comments and edits on 3/3/2019 (Seq 0046).
- 3/4/2019: The Applicant amended their submission to correct minor editorial errors and submitted the full REMS (Seq 0047).

3 THERAPEUTIC CONTEXT AND TREATMENT OPTIONS

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Major depressive disorder (MDD) is a life-threatening, chronic condition.⁴ Over 16 million people in the United States have depression.^{5, 6} Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized or attempt or commit suicide. MDD is considered the leading cause of disability worldwide and also is associated with increased mortality rates with a median rate of 10 years of life lost.⁷ About 30 to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all classes, this includes selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and/or psychotherapy.⁸ Patients who have failed at least two trials of antidepressant treatment generally comprise the population with TRD. Relative to other patients with MDD, patients with TRD experience more severe morbidity with higher rates of hospitalization, suicidal ideation and behavior, and medical complications. There is currently only one pharmacotherapy approved for TRD.

Table 1 Summary of FDA-Approved Treatments for Treatment-Resistant Depression

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Regulatory Body
FDA Approved Treatments						
Symbyax (Fluoxetine plus Olanzapine)	TRD	Dec 2003	Oral daily	MADRS Total Score Change from Baseline of -16 vs. olanzapine -12 and placebo -10 for Study 1, -18 vs. -14 and -9 for Study 2	Olanzapine is an antipsychotic associated with weight gain, hyperglycemia, and EPS/akathisia	CDER
Electroconvulsive therapy (ECT)	TRD (associated with either MDD or Bipolar)	1976 (updated Dec 2015)	Bitemporal or unilateral temporal; up to 3 times a week for 6 to	Not available; approval based on various studies from research	Memory concerns, use of general anesthesia	CDRH

⁴ Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease condition that is to be treated with the drug.*

⁵ World Health Organization. Depression and other common mental disorders. Global health estimates. (Geneva: World Health Organization; 2017.)

⁶ Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

⁷ Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry.* 2015;72:334-341.

⁸ Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163:1905-1917.

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Regulatory Body
	Disorder)		10 treatments initially	literature.		
Transcranial Magnetic Stimulation (TMS)	TRD (only failed 1 antidepressant)	2008	Transcranial; up to daily for 4 to 6 weeks initially (20 to 30 sessions)	MADRS Total Score Change from Baseline of -6 at Week 4 and Week 6 active TMS vs. -4 at Week 4 and Week 6 sham TMS. Approval based on post-hoc analysis and responder/remission rates.	No major safety issues, limited long-term safety data	CDRH
VNS	TRD	July 2005	Once (surgical implant)	12-week sham placebo-controlled study not statistically significant. Approval was based on long-term open-label HAM-D responder data (30% response in 1 year versus 13% treatment as usual). 12-week open-label pilot study showed 34% MADRS responders.	Surgical intervention risks (allergies, infection, etc.)	CDRH

Table 1 describes treatments available for TRD, Source: Jean Kim and Qi Chen Spravato Clinical Review, Table 1, March 4, 2019.

There are off-label pharmacological interventions for TRD. These include ketamine and augmentation of current therapy with other antidepressants or antipsychotics, lithium, thyroid hormone and buspirone. In addition, there are FDA-approved drugs for adjunctive therapy for partial response in MDD: quetiapine XR, aripiprazole, and brexpiprazole. The adjunctive therapy indication applies to patients

who have insufficient but partial response to their current oral antidepressant. There is an unmet need to provide treatment options for patients with TRD.⁹

4 BENEFIT ASSESSMENT¹⁰

The clinical program for NDA 211243 consisted of four main efficacy phase 3 studies which were randomized controlled trials. Three of them (3001, 3002, 3005) were short-term parallel-group design, and one (3003) was a randomized withdrawal maintenance-of-effect design. These studies compared IN Spravato and IN placebo added to one of four newly initiated oral antidepressants (duloxetine, venlafaxine XR, escitalopram, or sertraline). Each of these oral antidepressant therapies were dosed daily and titrated to therapeutic doses over the course of one to two weeks beginning at the start of the treatment phase (except for duloxetine which stayed at the same dose). For the first four weeks of treatment, the double-blind phase of the parallel-group studies, the nasal spray was administered twice weekly. For the maintenance-of-effect Study 3003 and for long-term open-label safety studies, Spravato was administered weekly for the next four weeks post-induction phase, then either weekly or every other week for ongoing maintenance

The primary outcome measure used for the studies was the Montgomery-Asberg Depression Rating Scale (MADRS). Scales were administered on study visit days prior to Spravato or placebo dosing and were meant to assess symptoms over the previous seven days. In two studies, one parallel-group study, 3002, and the randomized withdrawal study 3003, Spravato was statistically superior to placebo on the study's primary efficacy endpoint (p=0.010 and p=0.003 respectively); in the other two short-term parallel group studies (3001 and 3005), Spravato was not statistically superior. DPP had concerns regarding the results from studies that were considered to have positive outcomes, 3002 and 3003, in terms of secondary endpoint analyses and unblinding of patients that they are considering may have affected results. These concerns were discussed at the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee on February 12, 2019. The committee voted in favor that the Applicant had provided adequate efficacy data (voting 14 yes, 2 no, 1 abstain).

5 RISK ASSESSMENT & SAFE-USE CONDITIONS

A total of 1708 subjects with TRD received at least one Spravato treatment in a total of six completed phase 2 and 3 studies. The review team identified sedation, dissociation, and increased blood pressure as the primary safety concerns. Cognitive function impairment, liver function impairment, and interstitial or ulcerative cystitis have been reported in post marketing data for ketamine, but was not seen in the in the Spravato clinical trials.

⁹ Section 505-1 (a) of the FD&C Act: *FDAAA (C): The expected benefit of the drug with respect to such disease or condition.*

¹⁰ Kim J, Chen Q. FDA Clinical Review of NDA 211243 esketamine. March 4, 2019.

There were six deaths in the clinical program and all occurred in Spravato-treated subjects. Three of these deaths were by suicide—two after the patient’s last dose of Spravato (12 and 20 days), and one four days after the patient’s last dose of Spravato. Due to the small number of cases, the severity of the underlying illness, and the lack of a pattern with the cases, the FDA clinical safety reviewer, Dr. Qi Chen, did not determine that these deaths were drug-related.

Serious adverse events (SAEs) were reported in subjects treated with Spravato than placebo. The SAEs of depression and suicidal ideation were reported with higher incidence in subjects treated with Spravato than placebo in one of the studies, 3001. There was no obvious difference between the Spravato and placebo groups with other SAEs.

Patients experienced greater mean increases in systolic and diastolic blood pressure (SBP and DBP) in Spravato-treated groups compared to placebo. The observed changes in blood pressure generally resolved in less than four hours without clinical intervention and in most cases, the highest SBP was observed at the 40 minute check. Dr. Chen found that in 10 to 20% of visits, the highest observed SBP increase of at least 10 mmHg was at 1.5 hours post dose. Blood pressure showed consistent mean elevations 40 minutes post-dose (about 15 mm Hg SBP and 9 mm Hg DBP) around twice that seen on placebo (7 mm Hg SBP and 5 mm Hg DBP), with slightly higher BP increases in 84-mg versus 56-mg Spravato doses. The Division of Cardiovascular and Renal Products were asked to evaluate the blood pressure data from the clinical trials. In their review they noted that some patients experienced a substantial increase in blood pressure in the first 1.5 hours after dose administration. The reviewer, Dr. McDowell noted that in two of the phase 3 studies, 9.8% of patients treated with Spravato versus 1.4% of placebo treated patients had ≥ 40 mmHg increase in systolic blood pressure.¹¹

Adverse events involving the lower urinary tract occurred at higher rates in Spravato treated patients, at 6-10% compared to 1-3% in placebo in studies 3001 and 3002 (subjects < 65 years old), and 7% in Spravato vs. 4% in placebo in Study 3005 (subjects ≥ 65 years old). Although ketamine is associated with interstitial and ulcerative cystitis observed post-market in individuals who abuse ketamine, no cases of interstitial or ulcerative cystitis were observed in the clinical program. However, numerous subjects had mild urinary tract symptoms (32 patients treated with Spravato in the placebo controlled phase 3 studies versus 9 placebo treated patients) such as bladder discomfort and dysuria that could be associated with interstitial or ulcerative cystitis. Assessment of data within the FDA Adverse Event Reporting System (FAERS) and the published literature suggests a likely causal relationship between repeated ketamine exposure and the onset of genitourinary adverse events (e.g., cystitis). This is further described in the FDA PDAC and DSaRM AC Background Document Division of Pharmacovigilance (DPV) Review.¹²

¹¹ McDowell, Tzu-Yun. FDA DCRP Consult for NDA 211243 esketamine. Jan 24, 2019.

