



NDA 211243/S-27

## SUPPLEMENT APPROVAL

Janssen Research & Development, LLC  
Attention: Kara Christie  
Associate Director, Global Regulatory Affairs  
1125 Trenton-Harbourton Road  
Titusville, NJ 08560

Dear Kara Christie:

Please refer to your supplemental new drug application (sNDA) dated and received November 26, 2025, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spravato (esketamine) nasal spray.

This Changes Being Effected sNDA provides for proposed modifications to the approved Spravato Risk Evaluation and Mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

The REMS for Spravato was originally approved on March 5, 2019, and the most recent REMS modification was approved on October 9, 2025. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS which includes reverting the vendor related changes to the REMS Program Website that were approved on October 9, 2025 (Supplement 25) to the previously approved version.

Your proposed modified REMS, submitted on November 26, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on March 5, 2019.

The revised REMS assessment plan must include, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

## **Program Implementation and Operations**

### 1. REMS Operation and Performance Data

#### 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. Provide an assessment of contacts to the REMS Coordinating Center. Your assessment should include, but is not limited to, the following:
  - 1) Number and percentage of contacts by participant type [e.g., healthcare provider, patient, pharmacy, outpatient healthcare setting, inpatient healthcare setting, wholesaler-distributor, or other (specify)]
  - 2) Summary of reasons for calls (e.g., certification question, location of a certified pharmacy/healthcare setting), stratified by participant type making the call; limit to the top five reasons for call by participant type making the call
  - 3) Summary of frequently asked questions (FAQ) by stakeholder type
  - 4) Summary report of REMS-related problems identified and resulting corrective actions

### 2. REMS Participants Certification and Enrollment

#### a. Certified Inpatient and Outpatient Healthcare Settings

- i. Number of newly certified, newly certified and active, and active inpatient and outpatient healthcare settings (active settings are those that have received shipments of SPRAVATO) stratified by type of healthcare setting (i.e., group practice, independent practice, outpatient clinic, hospital-inpatient, hospital-emergency department, mental health facility, other), and geographic region (defined by US Census)
- ii. Number of outpatient healthcare settings that dispensed/provided SPRAVATO for administration stratified by the healthcare setting type and geographic region (defined by US Census); Outpatient healthcare settings that dispense/provide SPRAVATO

administration are defined as having at least one patient with at least one treatment of SPRAVATO as evidenced by submission of a Patient Monitoring Form

- iii. Healthcare settings that were unable to become certified and reasons why
- b. Certified Pharmacies
  - i. Number of newly certified, newly certified and active, and active pharmacies (active pharmacies defined as those that have received SPRAVATO) stratified by type of pharmacy (i.e., Retail, Specialty, other) and geographic region (defined by US Census)
  - ii. Pharmacies that were unable to become certified and reasons why
- c. Contracted Wholesalers/Distributors
  - i. Number of newly contracted, newly contracted and active, and active wholesalers/distributors (active wholesalers/distributors defined as those that have shipped SPRAVATO)
  - ii. Number of contracted wholesalers/distributors that shipped SPRAVATO
- d. Enrolled Outpatients
  - i. Number of newly enrolled, newly enrolled and active, and active outpatients (outpatients who have received at least one dose of SPRAVATO) stratified by age, sex, and geographic region (defined by US Census)

### 3. SPRAVATO Utilization Data

- a. Provide a summary of the distribution of SPRAVATO
  - i. Number of SPRAVATO shipments distributed by wholesalers/distributors, stratified by recipient setting type (inpatient healthcare settings, outpatient healthcare settings, and pharmacies)
  - ii. Number of devices (28 mg per device) distributed by wholesalers/distributors, stratified by recipient setting type
  - iii. Number of two blister pack kits distributed
  - iv. Number of three blister pack kits distributed
- b. Number of treatments administered at certified outpatient healthcare settings (based on submitted Patient Monitoring Forms) stratified by:
  - i. First treatment session and subsequent treatment session(s)
  - ii. Healthcare Setting type

