NDA 211243/S-004

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
Attention: Patricia K. Treichler, RAC
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Ms. Treichler:

Please refer to your supplemental new drug application (sNDA) dated October 2, 2019, received October 2, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spravato (esketamine) nasal spray.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated October 2, 2019.

This Prior Approval supplemental new drug application provides for the following changes: 1) modifications to the approved risk evaluation and mitigation strategy (REMS) and 2) a new indication for the depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are waiving the pediatric studies requirement for ages 0 to 8 years because necessary studies are impossible or highly impracticable. This is because of the rare incidence of the condition in this pediatric population. Furthermore, study enrollment in this patient population is also considered highly impracticable due to the limited number of patients in this age group.

We are deferring submission of your pediatric studies for ages 9 to <18 years for this application because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

3915-1 Double-blind, double-dummy, randomized, active-controlled dose-response efficacy and safety study in pediatric subjects with major depressive disorder ages 9 to <18.

Final Protocol Submission: 05/2017 (submitted)
Study Completion: 06/2022
Final Report Submission: 11/2022

3915-2 Double-blind, double-dummy, randomized, active-controlled study in pediatric subjects with major depressive disorder ages 9 to <18.

Final Protocol Submission: 07/2022
Study Completion: 04/2025
Final Report Submission: 09/2026

3915-3 Open-label safety study in pediatric subjects with major depressive disorder ages 9 to <18

Final Protocol Submission: 07/2023
Study Completion: 04/2026
Final Report Submission: 09/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit the protocol(s) to your IND 129516, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for SPRAVATO (esketamine) was originally approved on March 5, 2019, and the most recent modification was approved on June 25, 2019. 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 consist of changing the requirements for the certified healthcare setting based on inpatient or outpatient setting in the REMS document; aligning the patient enrollment form, REMS website, and REMS Program Overview with these requirements; and replacing the single healthcare setting enrollment form with setting specific enrollment forms.

Your proposed modified REMS, submitted on October 9, 2019, and 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:

Program Implementation and Operations

1. REMS Program Implementation (2-year assessment only)

    a. Date when the SPRAVATO REMS website became live and fully operational

    b. Date when inpatient and outpatient healthcare settings could become certified

    c. Date when pharmacies could become certified

    d. Date when outpatients could become enrolled

    e. Date when the REMS Coordinating Center was and fully operational with new

2. 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, inpatient healthcare settings, outpatient 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

3. REMS Enrollment Statistics (per reporting period and cumulatively)

    a. Certified Inpatient and Outpatient Healthcare Settings

        i. 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 the U.S. Census)

        ii. Number of outpatient healthcare settings that dispensed/provided SPRAVATO for administration stratified by the healthcare setting type and geographic region (defined by the U.S. 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 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 the U.S. Census)

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

c. Contracted Wholesalers/Distributors

i. Number of newly contracted 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 and active outpatients (outpatients who have administered at least one dose of SPRAVATO) stratified by age, sex, and geographic region (defined by the U.S. Census)

4. 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:

i. Healthcare Setting type

ii. Prescriber specialty, professional degree/credentials, geographic region (defined by the U.S. Census)

iii. Patient demographics (e.g., age, sex, geographic region (Defined by the U.S. Census))

5. 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 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 stakeholder would be suspended or decertified 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 contracted 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 1 month of audit
- For any that did not complete the CAPA within 1 month of the audit, describe actions taken
- Include a unique identification (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 sites' recertification
- Any of elements stated in 5. b-d. of this Assessment Plan that are noted as observations in the audit
- 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):

i. The number and type of certified Healthcare Settings for which noncompliance 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) 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 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 in an outpatient setting that were not enrolled

vii. Number of patients treated in an outpatient setting who were not observed for at least 2 hours after administration based on the *Patient Monitoring Form*:

- Number of events
- Number of outpatient 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 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 contracted wholesalers/distributors for which non-compliance with the REMS Program is detected

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

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

   iv. The number of contracted wholesalers/distributors suspended for non-compliance with REMS Program requirements and reasons for such actions

Safe Use Behaviors

6. *Patient Monitoring Forms* – Outpatient Use Only (per reporting period and cumulatively)

   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

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 sedation, dissociation, 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 are not limited to:

i. The SPRAVATO REMS *Patient Monitoring Form* – Outpatient Use Only

- Number of patients with sedation or dissociation and whether they required medical intervention and number of patients with a blood pressure increase reported on the *Patient Monitoring Forms*, including:
  - Number of patients with sedation, dissociation, or a blood pressure increase reported on the *Patient Monitoring Form* stratified by the total dose administered
  - Provide the number of patients where the time to resolution of sedation and dissociation symptoms was greater than 2 hours
- Number of patient treatment sessions with sedation or dissociation, whether the events required medical intervention, and number of treatment sessions with a blood pressure increase reported on the *Patient Monitoring Forms*, including:
  - Those events that resulted in monitoring greater than 2 hours in each treatment session; include the mean, median, and range of time to resolution
  - Number of treatment sessions with sedation, dissociation, or a blood pressure increase reported on the *Patient Monitoring Form* stratified by the total dose administered.
- Number of patients with serious adverse events reported on the *Patient Monitoring Forms*
- Number of patients who were considered ready for discharge prior to the 2-hour monitoring period reported on the *Patient Monitoring Forms*; provide the time in minutes from start of SPRAVATO administration to when the patient is considered ready for discharge; include the mean, median, and range
- Number of patients who 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 serious adverse event 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, or communication

8. Knowledge, Attitudes, and Behavior (KAB) stakeholder surveys (beginning with the 1-year assessment report and annually thereafter with each assessment report) to assess stakeholders' understanding of the risks of serious adverse outcomes from sedation and dissociation as a result of SPRAVATO administration and from the abuse and misuse of SPRAVATO and the REMS requirements to ensure safe use for patients; stakeholders include:

   a. Authorized representatives and healthcare providers within the certified Healthcare Settings

   b. 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.

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:

1. An evaluation of how the benefit-risk profile will or will not change with the new indication.

2. A determination of the implications of a change in the benefit-risk profile for the current REMS.

3. *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.

4. *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.

5. *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.

6. *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 a 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, potential effect on patient access to the drug, and potential effect on the associated health care delivery system burden; 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/
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

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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 Shin-Ye (Sandy) Chang, Regulatory Project Manager, at (301) 796-3971, or email shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- 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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