¹² FDA Briefing Document Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting February 12, 2019. Section 7.7, Downloaded from <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm630168.htm>

Also described in the DPV section of the AC Background Document, the Agency also reviewed a number of small studies (i.e., randomized controlled trials and observational studies) which suggested that subanesthetic doses of ketamine may have negative short-term effects on memory and cognitive function.

Due to the transient increases in blood pressure, Spravato will be contraindicated in patients that have a history of vascular disease. Warnings and Precautions will also address this risk along with unknown potential long-term cognitive effects, ulcerative cystitis and bladder effects. (b) (4)

5.1 POTENTIAL SERIOUS RISK OF SPRAVATO

The Agency is concerned that patients will experience serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration. The Agency also has concerns regarding potential misuse and abuse.

5.1.1 Sedation

In the clinical development program, sedation was observed at high rates in the treatment population with about 50% Spravato-treated patients experiencing sedation versus 15% in placebo-treated patients. Of the patients treated with Spravato in the phase 3 studies (n=1051), 24 participants experienced severe sedation after Spravato use. Severe sedation was defined by scores of 0-2 out of 5 total on the Modified Observer's Alertness/Sedation scale (MOAA/S) scale; on this scale 0 was patient response only to painful stimulus, 1 is patient response only after painful stimulus and 2 corresponded to response only after mild prodding or shaking. The majority of patients had onset of sedation within 15-30 minutes after Spravato administration; this peaked around 30-45 minutes and in most cases resolved (MOAA/S score of 5 corresponding to fully awake) by one hour and 15 minutes after administration. The Agency has been concerned that if Spravato is approved for TRD, patients who take Spravato are at risk for sedation and could be impaired and unable to perform certain gross motor tasks for a period of time after receiving their dose. Since nausea and vomiting was also seen at a high rate in the phase 3 clinical program in patients treated with Spravato versus placebo (nausea 27% in Spravato treated patients versus 7% in placebo and vomiting 2% in placebo versus 9%), Dr. Chen is also concerned about possible aspiration in sedated patients, though this was not observed in the clinical program.

The Boxed Warning in the label will include a warning that patients are at risk for sedation and after administration of Spravato and because of this risk, patients must be monitored for at least two hours after their dose. This risk is also included in Warnings and Precautions.

5.1.2 Dissociation

Spravato administration was also associated with dissociation. This was described in the clinical program with various terms including feeling "spacey" or a sensation of "floating." As part of the dissociation, patients experienced visual disturbances, had trouble speaking, and experienced confusion, numbness, and feelings of dizziness/faintness. In the clinical program, the Applicant also described the dissociative effects as perceptual changes include distortion of time and space, illusions, derealization, and depersonalization. Resolution of these symptoms generally occurred about one and a half hours after administration. Similar to the risks with sedation discussed above, patients would be at risk for potential

accidents if they experienced these dissociative effects and were allowed to leave the health care setting prior to resolution of these symptoms. In the clinical trials, patients were observed by a healthcare professional after Spravato dosing and did not leave the clinical site until they were clinically stable, and symptoms had resolved.

The dissociative sensations experienced in the Spravato program are known effects of ketamine.

The Boxed Warning in the label will include a warning that patients are at risk for dissociation and after administration of Spravato and because of this risk, patients must be monitored for at least two hours after their dose. This risk is also included in Warnings and Precautions.

5.1.3 Misuse and Abuse

Ketamine is classified as a Schedule III substance under the Controlled Substances Act. Ketamine is misused and abused for its dissociative and hallucinogenic effects. In the clinical program, Spravato was self-administered under medical supervision in healthcare settings; misuse and abuse were not observed. However, the potential for misuse and abuse remains a concern, especially if the distribution of Spravato was not restricted and Spravato was available in retail pharmacies for use outside of a healthcare setting. In the clinical program, Spravato was self-administered under supervision in a medically monitored setting; therefore, abuse and misuse of Spravato was not observed. However, as described in Dr. Amy Seitz's review from the FDA Office of Surveillance of Epidemiology, Division of Epidemiology review, ketamine is abused in the general population as national survey data and the published literature indicate that ketamine abuse occurs with a reported lifetime prevalence of 1.3% among persons age 12 years and older. This rate is lower than that for other hallucinogens such as ecstasy and lysergic acid diethylamide (LSD or Acid). Exposure calls to U.S. poison centers involving ketamine abuse or misuse declined slightly from 2013 to 2017 (176 calls in 2013 to 116 calls in 2017), despite the growth in non-veterinary ketamine sales. From 2015 to 2017, FAERS received 17 reports of death involving ketamine abuse. Only one of these reports listed ketamine as the only drug, and the drug-event causal association has not been assessed for any of these FAERS cases. Dr. Seitz's analysis suggests that ketamine abuse continues to occur but has remained "limited with modest associated harms." Because ketamine is a controlled substance abused for dissociative properties and there is a concern that Spravato may also be abused or misused for this purpose.¹³

6 EXPECTED POSTMARKET USE

During the clinical development period, Spravato was self-administered by TRD patients under supervision by a healthcare provider (HCP). The Applicant has proposed self-administration in supervised healthcare settings. Spravato was not studied or evaluated for self-administration in home settings. Treatment is likely to occur in private healthcare offices, outpatient clinics and larger healthcare settings such as hospitals. DPP is considering, based on their experience, that patients with TRD are more likely to be seen and managed by psychiatrists; however, MDD is very common and

¹³ Seitz, A. FDA Drug Abuse Epidemiology Review NDA 211243 esketamine. February 14, 2019.

treated by other medical specialties, the majority being primary care providers.¹⁴ The likely prescribers may be diverse with regard to medical specialty.

7 DISCUSSION OF NEED FOR A REMS

The Clinical Reviewers, Dr. Kim and Dr. Chen, recommend approval of Spravato with a REMS based on the efficacy and safety information currently available. The PDAC and DSaRM AC on 2/12/2019 also voted in favor of approval 14:2:1. Spravato was self-administered by patients in clinical settings in the development program and as such, misuse and abuse were unlikely to occur. Restricting administration of Spravato to a clinical setting will mitigate the risk of misuse and abuse by patients and provide monitoring of patients until they are clinically stable and able to leave the healthcare setting.

The Agency is very concerned that patients will have motor or cognitive impairment due to the sedation and dissociation that occurs as a result of Spravato administration. Due to the aforementioned risks, a REMS is necessary to ensure the benefits outweigh the risks of Spravato. The REMS would ensure that Spravato is administered under supervision of a HCP that can monitor patients for two hours after they receive their dose. The PDAC and DSaRM AC expressed concern over potential misuse and abuse and agreed that a REMS would be needed. They discussed the possibility of sites that would divert the product and were largely in favor of restricted distribution. Some committee members were concerned about maintaining strict standards on requirements for the settings. Other committee members expressed concern that patients with the debilitating and life-threatening disease of TRD may have difficulty accessing the product and felt that most practitioners could manage the monitoring needed for patients receiving Spravato and requirements on healthcare settings should not be too exclusive for REMS program enrollment. The proposed REMS, discussed below addresses the of sedation, dissociation, misuse and abuse.

8 RISK MANAGEMENT ACTIVITIES PROPOSED BY THE APPLICANT

The Applicant proposed a REMS with ETASU to ensure that Spravato is administered in a healthcare center and not dispensed directly to patients. They proposed a REMS after encouraged to do so at the Pre-NDA meeting where they had proposed a distribution scheme that was similar to a REMS program. The initial REMS proposal with the NDA did not consist of clear ETASU or any REMS materials. However after discussion with Applicant (see Section 2.2), they submitted a more complete proposal with outpatient healthcare setting certification in order to have patients monitored until they were clinically stable to leave the setting. After further discussion and alignment, the Applicant amendment their proposed REMS on March 3, 2019 is the subject of this review. The proposed REMS includes ETASU, and implementation plan and timetable for submission of assessments.

8.1 REVIEW OF APPLICANT'S PROPOSED REMS

8.2 REMS GOALS

¹⁴ Mark, TL, Levit, KR, Buck, JA. Psychotropic drug prescriptions by medical specialty. *Psychiatr Serv.* 2009;60(9):1167.

The sponsor has amended their goals based on comments and discussions with the Agency (See section 2.3, regulatory history). The proposed goals are listed below.



The goal represents the main safety concerns with Spravato. The serious adverse outcomes from sedation and dissociation are the most concerning risks with Spravato as the Agency has concerns that patients may be at risk for accidents after receiving their dose if they leave the health care setting prior to resolution of these symptoms. Since patients must be treated within a healthcare, the risk of abuse and misuse is also mitigated as Spravato should not leave the healthcare setting with a patient.

