

# Risk Evaluation and Mitigation Strategy (REMS) Document

## SPRAVATO (esketamine) REMS Program

### I. Administrative Information

Application Number: NDA 211,243

Application Holder: Janssen Pharmaceuticals, Inc.

Initial REMS Approval: 3/2019

Most recent REMS Update: 7/2020

### II. REMS Goal

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

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

### III. REMS Requirements

**Janssen Pharmaceuticals, Inc. must ensure that healthcare settings, patients, pharmacies, and wholesalers-distributors comply with the following requirements:**

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#### 1. Healthcare settings that dispense SPRAVATO for outpatient use must:

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To become certified to dispense

1. Have a prescriber onsite during SPRAVATO administration and monitoring.
2. Have healthcare provider(s) onsite to monitor patients.
3. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the healthcare setting.
4. Have the authorized representative review the SPRAVATO prescribing information and [REMS Program Overview](#).
5. Have the authorized representative enroll in the REMS Program by completing the [Outpatient Healthcare Setting Enrollment Form](#) and submitting it to the REMS Program.
6. Establish processes and procedures to enroll the patient in the REMS Program.
7. Establish processes and procedures to counsel the patient on the need for enrollment, monitoring, and risks of sedation and dissociation, and changes in vital signs.

8. Establish processes and procedures to verify the patient is enrolled in the REMS Program before each administration and that SPRAVATO is not dispensed for use outside the certified healthcare setting.
9. Establish processes and procedures to complete and submit the [Patient Monitoring Form](#) after each administration within 7 calendar days.
10. Train all relevant staff involved in prescribing, dispensing and administering SPRAVATO on 1) Counseling the patient on the need for monitoring and risks of sedation and dissociation, and changes in vital signs; 2) Patient administration under the supervision of a healthcare provider; and 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours.
11. Establish processes and procedures to identify all staff involved in prescribing, dispensing, and administering SPRAVATO and ensure they are trained on 1) Counseling the patient on the need for monitoring and risks of sedation and dissociation, and changes in vital signs; 2) Patient administration under the supervision of a healthcare provider; 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours.

Before treatment initiation (first dose)	<ol style="list-style-type: none"> <li>12. Counsel the patient on the risks and need for monitoring for resolution of sedation and dissociation and changes in vital signs.</li> <li>13. Enroll the patient by completing and submitting the <a href="#">Patient Enrollment Form</a> to the REMS Program.</li> </ol>
Before administering	<ol style="list-style-type: none"> <li>14. Counsel the patient on the need for monitoring for resolution of sedation and dissociation, and changes in vital signs.</li> <li>15. Verify the patient is enrolled in the REMS Program through the processes and procedures established as a requirement of the REMS Program.</li> </ol>
During and after administering, for at least 2 hours	<ol style="list-style-type: none"> <li>16. Assess the patient for administration of SPRAVATO and resolution of sedation and dissociation, and changes in vital signs.</li> </ol>
After administering, within 7 calendar days	<ol style="list-style-type: none"> <li>17. Document and submit to the REMS Program using the <a href="#">Patient Monitoring Form</a>.</li> </ol>
To maintain certification to dispense	<ol style="list-style-type: none"> <li>18. Have any new authorized representative enroll in the REMS Program by completing the <a href="#">Outpatient Healthcare Setting Enrollment Form</a>.</li> </ol>
At all times	<ol style="list-style-type: none"> <li>19. Not dispense SPRAVATO for use outside the certified healthcare setting.</li> <li>20. Not distribute, transfer, loan, or sell SPRAVATO.</li> <li>21. Maintain records documenting staff's completion of training.</li> </ol>

22. Maintain records that all processes and procedures are in place and are being followed.
23. Maintain records of all shipments of SPRAVATO received and dispensing information including patient name, dose, number of devices, and date administered.
24. Comply with audits carried out by Janssen Pharmaceuticals, Inc. or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.

