CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211243**Orig1s000**

Trade Name:	Spravato nasal spray, 28 mg
Generic or Proper Name:	esketamine
Sponsor:	Janssen Pharmaceuticals, Inc.
Approval Date:	March 5, 201
Indication:	Spravato is indicated for: Is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults.

CENTER FOR DRUG EVALUATION AND RESEARCH

211243Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211243Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211243

NDA APPROVAL

Janssen Pharmaceuticals, Inc.
Attention: Patricia K. Treichler, RAC
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Treichler:

Please refer to your New Drug Application (NDA) dated September 4, 2018, received September 4, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spravato (esketamine) nasal spray 28 mg single-use device.

This new drug application provides for the use of Spravato (esketamine) nasal spray for treatment of treatment-resistant depression.

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 text.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) 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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211243**." Approval of this submission by FDA is not required before the labeling is used.

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable given the low prevalence of treatment-resistant depression in this population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of cognitive decline, ulcerative or interstitial cystitis, and increased thyroid stimulating hormone levels.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cognitive decline, ulcerative or interstitial cystitis, and increased thyroid stimulating hormone levels.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3577-1 Conduct a 3-year open-label safety study to characterize the long-term effects of esketamine on cognitive function and urinary symptoms. Ongoing trial TRD 3008 will be adapted to meet this requirement.

The timetable you submitted on March 1, 2019 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	04/19
Trial Completion:	12/20
Final Report Submission:	05/21

3577-2 To further characterize the potential risk of increasing thyroid stimulating hormone levels, analyze biobank samples taken at screening and predose on Days 1, 8, 25 or early withdrawal visits from patients who participated in the TRD3001 and TRD3002 Phase 3 studies.

The timetable you submitted on March 1, 2019 states that you will conduct this trial according to the following schedule:

Final Report Submission:	09/19

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 114345 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3577-3 Conduct a study to evaluate the efficacy of esketamine monotherapy for the treatment of treatment-resistant depression. The study design must be agreed to by the Division prior to initiating the study.

The timetable you submitted on March 1, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/19
Study/Trial Completion:	03/22
Final Report Submission:	08/22

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 114345 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Spravato (esketamine) to ensure the benefits of the drug outweigh the risks of misuse, abuse, and serious adverse outcomes from dissociation and sedation.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Spravato can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of misuse, abuse, and serious adverse outcomes from dissociation and sedation listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- 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
- Each patient using the drug is enrolled in a registry

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified, the drug be dispensed to patients only in certain health care settings, and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on September 4, 2018, amended and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Spravato into interstate commerce.

The REMS assessment plan must include, 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
    d. 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 (per reporting period and cumulatively)
    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)
    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).
            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 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 site's recertification.
            9. 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:
      1. Number of events
      2. Number of healthcare settings
      3. Number of events per patient and per administration
      4. 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
         1. 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
         2. Number of patients that were ready for discharge prior to the 2-hour monitoring period reported on the Patient Monitoring Forms.
         3. Number of patients that were ready for discharge after the 2-hour monitoring period reported on the Patient Monitoring Forms.
         4. Number of adverse events reported on the Patient Monitoring Form stratified by the total dose administered
         5. Number of adverse events linked to patients who were not monitored for 2 hours
         6. Trend analysis of whether adverse events decrease or increase over time
      ii. Adverse events reported in the REMS registry
      iii. 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
2. 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.

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). 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, proposed 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 the 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 a REMS modification*, 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 CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

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

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 LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

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 REVISION 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

SPECIAL REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). In addition, we request that you expedite cases (i.e., submit these cases as 15-day Alert reports) of all serious adverse event reports for esketamine. Every effort should be made to obtain thorough and complete follow-up for each case of serious adverse events for esketamine. The clinical information collected will enhance the quality of adverse event reports submitted to FDA and facilitate our assessment of these reports. We also request that you include a summary and analysis of all serious adverse events for esketamine in the submission of the periodic reports for esketamine for each reporting period.

If you have any questions, call CDR Hiren D. Patel, Team Leader, Regulatory Project Management, at (301) 796-2087 or email Hiren.Patel@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director (Acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling
- 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
03/05/2019 06:23:27 PM