Reviewer comments: The proposed goals are acceptable.

8.3 REMS REQUIREMENTS-ETASU

The proposed REMS submitted on March 4, 2019 includes ETASU with the following requirements: (B) pharmacies and other healthcare setting that dispensed the drug are specially certified, (C) the drug be dispensed to patients only in certain healthcare settings, (D) patient be dispensed in the drug only with evidence or documentation of safe use requirements, (E) each patient using the drug be subject to certain monitoring and (F) each patient using the drug be enrolled in a registry.

The Agency has determined that all sites receiving product from the wholesaler/distributor should be certified and enrolled. This will ensure that in each case, under the various healthcare settings, there will be processes and procedures in place to ensure that dispensing staff are aware that Spravato cannot be given directly to patients, patients require at least two hours of monitoring after they self-administer their dose, patients are aware of the risks and must be enrolled in a registry. To assist healthcare providers with understanding the requirements of the REMS, the Agency is requiring a Fact Sheet that explains how obtain Spravato and in order to outline the basic REMS requirements.

8.3.1 Pharmacy Certification

The Agency and Applicant agree that pharmacies that dispense Spravato must be certified in order to ensure that it is not dispensed directly to patients and thereby preventing misuse and abuse by patients or others who could gain access to esketamine if it were available in the home, and supports restricting Spravato to certified healthcare settings. The pharmacy will be required to maintain dispensing records that will be subject to audit to ensure all patients who are dispensed Spravato are enrolled. For the full list of requirements refer to the REMS document and the pharmacy enrollment form.

8.3.2 Healthcare Setting Certification

The Agency and Applicant agree that healthcare settings must be certified to ensure that Spravato is self-administered by the patient under the direct supervision of a HCP and patients are monitored by a HCP for at least two hours after they self-administer their dose. The healthcare setting will need to appoint an authorized representative, who will be responsible for ensuring that the healthcare setting is able to meet all the REMS requirements. Patients must be enrolled into the REMS program prior to each Spravato administration. In addition to the enrollment form the Healthcare setting must complete a patient monitoring form for each patient after every dose and submit it to the REMS within 7 calendar days. The healthcare setting must have a prescriber onsite during Spravato administration and monitoring, have a healthcare provider(s) onsite to monitor each patient for at least 2 hours following administration of Spravato for resolution of sedation, dissociation and changes in vital signs. They must also ensure that Spravato is not dispensed for use outside the healthcare setting.

For a full list of the requirements please see the REMS document and healthcare setting enrollment form.

The healthcare setting will be required to maintain dispensing records that will be subject to audit to ensure all patients who are dispensed Spravato are enrolled in the registry.

8.3.3 Patient Monitoring

Due to the risks of adverse outcomes from sedation and dissociation, patients must be monitored for at least two hours¹⁵ after self-administering Spravato. The patient cannot leave the healthcare setting until these effects resolve in order to prevent accident, injury or cognitively impaired behavior. Patients will be counseled that they should make arrangements to safely leave the healthcare setting and get home (e.g. be accompanied or make arrangements for transportation when they leave the site).

8.3.4 Safe Use Conditions

The safe use conditions will ensure that patients are informed of and counseled about the risk of adverse outcomes from sedation and dissociation that may be associated with Spravato, informed of the monitoring requirements and enrolled into the REMS.

8.3.5 Patient Registry

All patients are enrolled in the registry prior to receiving their first dose of Spravato. Baseline health information on patients will be captured at the time of enrollment and with subsequent doses using the monitoring form to better characterize the risk and safe use. The monitoring form will collect adverse events that require intervention during the patients stay in the facility and capture events that may be related to the drug that occurred in between patient visits. Serious adverse events that require medical intervention or lead to hospitalization are of particular interest. This form will also capture monitoring times and changes in vital signs. Clinically important drug interactions have not been studied with esketamine, concomitant medications that are included in labeling that can potentiate sedation are

¹⁵ The Applicant initially proposed (b) (4) for the monitoring period. The 2 hour time period reflects DPP clinical reviewer recommendations and the label.

listed on the form. This form will serve to inform both the Applicant and the Agency about signification variations in resolution of sedation and dissociation and to further characterize the risks and support safe use.

After discussions with our colleagues in the Division of Epidemiology we did not establish an *a priori* data collection stop date for the registry because there was not enough information to quantify the amount of REMS registry data that would be informative. This can be assessed with future REMS assessments reports.

8.3.6 Implementation System

The Applicant has proposed to include an implementation system including establishing and maintaining a validated and secure database of all REMS participants who are enrolled and/or certified in the REMS program, a Spravato REMS coordinating center, and a Spravato REMS website

8.3.7 Timetable for Submission of Assessments

The REMS includes a timetable for submission of assessments to the FDA at 6 months and 12 months post approval of the REMS and annually thereafter from the date of the initial approval of the Spravato REMS.

8.4 REMS MATERIALS

The Applicant submitted the required materials with the necessary information. These include:

- Spravato REMS Dear Healthcare Provider Letter - letters to be sent to the healthcare providers likely to prescribe and dispense Spravato to describe the risks and the REMS
- Spravato REMS Fact Sheet—this material details the process for obtaining Spravato and the REMS requirements
- Spravato REMS Pharmacy Enrollment Form
- Spravato REMS Healthcare Center Enrollment Form
- Spravato REMS Patient Enrollment Form
- Spravato REMS Patient Monitoring Form

Reviewer comments: *The materials amended and submitted on March 4, 2019 are acceptable.*

8.5 REMS ASSESSMENT PLAN

The Applicant and the Agency agree on the proposed REMS Assessment Plan for Spravato to include the following for the reporting period:

The SPRAVATO™ REMS Assessment Plan includes, but is not limited to, the following:

1. REMS Program Implementation (6-month and 1-year assessments only)

- a. Date of first commercial distribution of SPRAVATO
 - b. Date when the SPRAVATO REMS website became live and fully operational
 - c. Date when healthcare settings could become certified
 - d. Date when pharmacies could become certified
 - e. Date when patients could become enrolled
 - f. Date when the REMS coordinating center was established and fully operational
2. REMS Outreach and Communication (6-month, 1-year, and 2-year assessments)
 - a. Sources of the distribution list of healthcare providers
 - b. Number of healthcare providers targeted
 - c. The date(s), number, and medical specialty of healthcare providers who were sent the *REMS Letter for Healthcare Providers* by method of distribution
 - d. The number of mailings returned or undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
3. REMS Program Operation and Performance Data (per reporting period and cumulatively)
 - a. REMS Website
 - i. Number of visits and unique visits to the REMS Program website
 - ii. Number of REMS materials downloaded or printed for each material
 - b. REMS Coordinating Center
 - i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, healthcare settings, wholesaler/distributors, other)
 - ii. Summary of reasons for calls (e.g., enrollment question, location of a certified healthcare setting) and by reporter (authorized representative, healthcare setting, patient/caregiver, other)
 - iii. Summary of frequently asked questions (FAQ) by stakeholder type
 - iv. Summary report of REMS-related problems identified and resulting corrective actions
4. REMS Enrollment Statistics (per reporting period and cumulatively)
 - a. Certified Healthcare Settings

- i. Number of newly enrolled and active healthcare settings (active settings are those that have received SPRAVATO) stratified by type of healthcare setting (e.g., group practice, independent practice, outpatient clinic, hospital, mental health facility, long-term care, other), and geographic region
 - ii. Number of healthcare settings that dispensed SPRAVATO for administration stratified by type of healthcare setting and geographic region
 - iii. Healthcare settings that were unable to become certified and reason
 - b. Certified Pharmacies
 - i. Number of newly enrolled and active pharmacies (have received SPRAVATO) stratified by type of pharmacy (e.g., Specialty, Clinic, Outpatient, Hospital, Mental Health Facility, other) and geographic region
 - ii. Number of certified pharmacies that dispensed SPRAVATO stratified by type of pharmacy, and geographic region
 - iii. Pharmacies that were unable to become certified and reason
 - c. Enrolled Wholesalers/distributors
 - i. Number of newly enrolled and active wholesalers/distributors (have shipped SPRAVATO)
 - ii. Number of enrolled wholesalers/distributors that shipped SPRAVATO
- b. Enrolled Patients
 - i. Number of newly enrolled and active patients (i.e., have self-administered at least one dose of SPRAVATO) stratified by age, gender, and geographic region

5. SPRAVATO Utilization Data

- a. The number of cartons distributed to certified healthcare setting and certified pharmacies
- b. Number of prescriptions (new and refills) dispensed to certified healthcare settings from certified pharmacies stratified by:
 - i. Pharmacy type
 - ii. Prescriber specialty, professional degree/credentials, geographic region
 - iii. Patient demographics (ex. age, gender, geographic region)