- iii. Prescriber specialty, professional degree/credentials, geographic region (defined by US Census)
- iv. Patient demographics (e.g., age, sex, geographic region (Defined by US Census))

#### 4. REMS Compliance

- a. Provide a copy of the audit plan for each audited REMS participant type
  - i. The proportion of audits completed out of the total number of audits expected (per REMS Document requirements) for each audited REMS participant type, stratified by audit type
    - 1) Include how the expected number of audits was calculated for each REMS participant type
    - 2) Include reasons that any expected audits were not completed, and follow-up actions taken to complete these outstanding audits
    - 3) For audit questionnaires not returned, describe follow-up actions taken to complete outstanding audits (e.g., inactivated or decertified)
  - ii. The number of for-cause audits. Include the reason(s) why each for-cause audit was conducted
  - iii. For all audit types provide a tabular summary of all audit findings stratified by REMS participant type, by finding severity (critical, major, minor), and by finding type
    - 1) For each finding type, provide a brief description of the finding
  - iv. Provide a tabular summary of each REMS participant with audit findings, including, but not limited to the following:
    - 1) Date of the audit, REMS participant type, unique ID, a brief description of the audit finding, and the severity categorization of the finding (critical, major, minor)
    - 2) Whether the audit finding was recurring (i.e., occurred for the REMS participant during any previous assessment period)
    - 3) Time (in years) since the previous audit, if applicable
    - 4) Results of the root cause analysis, if applicable
    - 5) Whether audit findings were corrected during the audit and how they were corrected

- 6) Whether a corrective and preventative action (CAPA) plan was required, and a description of and completion of any CAPA
- v. Of the total number of REMS participants audited, stratified by the audited REMS participant type, provide the number and proportion that did not:
- 1) Have documentation of completed training for all relevant staff
  - 2) Have documentation that all processes and procedures for complying with the REMS were being followed, including ensuring that patients are not given SPRAVATO for home use
  - 3) Inform the REMS of a change in their Authorized Representative
  - 4) For healthcare settings and pharmacies: Have sufficient records of shipments received and dispensing information (patient name, dose, number of devices, date dispensed/administered)
  - 5) For wholesalers-distributors: Have sufficient records of shipments sent
- b. Provide a copy of the SPRAVATO REMS Compliance Assessment Action Plan including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a participant would be suspended or de-certified from the REMS
- i. Any other SPRAVATO REMS non-compliance (e.g., identified from complaints made to REMS Coordinating Center, follow-up after adverse event reporting), source of report and resulting corrective actions
  - ii. For each noncompliance event, report the following in tabular format:
    - 1) The unique ID(s) of the participant(s) associated with the noncompliance event or deviation to enable tracking over time, and whether the site has been decertified for noncompliance previously
    - 2) A description of the noncompliance event, including the severity of categorization
    - 3) The source(s) of the noncompliance data or report (e.g., REMS Coordinating Center, spontaneous reports, audit findings, Diversion Mitigation monitoring)

- 4) If the noncompliance event was recurring per individual REMS participant
  - 5) Whether the REMS participant was previously inactivated and/or decertified
  - 6) The results of root cause analysis
  - 7) Corrective and preventative actions
  - 8) Monitoring plan to determine success of corrective and preventative actions
- iii. Provide a trend analysis of the number and types of noncompliance events, stratified by REMS participant type and severity categorization (minor, major, critical)
  - iv. The number of certified healthcare settings, pharmacies, and wholesalers-distributors that were inactivated and/or decertified/unauthorized to distribute/dispense and the reason(s) (e.g., nonresponse to audits, critical noncompliance, failure to complete a CAPA, etc.), stratified by REMS participant type
  - v. The number of healthcare settings and pharmacies that received SPRAVATO while inactivated and/or decertified. Include the number of shipments each REMS participant received and the number of devices per shipment.
  - vi. The number of healthcare settings and pharmacies that administered or dispensed SPRAVATO while inactivated/and or decertified. Include the number of administrations or dispenses per REMS participant.
    - 1) For healthcare settings, include whether **Patient Monitoring Forms** were submitted for patients that received SPRAVATO while the healthcare settings were inactivated and/or decertified
  - vii. The number of wholesalers-distributors that shipped SPRAVATO while inactivated and/or unauthorized to distribute. Include the number of shipments sent.
  - viii. The number of times a healthcare setting and/or pharmacy dispensed SPRAVATO for use outside of the certified healthcare setting (i.e., for home use), stratified by certification status
  - ix. The number of times SPRAVATO was distributed, transferred, or loaned from one Healthcare Setting to another, stratified by certification status
  - x. The number of patients who received a SPRAVATO administration in an outpatient setting that were not enrolled.

