NDA 211243/S-25

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 July 18, 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 July 31, 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 include updates to the website to change the login process, enhancements to improve system usability and stakeholder workflows, and to add links to Spanish language materials. Additional modifications to the REMS consist of changes to the audit requirements for pharmacies and healthcare settings in the REMS Document, and a correction to the Program Overview to include missing risk information.

Your proposed modified REMS, submitted on July 18, 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
    iii. REMS Coordinating Center
        iv. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, inpatient healthcare settings, outpatient healthcare settings, wholesaler/distributors, other)
        v. 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)
        vi. Summary of frequently asked questions (FAQ) by stakeholder type
        vii. Summary report of REMS-related problems identified and resulting corrective actions

2. REMS Enrollment Statistics
    a. Certified Inpatient and Outpatient Healthcare Settings
        viii. Number of newly enrolled 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)
        ix. 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**
        x. Healthcare settings that were unable to become certified and reasons why

b. Certified Pharmacies

xi. Number of newly enrolled 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)

xii. Pharmacies that were unable to become certified and reasons why

c. Contracted Wholesalers/Distributors

xiii. Number of newly contracted and active wholesalers/distributors (active wholesalers/distributors defined as those that have shipped SPRAVATO)

xiv. Number of contracted wholesalers/distributors that shipped SPRAVATO

d. Enrolled Outpatients

xv. Number of newly enrolled and active outpatients (outpatients who have administered at least one dose of SPRAVATO) stratified by age, sex, and geographic region (defined by US Census)

3. SPRAVATO Utilization Data

a. The number of devices distributed to certified inpatient healthcare settings, outpatient healthcare settings, and pharmacies

b. Number of treatments administered at certified outpatient healthcare settings (first treatment session and subsequent treatment sessions) stratified by:

xvi. Healthcare Setting type

xvii. Prescriber specialty, professional degree/credentials, geographic region (defined by US Census)

xviii. Patient demographics (e.g., age, sex, geographic region (Defined by US Census))

4. REMS Compliance

a. Provide a summary report of non-compliance identified, including but not limited to:

xix. Provide a copy of the SPRAVATO REMS Compliance Assessment Action Plan including the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS.

xx. Provide a copy of the audit plan for each stakeholder.

xxi. Report of audit findings for each stakeholder group (certified Healthcare Settings, certified Pharmacies, and contracted wholesalers/distributors).

1) The number of audits expected, and the number of audits performed.
2) The number and types of deficiencies noted for each group of audited stakeholders.
3) For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
4) For any that did not complete the CAPA within one month of the audit, describe actions taken.
5) Include a unique identification (ID) for each stakeholder that had deviations to track deviations by stakeholder over time.
6) Documentation of completion of training for relevant staff.
7) The existence of documented processes and procedures for complying with the REMS Program, including ensuring that patients are not given SPRAVATO for home use.
8) 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 sites' recertification.
9) Any of elements stated in 4. b-d. of this Assessment Plan that are noted as observations in the audit.
10) Any other SPRAVATO REMS non-compliance, source of report and resulting corrective actions

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):

xxii. The number and type of certified Healthcare Settings for which non-compliance with the REMS Program is detected.

xxiii. The number and type of non-certified Healthcare Settings that administered SPRAVATO and the number of incidents for each.

xxiv. 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.

xxv. Number of times SPRAVATO was distributed, transferred, or loaned from one Healthcare Setting (certified or non-certified) to another.

xxvi. The number of certified Healthcare Settings suspended and/or de-certified for non-compliance with REMS Program requirements and reasons for such actions.

xxvii. The number of patients who received a SPRAVATO administration in an outpatient setting that were not enrolled.

xxviii. 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

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):

xxix. The number of certified Pharmacies for which non-compliance with the REMS Program is detected.

xxx. The number and type of non-certified Pharmacies that dispensed SPRAVATO and the number of incidents for each.

xxxi. 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):

xxxii. The number of contracted wholesalers/distributors for which noncompliance with the REMS Program is detected.

xxxiii. The number and type of non-contracted wholesalers/distributors that shipped SPRAVATO and the number of incidents for each.

xxxiv. The number of instances where contracted wholesalers/distributors shipped SPRAVATO directly to noncertified Healthcare Settings, non-certified Pharmacies, or directly to patients.

xxxv. The number of contracted wholesalers/distributors suspended for noncompliance with REMS Program requirements and reasons for such actions.

Safe Use Behaviors

1. **Patient Monitoring Forms** – Outpatient Use Only
    a. Number of SPRAVATO REMS Patient Monitoring Forms received as of the assessment report cut-off date by the number of active outpatients.
    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).

Health Outcomes and/or Surrogates of Health Outcomes

5. Safety Surveillance
    a. An analysis of serious adverse events of interest (SAEIs), defined as any event involving sedation, dissociation, respiratory depression, or hypertension. The analysis should include evaluation of whether the REMS processes for patient monitoring were followed. Sources of the reports are to include but not be limited to:

        xxxvi. The SPRAVATO REMS **Patient Monitoring Form** – Outpatient Use Only
            1) Number of patients with SAEIs reported on the **Patient Monitoring Forms**.
            2) Number of patients who were ready for discharge after the twohour monitoring period reported on the **Patient Monitoring Forms**.
            3) Number of patients whose vital signs were not considered in acceptable range prior to administration and at treatment session completion
            4) Number of patients whose pulse oximetry was not considered at an acceptable level prior to administration, during treatment, and at treatment session completion.

5) Number of SAEIs reported on the **Patient Monitoring Form** stratified by the total dose administered.

6) Number of SAEIs linked to patients who were not monitored for two hours.

7) Trend analysis of whether SAEIs decrease or increase over time.

xxxvii. SAEIs reported in the REMS registry

xxxviii. Spontaneous adverse event reports

1) Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest.

xxxix. 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.

Evaluation of Knowledge

6. Knowledge Surveys (beginning with the 1year assessment report and annually thereafter with each assessment report) to assess patients' understanding of the risk of serious adverse outcomes from sedation, dissociation, and respiratory depression as a result of SPRAVATO administration, and abuse and misuse of SPRAVATO and the REMS requirements to ensure safe use:

a) Enrolled Patients

Overall Assessment of REMS Effectiveness

7. 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 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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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.

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

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
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