6. REMS Compliance (per reporting period and cumulatively, starting with the 1-year Assessment)

- a. Provide a summary report of non-compliance identified, including but not limited to:
 - i. Provide a copy of the Non-Compliance plan including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
 - ii. Provide a copy of the audit plan for each stakeholder.
 - iii. Report of audit findings for each stakeholder group (certified Healthcare Settings, certified Pharmacies, and enrolled wholesalers/ distributors).
 - The number of audits expected, and the number of audits performed.
 - The number and types of deficiencies noted for each group of audited stakeholders.
 - For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
 - For any that did not complete the CAPA within one month of the audit, describe actions taken.
 - Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
 - Documentation of completion of training for relevant staff.
 - The existence of documented processes and procedures for complying with the REMS Program, including ensuring that patients are not given SPRAVATO for home use.
 - Verification for each audited stakeholder's site that the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification.
 - Any of elements stated in 6. b-e. of this Assessment Plan that are noted as observations in the audit.
- b. Healthcare Settings (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
 - i. The number and type of certified Healthcare Settings for which non-compliance with the REMS Program is detected
 - ii. The number and type of non-certified Healthcare Settings that administered SPRAVATO and the number of incidents for each

- iii. The number of times a Healthcare Setting (certified or non-certified) and/or a Pharmacy (certified or non-certified) dispensed SPRAVATO for use outside of the certified Healthcare Setting
 - iv. Number of times SPRAVATO was distributed, transferred, or loaned from one Healthcare Setting (certified or non-certified) to another
 - v. The number of certified Healthcare Settings suspended and/or de-certified for non-compliance with REMS Program requirements and reasons for such actions.
 - vi. The number of patients who received a SPRAVATO administration that were not enrolled.
 - vii. Number of patients who were not observed for at least 2 hours after administration:
 - Number of events
 - Number of healthcare settings
 - Number of events per patient and per administration
 - Number of patients who refused to comply with the 2 hours monitoring after administration
- c. Certified Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
- i. The number of certified Pharmacies for which non-compliance with the REMS Program is detected
 - ii. The number and type of non-certified Pharmacies that dispensed SPRAVATO and the number of incidents for each
 - iii. The number of certified Pharmacies suspended and/or de-certified for non-compliance with REMS Program requirements and reasons for such actions.
- d. Wholesalers/Distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
- i. The number of enrolled wholesalers/distributors for which non-compliance with the REMS Program is detected
 - ii. The number and type of non-certified wholesalers/distributors that shipped SPRAVATO and the number of incidents for each
 - iii. The number of instances where enrolled wholesalers/distributors shipped SPRAVATO directly to certified Healthcare Settings, non-certified Healthcare Settings, non-certified Pharmacies, or directly to Patients.

- iv. The number of enrolled wholesalers/distributors suspended and/or de-enrolled for non-compliance with REMS Program requirements and reasons for such actions
- v. Any other SPRAVATO REMS noncompliance, source of report and resulting corrective actions.

e. Patient Monitoring Forms

- i. Number of SPRAVATO REMS Patient Monitoring Forms expected, received, and outstanding as of the assessment report cut-off date by the number of active patients.
- ii. Number of Patient Monitoring Forms not received within 60 calendar days from the date of submission of the Patient Enrollment Form. Include outreach activities performed to collect the forms
- iii. Number of Patient Monitoring Forms outstanding from previous reporting periods (if applicable)
- iv. Any other evidence that safe use was not demonstrated (patient was not monitored for sufficient period or appropriate monitoring was not done).

7. Safety Surveillance (per reporting period and cumulatively)

a. Known, or suspected adverse events related to abuse or misuse of SPRAVATO, as well as known or suspected cases of dissociation, sedation, and changes in vital signs (e.g., an increase in blood pressure) are to be reported regardless of outcome. Root cause analyses of whether REMS Program processes for patient monitoring were followed are to be included. Sources of the reports are to include but not be limited to:

i. The SPRAVATO REMS Patient Monitoring Form

- Number of cases of excessive sedation, dissociation, vital signs changes, and other AEs requiring medical intervention reported on the Patient Monitoring Forms, including:
 - a. Those cases that resulted in monitoring greater than 2 hours
 - b. Those cases stratified by sedation, dissociation, changes in vital signs or other that required a medical intervention
- Number of patients that were ready for discharge prior to the 2-hour monitoring period reported on the Patient Monitoring Forms.
- Number of patients that were ready for discharge after the 2-hour monitoring period reported on the Patient Monitoring Forms.

- Number of adverse events reported on the Patient Monitoring Form stratified by the total dose administered
 - Number of adverse events linked to patients who were not monitored for 2 hours
 - Trend analysis of whether adverse events decrease or increase over time
- ii. Adverse events reported in the REMS registry
 - iii. Spontaneous adverse event reports
 - Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest
 - Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report
 - iv. Literature searches
 - v. Social Media
 - vi. National databases that include poison center calls as well as data regarding drug diversion.
- b. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.
8. Stakeholder Surveys (beginning with the 1-year assessment report and annually thereafter with each assessment report) to assess stakeholders' understanding of the risk of serious adverse outcomes from sedation and dissociation as a result of SPRAVATO administration, and abuse and misuse of SPRAVATO:
- a. Certified Healthcare Settings' authorized representatives and administering healthcare professionals
 - b. Certified Pharmacies' authorized representatives and SPRAVATO dispensing pharmacists
 - c. Enrolled Patients
9. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

9 CONCLUSION & RECOMMENDATIONS

The Agency is concerned about serious adverse outcomes which may result from the sedation and dissociation that occur with the use of Spravato. There is also concern for misuse and abuse of the product due to known misuse and abuse of ketamine. DRISK is recommending a REMS consisting of elements to assure safe use to ensure that the benefits outweigh the aforementioned risks. Certifying healthcare settings and pharmacies that order and receive Spravato from the wholesaler/distributor will help to ensure that all the dispensing sites have policies and procedures in place to ensure that Spravato is administered in a medically supervised setting that provides monitoring, that it is not dispensed directly to patients, that patients are informed about the risks and enrolled into the program, and monitored for at least two hours after receiving their dose.

The Applicant's amended REMS submission received March 4, 2019 has included all the necessary changes communicated on February 1, 2019, February 26, 2019, February 28, 2019, March 1, 2019 and March 3, 2019. DRISK is recommending approval of the Spravato REMS.

10 APPENDICES

1. Spravato REMS Document
2. Spravato REMS Healthcare Setting Enrollment Form
3. Spravato REMS Patient Enrollment Form
4. Spravato REMS Pharmacy Enrollment Form
5. Spravato REMS Patient Monitoring Form
6. Spravato REMS Dear Healthcare Provider Letter
7. Spravato REMS Fact Sheet
8. Spravato REMS Website Screenshots

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/s/

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SELENA D READY
03/04/2019 10:10:25 PM

CYNTHIA L LACIVITA
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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
PDUFA Goal Date	March 3, 2019
OSE RCM #	2018-1874
Reviewer Name(s)	Somya Dunn, MD Anahita Tavakoli, M.A.
Team Leader	Selena Ready, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 3, 2019
Subject	Interim comments for the proposed REMS
Established Name	esketamine
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation(s)	28 mg esketamine solution drug-device combination for intranasal (IN) administration
Dosing Regimen	<ul style="list-style-type: none">• Induction Phase: The proposed initial dose is 28 to 56 mg at each administration twice weekly for weeks 1-4; (b) (4) to 84 mg (b) (4)• Maintenance Phase: Continuation of treatment once weekly for an additional 4-week (b) (4), and then weekly or every other week during an ongoing maintenance phase

1 INTRODUCTION

The following comments are based on the Agency’s review of the proposed REMS for esketamine nasal spray (Spravato) submitted to NDA 211243 as a REMS amendment on December 14, 2018, February 15, 2019, February 28, 2019 and March 1, 2019. Janssen Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) 211243 for Spravato on September 1, 2018, with a REMS, with the proposed indication to treat treatment-resistant depression (TRD). This application is under review in the Division of Psychiatry Products (DPP). The Applicant’s proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Spravato outweigh the risks of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and abuse and misuse of Spravato. DRISK and DPP agree that a REMS with ETASU is required and has determined that ETASU B (pharmacy certification), C (healthcare setting certification), E (monitoring), and F (registry) are necessary for the benefits of Spravato to outweigh the potential risks of misuse, abuse and serious adverse outcomes from sedation and dissociation.

2 COMMENTS TO THE APPLICANT

The following comments are based on the Agency’s review of the proposed REMS for Spravato submitted to NDA 211243 on March 1, 2019. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS amendment by 6:00 PM EST Sunday March 3, 2019.