- xi. Number of patients treated in an outpatient setting who were not observed for at least two hours after administration based on the Patient Monitoring Form:
  - 1) Number of events
  - 2) Number of outpatient healthcare settings
  - 3) Number of events per patient and per administration
  - 4) Number of patients who refused to comply with the two hours monitoring after administration
- xii. Total number of outpatient HCSs that received subsequent shipments of SPRAVATO without submitting any PMFs to the REMS for their previous shipments. Provide the following for each identified HCS:
  - 1) REMS certification status
  - 2) Total number of subsequent shipments received by each HCS and the number of individual devices per shipment
  - 3) The number of HCSs that administered SPRAVATO to non-enrolled patients and the number of times non-enrolled patient administrations occurred
- xiii. The number of instances where contracted wholesalers/distributors shipped Spravato directly to non-certified healthcare settings, non-certified pharmacies, or directly to patients
- xiv. Include the number of incidents where a healthcare setting or pharmacy that was never certified in the REMS administered or dispensed SPRAVATO

### **Safe Use Behaviors**

- 5. **Patient Monitoring Forms – Outpatient Use Only**
  - a. Number of SPRAVATO REMS Patient Monitoring Forms received
  - b. 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 and the reasons why the forms were not submitted.
  - c. Number of Patient Monitoring Forms outstanding from previous reporting periods.
  - d. Any other evidence that safe use was not demonstrated (patient was not monitored for sufficient period or appropriate monitoring was not done).
- 6. Provide an assessment of whether patients treated in an outpatient healthcare setting were monitored for resolution of sedation, dissociation, respiratory depression using pulse oximetry and other changes in vital signs for a minimum

of two hours. List all data sources used in your analysis. Your assessment is to include but is not limited to the following:

- a. The number and proportion of treatment sessions where the total treatment duration (from first device administration to completion of monitoring) was at least two hours out of all treatment sessions in an outpatient healthcare setting. If not 100%, provide the reasons why and any actions taken or planned to remediate.
  - i. Provide the mean, median, and range of the total treatment duration (in minutes) for all outpatient treatment sessions
- b. Provide the number and proportion of unique patients who had at least one treatment session where the total treatment duration was less than two hours out of all active patients
- c. Include any noncompliance that would inform on this assessment (e.g., missing or incomplete Patient Monitoring Forms) and the impact on the metric

### **Health Outcomes and/or Surrogates of Health Outcomes**

7. Serious adverse outcomes resulting from sedation and dissociation and respiratory depression, or hypertension
  - a. Analyze confirmed U.S. Serious Adverse Events (SAEs) of interest, described on the Patient Monitoring Form as any event involving sedation, dissociation, respiratory depression, or hypertension that results in death, is life-threatening, hospitalization, disability/permanent damage, or is an important medical event (any event that may jeopardize the patient or may require intervention to prevent one of the above outcomes) and provide a summary as described below. Sources of the reports are to include SPRAVATO REMS Patient Monitoring Forms, the REMS registry, and spontaneous adverse event reports. In your analysis, include the following:
    - i. Include the search strategy used for each data source, the case definition, and the causality criteria used to identify cases of interest. Include search dates and specific Medical Dictionary for Regulatory Activities (MedDRA) terms used
    - ii. Provide a tabular summary of the cases including the following:
      - 1) Number of confirmed serious adverse events involving sedation, dissociation, respiratory depression, or hypertension from all sources, stratified by adverse event type
      - 2) Seriousness (e.g., number of serious adverse events categorized as fatal, life-threatening, requiring initial or