- The recommendations provided here are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.
- The attestations on all enrollment forms should reflect the REMS document and SPRAVATO REMS requirements. You must align all documents with the Agency-cleared attestations and re-submit for review.
- Remove reference to the following in any materials: [REDACTED] (b) (4)

REMS Document

See attached REMS Document which is considered final; we accepted all edits except for removing the word “program.” The word “program” is not used in the REMS materials; however, our templated language does retain this word in the REMS Document.

REMS Supporting Document

The Agency has made edits to align the document with the current indication and labeling. The communication materials will be included the required ETASU certification of health care settings. Refer to the redlined version of the document.

REMS Letter for Healthcare Providers

Please see redlined version of document (attached).

1. Update the language in the box as follows (italics are only to show you the new part):

SPRAVATO™ is intended for patient administration under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours after SPRAVATO™ administration. *Do not dispense SPRAVATO directly to a patient for home use.*

REMS Fact Sheet

Please see redlined version of document (attached)

1. Update the language in the box as follows:

SPRAVATO™ is intended for patient administration under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours after SPRAVATO™ administration. SPRAVATO must never be dispensed directly to a patient for home use.

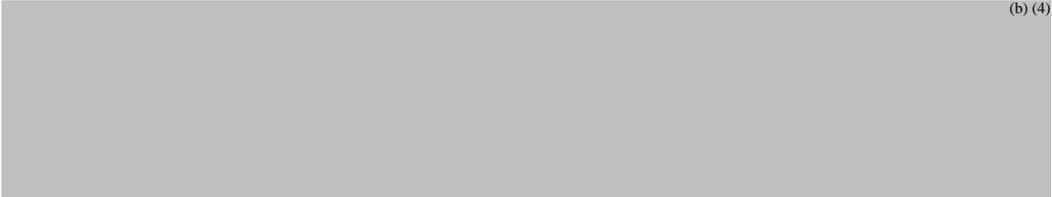
Patient Enrollment Form

Please see redlined version of document (attached).



This language has been removed and amended.

1. Therefore, remove the following questions from the form:

-  (b) (4)
-
-

2. Update the instructions section at the beginning of the form
3. *Italicize*, remove **a**, increase font, and move **Indicates a Required Field** in the shaded sections next to the titles, to above the first section titled **Patient Information**

Healthcare Setting Enrollment Form

Please see redlined version of document (attached).

1. *Italicize*, remove **a**, increase font, and move **Indicates a Required Field** in the shaded sections next to the titles, to above the first section titled **Healthcare Setting Information**

Pharmacy Enrollment Form

Please see redlined version of document (attached).

1. *Italicize*, remove **a**, increase font, and move **Indicates a Required Field** in the shaded sections next to the titles, to above the first section titled **Pharmacy Information**

Patient Monitoring Form

Please see redlined version of document (attached).

REMS Website

Please see redlined version of document (attached)

1. Update the following language throughout the content of the website:

SPRAVATO™ is intended for patient administration under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours after SPRAVATO™ administration. SPRAVATO must never be dispensed directly to a patient for home use.

Resubmission Instructions

Your complete REMS proposal should be submitted as separate documents in the same submission, to include a Word tracked changes version, a Word clean version, as well as a .pdf version of each of the previously mentioned documents and appended materials. Send all the versions, including Word versions in the email as well as to the Gateway.

3 APPENDICES

Spravato REMS Document

Spravato REMS Patient Enrollment Form

Spravato REMS Pharmacy Enrollment Form

Spravato REMS Healthcare Setting Enrollment Form

Spravato REMS Fact Sheet

Spravato REMS Letter for Healthcare Providers

Spravato REMS Patient Monitoring Form

Spravato REMS Website

Spravato REMS Supporting Document (email only)

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/s/

SOMYA V DUNN
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SELENA D READY
03/03/2019 09:15:37 AM

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
PDUFA Goal Date	March 4, 2019
OSE RCM #	2018-1874
Reviewer Name(s)	Somya Dunn, MD Anahita Tavakoli, M.A.
Team Leader	Selena Ready, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	February 28, 2019
Subject	Interim comments for the proposed REMS
Established Name	esketamine
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation(s)	28 mg esketamine solution drug-device combination for intranasal (IN) administration
Dosing Regimen	<ul style="list-style-type: none">• Induction Phase: The proposed initial dose is (b) (4) 56 mg at each administration twice weekly for weeks 1-4; (b) (4) to 84 mg (b) (4)• Maintenance Phase: Continuation of treatment once weekly for an additional 4-week (b) (4), and then weekly or every other week during an ongoing maintenance phase

1 INTRODUCTION

The following comments are based on the Agency’s review of the proposed REMS for esketamine nasal spray (Spravato) submitted to NDA 211243 as a REMS amendment on December 14, 2018, February 15, 2019 and February 28, 2019. Janssen Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) 211243 for Spravato on September 1, 2018, with a REMS, with the proposed indication to treat treatment-resistant depression (TRD). This application is under review in the Division of Psychiatry Products (DPP). The Applicant’s proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Spravato outweigh the risks of “misuse, abuse, and potential serious outcomes from transient sedation, dissociation and increase in blood pressure resulting from Spravato administration.” DRISK and DPP agree that a REMS with ETASU is required but differ from the Applicant regarding the REMS risks. The Agency has determined that ETASU B (pharmacy certification), C (healthcare setting certification), E (monitoring), and F (registry) are necessary for the benefits of Spravato to outweigh the potential risks of misuse, abuse and serious adverse outcomes from sedation and dissociation.

2 COMMENTS TO THE APPLICANT

The following comments are based on the Agency’s review of the proposed REMS for Spravato submitted to NDA 211243 on February 28, 2019. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS amendment by 6:00 PM EST Friday, March 1, 2019. Note that the REMS Document, Patient Attestations, Pharmacy Attestations, Healthcare Setting Attestations and Assessment Plan have been undergoing internal review and clearance processes. Therefore, the Agency cannot accept some of the edits made in your submission that are relevant to these documents. For consistency and standardization with other REMS Documents and Attestations, you will need to align with the documents we are sending you.

- Note that the REMS Goal has been updated, in part to align with labeling changes. The goal and the order of the risks stated in the goal should be aligned in any parts of the materials that are relevant. The Agency request that you update all materials to include the accurate order as written in the previous sentence and in the PI.
- The recommendations provided here are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.
- The attestations on all enrollment forms should reflect the REMS document and SPRAVATO REMS requirements. Please align all documents with the Agency-cleared attestations and re-submit for review.

REMS Document:

We’ve attached the draft REMS Document for your reference.

The current REMS goal has **changed** since our last communication, the Agency is proposing:

The goal of the REMS is to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO administration, and abuse and misuse of SPRAVATO by:

- Ensuring that SPRAVATO is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients
- Ensuring pharmacies and healthcare settings that dispense SPRAVATO are certified
- Ensuring that each patient is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring
- Enrollment of all patients in a registry to further characterize the risks and support safe use

Note that we have changed the order of the risks to align with the current draft label. We ask that you continue to adjust for labeling updates for this and any other materials as needed.

We need you to address the following: What is your projection for the number of healthcare sites expected to complete certification in the first year of marketing? That information will assist us in determining the number of audits that will be necessary.

For example, audit 50 healthcare settings or 10%, whichever is greater for each stakeholder.

Replace this language in the SD to align with the audit language in the REMS Document.

REMS Supporting Document:

See the Assessment Plan that will be appended to the Approval Letter and other edits in the attached redlined version.

REMS Materials:

REMS Letter for Healthcare Providers

1. Update the language in the box as follows:

SUBJECT: SPRAVATO™: Risk of serious adverse outcomes resulting from sedation and dissociation, and abuse and misuse

2. Replace the following language:

[Redacted] (b) (4).

With

SPRAVATO must never be dispensed directly to a patient for home use.

REMS Factsheet

1. Replace the following language:

[REDACTED] (b) (4)

With

The goal of the REMS is to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO administration, and abuse and misuse of SPRAVATO by:

2. Replace the following language:

[REDACTED] (b) (4)

With

SPRAVATO must never be dispensed directly to a patient for home use.

Patient Enrollment Form

Note that the comments and edits provided must be incorporated into the form for the form to be acceptable.

Per last communication provided by the Agency, you need a field to capture:

- The specialty of the prescriber
- History of contraindicated (vascular) diseases (refer to draft of label) such as:
 - “History of aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels)
 - intracerebral hemorrhage”

Patient Monitoring Form

Note that the comments and edits provided must be incorporated into the form for the form to be acceptable.

Please see redlined version of document (attached)

1. Update the instructions section at the top of the page as follows:

Complete this form after every treatment session to record the administration and monitoring for all patients enrolled in the SPRAVATOTM REMS [REDACTED] (b) (4) starting from the first dose

2. We ask that you move the concomitant medication section immediately below **Patient Information.**
3. Include the sentence drafted below, immediately under *“If Yes, when was the patient ready for discharge? _____ minutes from start of administration”*

“If No, describe as to why, in one or both of the sections below”

4. We also ask that you created a section, with three columns, below the **Time of Start of Administration** to capture the patient’s blood pressure at the following intervals:
 - Onset
 - Peak
 - Discharge

5. Under the **Serious Adverse Events** sections, update the language below as follows:

Did the patient experience a serious adverse event during this treatment session or since the last treatment session? A serious adverse event is one which is any undesirable experience associated with the use of SPRAVATO that resulted in patient hospitalization, a disability or permanent damage, death, required medical intervention, or was life threatening.

Resubmission Instructions

Your complete REMS proposal should be submitted as separate documents in the same submission, to include a **Word tracked changes** version, a Word clean version, as well as a .pdf version of each of the previously mentioned documents and appended materials.

Appendices

Spravato REMS Document

Spravato REMS Patient Monitoring Form

Patient Attestations

Healthcare Settings and Pharmacy Attestations

Spravato REMS Supporting Document (email only)

12 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SOMYA V DUNN
02/28/2019 07:40:13 PM

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02/28/2019 08:14:37 PM

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
PDUFA Goal Date	March 4, 2019
OSE RCM #	2018-1874
Reviewer Name(s)	Somya Dunn, MD Anahita Tavakoli, M.A. Joan E. Blair, RN, MPH
Team Leader	Selena Ready, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	February 25, 2019
Subject	Interim comments for the proposed REMS
Established Name	esketamine
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation(s)	28 mg esketamine solution drug-device combination for intranasal (IN) administration
Dosing Regimen	<ul style="list-style-type: none">• Induction Phase: The proposed initial dose is (b) (4) 56 mg at each administration twice weekly for weeks 1-4; (b) (4) to 84 mg (b) (4)• Maintenance Phase: Continuation of treatment once weekly for an additional 4-week (b) (4), and then weekly or every other week during an ongoing maintenance phase

1 INTRODUCTION

The following comments are based on the Agency’s review of the proposed REMS for esketamine nasal spray (Spravato) submitted to NDA 211243 as a REMS amendment on December 14, 2018 and February 15, 2019. Janssen Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) 211243 for Spravato on September 1, 2018, with a REMS, with the proposed indication to treat treatment-resistant depression (TRD). This application is under review in the Division of Psychiatry Products (DPP). The Applicant’s proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Spravato outweigh the risks of “misuse, abuse, and potential serious outcomes from transient sedation, dissociation and increase in blood pressure resulting from Spravato administration.” DRISK and DPP agree that a REMS with ETASU is required but differ from the Applicant regarding the REMS risks. The Agency has determined that ETASU B (pharmacy certification), C (healthcare setting certification), E (monitoring), and F (registry) are necessary for the benefits of Spravato to outweigh the potential risks of misuse, abuse and serious adverse outcomes from sedation and dissociation.

2 COMMENTS TO THE APPLICANT

The following comments are based on the Agency’s review of the proposed REMS for Spravato submitted to NDA 211243 on February 15, 2019. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS amendment by 9:00 AM EST Thursday, February 28, 2019. Review of your application and of the REMS Document, Supporting Document, and appended materials is ongoing; therefore, these comments should not be considered final.

REMS Document:

The draft REMS Document is undergoing internal review and therefore, should not be considered final. We’ve attached the draft REMS Document for your reference.

The current **draft** REMS goal has **changed** since our last communication, the Agency is proposing:

The goal of the Spravato REMS is to mitigate the risks of misuse, abuse and serious adverse outcomes from dissociation and sedation as a result of Spravato administration by:

- Ensuring that Spravato is only dispensed and administered in medically supervised healthcare settings that can provide patient monitoring
- Ensuring pharmacies and healthcare settings that dispense Spravato are certified
- Ensuring that each patient is informed about the serious adverse outcomes from dissociation and sedation and need for monitoring
- Enrollment of patients in a registry to further characterize the risks and safe use of Spravato

REMS Supporting Document:

The Supporting Document should be updated with REMS operational details regarding each element of the REMS and incorporate any changes relevant to the edits you are receiving today. We are not planning to require a REMS training program for healthcare settings, pharmacies or healthcare providers. Therefore, you will not need a knowledge assessment of the training for this REMS program. Note the edits and comments on the proposed Assessment Plan. We would like you to update your distribution plan and describe how you plan to track the product, describe the methods, as well as details on how you plan to track product that is stocked at large healthcare settings that are not hospitals, such as large practices and clinics.

Also note that with a Patient Monitoring Form used for each dose, the REMS Call Center, or some similar coordination center, will serve to organize and reconcile any discrepancies between a patient's enrollment and monitoring forms. This process needs to be described along with further details on the Call Center operations.

The Agency disagrees with the (b) (4) monitoring time. The Agency has had further internal discussion and will require a minimum of two hours of monitoring. This must be replaced/incorporated into all the relevant places in the materials.

REMS Materials:

- The recommendations provided here are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.
- The attestations on all enrollment forms are still in draft mode and should ultimately reflect the REMS document and SPRAVATO REMS requirements. Once the Agency-redlined REMS Document is received, you will need to align attestations.
- Remove any and all references to SPRAVATO REMS Knowledge Assessment to assess training of the Authorized Representative.

REMS Letter for Healthcare Providers

Please see redlined version of document (attached)

Healthcare Setting Enrollment Form

Please see redlined version of document (attached)

Incorporate these attestations:

I am the authorized representative designated by my Healthcare Setting to oversee implementation and coordinate the activities of the SPRAVATO REMS. By signing this form, I agree, on behalf of myself and my Healthcare Setting, to comply with the following REMS requirements:

I will:

- Review the SPRAVATO Prescribing Information and SPRAVATO REMS Fact Sheet.*

- Enroll in the SPRAVATO REMS by completing this SPRAVATO REMS Healthcare Setting Enrollment Form and submitting this form to the SPRAVATO REMS.*
- Have a prescriber onsite during SPRAVATO administration and monitoring.*
- Have a healthcare provider(s) onsite to monitor each patient for at least 2 hours following administration of SPRAVATO for resolution of sedation and dissociation and changes in vital signs.*
- Train all relevant staff involved in prescribing, dispensing, and administering SPRAVATO and establish processes and procedures to ensure that the following take place in my setting:*
 - Healthcare provider counsels the patient on the need for enrollment, monitoring and risks of sedation and dissociation prior to receiving SPRAVATO.*
 - Patients are enrolled in the SPRAVATO REMS and that the Patient Enrollment Form is submitted to the REMS.*
 - No patient is administered SPRAVATO until enrolled in the REMS.*
 - SPRAVATO must be self-administered by the patient under the direct supervision of a healthcare provider.*
 - All patients must be monitored by a healthcare provider for at least 2 hours for resolution of dissociative changes, sedation, and changes in vital signs prior to discharge.*
 - A Patient Monitoring Form must be submitted to the SPRAVATO REMS for every patient following each administration from initial dose.*
 - A Patient Monitoring Form must be submitted to the SPRAVATO REMS for every patient following each administration for any dose with an associated serious adverse event within 7 days.*
 - SPRAVATO must never be sent home with the patient.*
 - The patient should arrange transportation from the facility after administration of SPRAVATO and the 2-hour monitoring period.*
- Have a new Authorized Representative enroll in the REMS by completing the Healthcare Setting Enrollment Form if the Authorized Representative changes.*
- Maintain records of all processes and procedures including compliance with those processes and procedures.*
- Maintain records on the shipments of SPRAVATO received and a dispensing record that includes information on patients that received SPRAVATO including dose, number of devices and date administered.*

- Comply with audits carried out by Janssen or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.*

Pharmacy Enrollment Form

Please see redlined version of document (attached)

Incorporate these attestations:

I am the authorized representative designated by my pharmacy to oversee implementation and coordinate the activities of the SPRAVATO REMS. By signing this form, I agree, on behalf of myself and pharmacy, to comply with the following REMS requirements:

I will:

- Enroll in the SPRAVATO REMS by completing this SPRAVATO REMS Pharmacy Enrollment Form and submitting this form to the SPRAVATO REMS.*
- Train all relevant staff involved in dispensing SPRAVATO on the following:*
 - SPRAVATO can only be dispensed to a certified healthcare setting.*
 - SPRAVATO must never be dispensed directly to a patient for home use.*
- Establish processes and procedures to verify that the patient is enrolled in the SPRAVATO REMS prior to dispensing SPRAVATO, and the healthcare setting is certified through the processes and procedures established as a requirement of the REMS.*
- Not distribute, transfer, loan or sell SPRAVATO.*
- Maintain records that all REMS processes and procedures are in place and are being followed.*
- Maintain records on the shipments of SPRAVATO received and a dispensing record that includes information on patients that received SPRAVATO including dose, number of devices and date dispensed.*
- Comply with audits carried out by Janssen Pharmaceuticals, Inc. or third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.*

REMS Factsheet

Please see redlined version of document (attached)

Patient Enrollment Form

We have made edits to the form. Please see redlined version of document (attached)

In addition, we request that you update the patient information section for the provider to fill out (not on the patient signature section) to include the following questions:



Has the patient previously been treated with ketamine for Treatment Resistant Depression, Pain Syndromes or any other condition? (Check one) Yes No

If YES, list all pre-existing conditions:

(b) (4)

List all pre-existing medical and psychiatric conditions:

List concomitant medications and doses not previously mentioned (adjunctive depression medications, sedative- hypnotics, amphetamines, etc.)