- prolonged hospitalization, disability, or permanent damage, etc.)
- 3) Number that occurred during a treatment session and number that occurred after a treatment session (i.e., after the patient left the healthcare setting)
  - 4) Number that required medical intervention
  - 5) Outcome of Event (e.g., number of serious adverse events categorized as recovered/resolved, recovering/resolving, not recovered/not resolved/ongoing, recovered/resolved with sequelae, fatal, unknown)
  - 6) Assessment of relatedness of drug to event
  - 7) Root cause analyses of whether the REMS requirements for patient monitoring were followed
  - 8) Include a reference list of case identifiers (e.g., manufacturer control numbers) for all cases included in the analysis above
- b. Provide an analysis of data from the SPRAVATO REMS Patient Monitoring Form – Outpatient Use Only, including:
- i. Number of patients with SAEs of interest reported on the Patient Monitoring Forms.
  - ii. Number of patients who were ready for discharge after the -two-hour monitoring period reported on the Patient Monitoring Forms.
  - iii. Number of patients whose vital signs were not considered in acceptable range prior to administration and at treatment session completion
  - iv. Number of patients whose pulse oximetry was not considered at an acceptable level prior to administration, during treatment, and at treatment session completion.
  - v. Number of SAEs of interest reported on the Patient Monitoring Form stratified by the total dose administered.
  - vi. Number of SAEs of interest linked to patients who were not monitored for two hours. Summarize the adverse events reported for patients who were not monitored for two hours
  - vii. Trend analysis of whether SAEs of interest decrease or increase over time, including contributing factors.
- c. Provide an analysis of national databases that include poison center calls as well as data regarding drug diversion

### **Evaluation of Knowledge**

#### 8. Patient/Caregiver Knowledge Surveys (to be conducted annually):

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

- a. Assess patient/caregiver knowledge of the serious adverse outcomes resulting from sedation, dissociation and respiratory depression associated with SPRAVATO
- b. Assess patient/caregiver knowledge of the need for monitoring while being treated with SPRAVATO
- c. Provide a comparison of knowledge scores across both survey knowledge domains for the current and two previous reporting periods
  - i. Identify any trends in patient/caregiver comprehension and provide an analysis of contributing factors
  - ii. Provide actions taken to address any knowledge gaps

### **Overall Assessment of REMS Effectiveness**

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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 211243 REMS ASSESSMENT METHODOLOGY**

(insert concise description of content in bold capital letters, e.g.,

**ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed

**U.S. Food and Drug Administration**

Silver Spring, MD 20993

[www.fda.gov](http://www.fda.gov)

modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 211243 REMS ASSESSMENT**

*or*

**NEW SUPPLEMENT FOR NDA 211243/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 211243/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 211243/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING  
CHANGES SUBMITTED IN SUPPLEMENT XXX**

*or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 211243/S-000  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISIONS FOR NDA 211243**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

**SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

As soon as possible, but no later than 14 days from the date of this letter, submit the

REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For more information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto:FDAREMSwebsite@fda.hhs.gov).

### **PATENT LISTING REQUIREMENTS**

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ermias Zerislassie, Associate Director for Postmarket Regulatory Science, at 301-796-2770.

Sincerely,

*{See appended electronic signature page}*

Tiffany R. Farchione, MD  
Director  
Division of Psychiatry  
Office of Neuroscience  
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

U.S. Food and Drug Administration  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

-----  
**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/  
-----

TIFFANY R FARCHIONE  
01/23/2026 05:14:50 PM