(b) (4)

(You can modify this question if needed based on contraindications in the label.)

If YES, list condition:

Incorporate these attestations:

SPRAVATO is available only through the SPRAVATO REMS, a restricted distribution program. Only healthcare settings, pharmacies, and patients enrolled in the program are able to dispense, and receive SPRAVATO. Your prescriber will explain the risks, of taking SPRAVATO, so you can understand and make an informed decision. This form enrolls you in the SPRAVATO REMS.

By signing this form, I understand and acknowledge that:

- My healthcare provider has explained that dissociation and sedation can result from treatment with SPRAVATO and I must stay after my dose until these effects resolve, I may have increases in blood pressure and feel:
 - sleepy
 - disconnected from myself, my thoughts, feelings and things around me*
- I agree to contact my doctor or inform him/her at my next visit if I believe I have a side effect or reaction from SPRAVATO.*
- I have discussed any questions or concerns about my treatment with SPRAVATO with my doctor.*
- I give permission and allow for the sharing of my health information collected through the SPRAVATO REMS Registry.*

Before my treatment begins, I will:

- Enroll in the SPRAVATO REMS by completing this Patient Enrollment Form with my healthcare provider. Enrollment information will be provided to the REMS.*
- Receive counseling on the need for monitoring for resolution of sedation, dissociation and increases in blood pressure.*

During treatment, and after administration, I understand that:

- I will use the SPRAVATO nasal spray myself under the direct observation of a healthcare provider*
- I will be observed at the healthcare setting where I get SPRAVATO for at least 2 hours after each treatment until the healthcare provider determines I am ready to leave the healthcare setting.*
- I must make arrangements to safely leave the healthcare setting and get home.*
- I cannot drive or use heavy machinery for the rest of the day on which I receive SPRAVATO.*
- I cannot take SPRAVATO home.*

By signing this form, you agree that Janssen Pharmaceuticals, Inc. and its affiliates, agents and contractors may collect, share, and use your personal health information in the following ways:

- *Your information will be stored in a secure and confidential Patient Registry (database) of all patients who have been prescribed SPRAVATO in the United States*

- *Your information will be used for the purposes of administering the SPRAVATO REMS*
- *Janssen Pharmaceuticals, Inc. and its affiliates, agents and contractors may contact you or your healthcare provider via phone, SMS (text), mail, or email in connection with administering the SPRAVATO REMS*

Patient Monitoring Form

See the attached redlined version of document. Note that the timing of the submission of this form is still under internal Agency discussion. The need to collect the monitoring form for every dose for a longer period of time than the first three months of the patient's treatment is still under discussion.

REMS Website

We have made edits to the webpages. Please see redlined version of document (attached).

Clarify when you expect pharmacy enrollment to be available on the REMS website. If this enrollment will not be available at the time the REMS is approved, the pharmacy enrollment screenshots should not be part of the final REMS submission. Once pharmacy enrollment is available online, you must submit a REMS modification, so this option can be noted in the REMS materials, updated screenshots, and on the printed version of the Pharmacy Enrollment Form. If online enrollment will be immediately available, delete the "Coming Soon" screenshot.

Include screenshots illustrating all aspects of online patient enrollment and online patient reporting.

In addition, we request that you update the document as follows:

Page 1:

What is the SPRAVATO™ REMS (Risk Evaluation and Mitigation Strategy)?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product

The goal of the SPRAVATO™ REMS is to mitigate the risk of misuse, abuse, and serious adverse outcomes from dissociation and sedation, as a result of SPRAVATO™ administration by:

- Ensuring that SPRAVATO™ is only dispensed to and administered in medically supervised healthcare setting that provides patient monitoring
- Ensuring that pharmacies and healthcare settings that dispense SPRAVATO are certified
- Ensuring that each patient is informed about serious adverse outcomes from dissociation and sedation and need for monitoring
- Enrollment of all patients in a registry to further characterize the risks and support safe use

SPRAVATO™ is intended for patient administration under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours. SPRAVATO™ must not be dispensed for patients to take home.

PROGRAM REQUIREMENTS

Healthcare Setting	Pharmacy	Patient
<p>Healthcare Settings must be certified in the SPRAVATO™ REMS in order to treat patients with SPRAVATO™.</p> <p>Learn more about Healthcare Setting certification [link to Healthcare Settings page]</p>	<p>Pharmacies must be certified in the SPRAVATO™ REMS in order to dispense SPRAVATO™</p> <p>Learn more about Pharmacy certification [link to Pharmacy page]</p>	<p>Patients must be enrolled in the SPRAVATO™ REMS in order to receive SPRAVATO™ treatment</p> <p>Learn about Patient enrollment [links to patient page]</p>

INDICATION

SPRAVATO™ is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated for the treatment of treatment-resistant depression (TRD) in adults.

Resubmission Instructions

Your complete REMS proposal should be submitted as separate documents in the same submission, to include a Word tracked changes version, a Word clean version, as well as a .pdf version of each of the previously mentioned documents and appended materials. Screenshots showing all content and functionality of the website must also be submitted for the Agency's review.

Appendices

Spravato REMS Document

Spravato REMS Dear Healthcare Provider Letter

Spravato REMS Pharmacy Enrollment Form

Spravato REMS Healthcare Setting Enrollment Form

Spravato REMS Patient Enrollment Form

Spravato REMS Website

Spravato REMS Patient Monitoring Form

Spravato REMS Fact Sheet

Spravato REMS Supporting Document (email only)

55 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SOMYA V DUNN
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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211243
PDUFA Goal Date	March 4, 2019
OSE RCM #	2018-1874
Reviewer Name(s)	Somya Dunn, MD Anahita Tavakoli
Team Leader	Selena Ready, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	February 1, 2019
Subject	Interim comments for the proposed REMS
Established Name	esketamine
Trade Name	Spravato
Name of Applicant	Janssen Pharmaceuticals, Inc.
Therapeutic Class	S-enantiomer of ketamine, a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist
Formulation(s)	28 mg esketamine solution drug-device combination for intranasal (IN) administration
Dosing Regimen	<ul style="list-style-type: none">• Induction Phase: The proposed initial dose is (b) (4) 56 mg at each administration twice weekly for weeks 1-4; (b) (4) to 84 mg (b) (4)• Maintenance Phase: Continuation of treatment once weekly for an additional 4-week (b) (4), and then weekly or every other week during an ongoing maintenance phase

1 INTRODUCTION

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2 COMMENTS TO THE APPLICANT

The following comments are based on the Agency's review of the proposed REMS for Spravato submitted to NDA 211243 on December 14, 2018. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS amendment within 14 calendar days. Review of your application and of the REMS Document, Supporting Document, and appended materials is ongoing; therefore these comments should not be considered final.

REMS Document:

The draft REMS Document is undergoing internal review and cannot be provided at this time.

The current **draft** REMS goal the Agency is proposing is:

The goal of the Spravato REMS is to mitigate the risks of misuse, abuse and serious adverse outcomes from dissociation and sedation as a result of Spravato administration by:

- Ensuring that Spravato is only dispensed and administered in medically supervised healthcare settings that can provide patient monitoring
- Enrollment of patients in a registry to further characterize the risks and safe use of esketamine

The Agency is considering that the REMS will include certification of ALL healthcare settings that dispense and monitor patients for at least two hours post administration, and a patient registry to further characterize the REMS risks and safe use of esketamine. This registry will require patient enrollment.

REMS Supporting Document:

The Supporting Document should be updated with the REMS Communication Plan and ETASU to provide REMS operational details regarding each element of the REMS. All healthcare settings, including

inpatient settings, would need to be aware of these requirements and ensure they are upheld. As the draft REMS goal proposes, the patients will be enrolled and data collected regarding the REMS risks. As well, healthcare settings will likely be required to submit dispensing data to the REMS for assessments to reconcile distribution data from the wholesaler/distributor and certified pharmacies. In addition, in healthcare settings such as large clinics or private offices with multiple practitioners that may store Spravato for patient administration, you must include how you plan to ensure that patients are enrolled and monitored. Certified pharmacies will likely be required to submit dispensing data to the REMS as well. We will provide comments on the proposed Assessment Plan in the coming weeks.

REMS Materials:

The recommendations for materials are based on the current proposed labeling and current Agency considerations for the REMS. However, all materials must be revised to be consistent with the final FDA-approved labeling and REMS Document.

- The Agency’s current thinking has changed regarding the naming of REMS programs. The word “program” is no longer used in the complete title of the REMS in the communication materials. Therefore, references to the “SPRAVATO REMS Program” should be revised to “SPRAVATO REMS.” Please note, this only applies to content within the REMS communication materials and does not apply to the REMS Document or REMS Supporting Document.
- Phone numbers used by the SPRAVATO REMS may not link to information that is promotional in tone.
- Include a prominent REMS-specific link to the SPRAVATO REMS website on all product websites for consumers and healthcare providers.
- Capitalize SPRAVATO for consistency throughout all REMS materials.
- Include all formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features.

You submitted the following REMS appended materials:

- **Dear HCP Letter**
- **Fact Sheet**

REMS Letter for Healthcare Providers

Your Dear HCP Letter can be part of the Communication Plan and sent with attachments of the relevant materials. You must revise the letter to align with the proposed goal, elements, and Prescribing Information. The letter should be specific to the REMS and not promotional in tone. The letters can also reflect information captured in the Fact Sheet.

REMS Fact Sheet

The proposed Fact Sheet must be revised to align with the proposed draft REMS goal and include details for all healthcare settings regarding how the healthcare setting can obtain Spravato for their patients. It should also contain information about the Patient Enrollment in the REMS. The Fact Sheet should be specific to the REMS and not promotional in tone.

New Materials that must be developed to support the REMS:

Healthcare Setting Enrollment Form

In the Fact Sheet, you reference the [REDACTED] (b) (4) [REDACTED] is not acceptable. You must align the Healthcare Setting enrollment form to meet the requirements of the proposed draft REMS and develop a Healthcare Setting Enrollment Form for healthcare settings to be certified in the REMS Program. All healthcare settings that dispense Spravato must be certified in the SPRAVATO REMS Program to ensure that Spravato is dispensed and administered only in a healthcare setting to patients and to ensure that patients are monitored during administration of drug. Therefore, certification is not limited to outpatient settings only. Inpatient settings may dispense and administer the product and will be required to enroll and monitor the patient. The attestations on this form should reflect the final REMS document and program requirements. Once the Agency-redlined REMS Document is received, you will need to align attestations.

We've included some proposed draft attestations as a guide:

I am the authorized representative designated by my Healthcare Setting to coordinate the activities of the SPRAVATO REMS. By signing this form, I agree, on behalf of myself and Healthcare Setting, to comply with the following REMS requirements:

I will:

- Have a healthcare provider(s) onsite to monitor patients for at least 2 hours for resolution of sedation and dissociation.
- Designate an authorized representative to complete the certification process and oversee implementation and compliance with the REMS on behalf of the healthcare setting.
- Have the authorized representative review the [list the educational materials].
- Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS.
- Have the authorized representative enroll in the REMS by completing the Healthcare Setting Enrollment Form and submitting it to the REMS.
- Train all relevant staff involved in prescribing, dispensing and administering SPRAVATO on
- Risks of abuse and misuse

- o Patient self-administration under the supervision of a healthcare provider
- o Monitoring for dissociative changes and sedation.
- Establish processes and procedures to enroll the patient in the REMS.
- Establish processes and procedures to counsel the patient.
- Establish processes and procedures to verify the patient is enrolled in the REMS before administration.
- Establish processes and procedures to verify SPRAVATO™ is not dispensed to the patient to take home.
- Establish processes and procedures to submit the FORM to the REMS.
- Counsel the patient on need for enrollment, monitoring and risks of sedation and dissociation.
- Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS.
- Document and submit the patient's outcome to the REMS using the Adverse Event Report FORM 1 Month.
- Document and submit the patient's outcome to the REMS using the Adverse Event Report FORM 3 Month.
- Have a new Authorized Representative enroll in the REMS by completing the Healthcare Setting Enrollment Form if the Authorized Representative changes.
- Maintain records of all processes and procedures including compliance with those processes and procedures.
- Maintain records of dispensing.
- Comply with audits carried out by Janssen or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

Pharmacy Enrollment Form

Pharmacies that dispense Spravato must be certified in the SPRAVATO REMS to ensure Spravato is only dispensed to certified healthcare settings to a named-patient.

You must develop a Pharmacy Enrollment Form for pharmacies to be certified in the REMS. The form should include any attestations required of the pharmacy before dispensing to certified healthcare settings and should reflect the final REMS document and program requirements. Once the Agency-redlined REMS document is received align attestations.

We've included some proposed draft attestations as a guide:

I am the authorized representative designated by my Pharmacy to coordinate the activities of the SPRAVATO REMS. By signing this form, I agree, on behalf of myself and Pharmacy, to comply with the following REMS requirements:

I will

- Verify that the patient is enrolled, and the healthcare setting is certified through the processes and procedures established as a requirement of the REMS.
- Maintain records documenting staff's completion of training.
- Not distribute, transfer, loan or sell SPRAVATO except to certified dispensers
- Maintain records that all REMS processes and procedures are in place and are being followed.
- Comply with audits carried out by Janssen Pharmaceuticals, Inc. or third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

Patient Enrollment Form

As provided in the draft proposed REMS Goal above, patients receiving Spravato must be enrolled in the SPRAVTO REMS. Healthcare providers at certified healthcare settings will be responsible for enrolling patients. You must develop a patient enrollment form to inform the patient of the REMS, risks and include any attestations required of the patient before receiving drug. The attestations on this form should reflect the final REMS document and program requirements. The form should be 2-sided and include a section to capture data from the first dose post-administration. Examples of information that you may want to collect: Did the patient experience sedation? Did the patient experience dissociation? Time to resolution of these effects? Time of administration? Time to patient discharge? Did the patient have any severe adverse effects that required intervention? Did the patient stay for monitoring as required? Once the Agency-redlined REMS document is sent to you, you will need to align attestations.

You can refer to another REMS program with a registry for reference such as Adasuve, Aveed or Adempas on REMS@FDA: <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>

The form should be brief and easy to use, with submission instructions included.

Forms to capture follow-up information as part of the Registry

The form should capture information about the patient (i.e. name/patient identifier, etc.), and information regarding events that occurred during administration of drug.

These forms are to be submitted 1 month post initial treatment and 3 months post initial treatment to capture events likely related to the REMS risks. These forms are to be completed by a provider will be sent in to capture any event that the provider is aware of and considers related to sedation or dissociation, such as falls or other types of accidents. Some suggested AEs should be provided as

examples for the provider. The form should be brief and easy to use, with submission instructions included. The forms should be designed to be associated with patients that have been enrolled into the registry with the initial enrollment form. There should also be an inquiry on the forms for monitoring times and capture if the patient has been staying for the full two hours or if longer was needed. In addition, if the patient did not stay as required.

REMS Website

Create a REMS-specific Website. The REMS Website must align with the REMS. The REMS-related webpage(s) should not be a means to promote SPRAVATO or any other Janssen, Inc. product.

Submit a complete set of REMS website screenshots showing all content and functionality of the website. If online enrollment is an option, you must submit a screenshot(s) of what the new window(s) would look like as part of the functionality of your website submission. This would include the data fields to complete, and the information that pops up for the provider to read.

The screenshots should include links to access all REMS materials.

We recommend that you include a prominent link on the product website's homepage for REMS materials. This link should direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. For example, the link could state **REMS**, or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information."

These attestations should reflect the final REMS document and SPRAVATO REMS requirements. Once the Agency-redlined REMS Document is received, you will need to align attestations.

Resubmission Instructions

Your complete REMS proposal should be submitted as separate documents in the same submission, to include a Word tracked changes version, a Word clean version, as well as a .pdf version of each of the previously mentioned documents and appended materials. Update your REMS Supporting Document and send in as well. You do not need to update your REMS Document.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SOMYA V DUNN
02/01/2019 03:00:39 PM

SELENA D READY
02/01/2019 03:08:41 PM