**2. Healthcare settings that dispense SPRAVATO for inpatient use (including emergency departments within certified healthcare settings) must:**

To become certified to dispense

1. Have a prescriber onsite during SPRAVATO administration and monitoring.
2. Have healthcare provider(s) onsite to monitor patients.
3. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the healthcare setting.
4. Have the authorized representative review the SPRAVATO prescribing information and [REMS Program Overview](#).
5. Have the authorized representative enroll in the REMS Program by completing and submitting the [Inpatient Healthcare Setting Enrollment Form](#).
6. Establish processes and procedures to counsel the patient on the need for monitoring and risks of sedation and dissociation, and changes in vital signs.
7. Establish processes and procedures to verify SPRAVATO is not dispensed for use outside the certified healthcare setting.
8. Train all relevant staff involved in prescribing, dispensing and administering SPRAVATO on 1) Counseling the patient on the need for monitoring, risks of sedation and dissociation, changes in vital signs, and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities; 2) Patient administration under the supervision of a healthcare provider; and 3) Monitoring for resolution of sedation and dissociation and changes in vital signs for a minimum of 2 hours.

Before administering

9. Counsel the patient on the need for monitoring for resolution of sedation and dissociation, and changes in vital signs and the need to have arrangements to safely leave the healthcare setting and not engage in potentially hazardous activities

During and after administering, for at least 2 hours

10. Assess the patient for administration of SPRAVATO and resolution of sedation and dissociation, and changes in vital signs.

To maintain certification to dispense	11. Have any new authorized representative enroll in the REMS Program by completing the <a href="#">Inpatient Healthcare Setting Enrollment Form</a> .
At all times	<p>12. Not dispense SPRAVATO for use outside the certified healthcare setting.</p> <p>13. Not distribute, transfer, loan, or sell SPRAVATO.</p> <p>14. Maintain records documenting staff's completion of training.</p> <p>15. Maintain records that all processes and procedures are in place and are being followed.</p> <p>16. Maintain records of all shipments of SPRAVATO received and dispensing information including patient name, dose, number of devices, and date administered.</p> <p>17. Comply with audits carried out by Janssen Pharmaceuticals, Inc. or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.</p>

### 3. Patients who are prescribed SPRAVATO:

Before treatment initiation (first dose)	<p>1. Receive counseling from a healthcare provider on risks and the need for monitoring for resolution of sedation and dissociation, and changes in vital signs.</p> <p>2. For outpatients: Enroll in the REMS Program by completing the <a href="#">Patient Enrollment Form</a> with a healthcare provider. Enrollment information will be provided to the REMS Program.</p>
During treatment, before each dose	3. Receive counseling from a healthcare provider on the need for monitoring for resolution of sedation and dissociation; and change in vital signs.
During treatment, during and after administration for at least 2 hours	4. Be monitored for taking SPRAVATO, resolution of sedation and dissociation, and changes in vital signs at the healthcare setting.

### 4. Pharmacies that dispense SPRAVATO must:

To become certified to dispense	<p>1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.</p> <p>2. Have the authorized representative enroll in the REMS Program by completing the <a href="#">Pharmacy Enrollment Form</a> and submitting it to the REMS Program.</p> <p>3. Establish processes and procedures to verify that a healthcare setting is certified in the REMS Program before dispensing SPRAVATO.</p> <p>4. Train all relevant staff involved in dispensing that SPRAVATO must only be dispensed to a certified healthcare setting.</p>
Before dispensing	5. Verify that the healthcare setting is certified through the processes and procedures established as a requirement of the REMS Program.

At all times	<ol style="list-style-type: none"> <li>6. Not distribute, transfer, loan or sell SPRAVATO except to certified dispensers.</li> <li>7. Not dispense SPRAVATO for use outside a certified healthcare setting.</li> <li>8. Maintain records documenting staff's completion of training.</li> <li>9. Maintain records that all processes and procedures are in place and are being followed.</li> <li>10. Maintain records of all shipments of SPRAVATO received and dispensing information including patient name, dose, number of devices, and date dispensed.</li> <li>11. Comply with audits carried out by Janssen Pharmaceuticals, Inc. or third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.</li> </ol>
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**5. Wholesalers-distributors that distribute SPRAVATO must:**

To be able to distribute	<ol style="list-style-type: none"> <li>1. Establish processes and procedures to ensure that SPRAVATO is distributed only to certified healthcare settings and certified pharmacies.</li> <li>2. Train all relevant staff involved in distributing on the REMS Program requirements.</li> </ol>
At all times	<ol style="list-style-type: none"> <li>3. Distribute only to certified healthcare settings and certified pharmacies.</li> <li>4. Maintain and submit records of all shipments of SPRAVATO.</li> <li>5. Comply with audits carried out by Janssen Pharmaceuticals, Inc. or a third party acting on behalf of Janssen Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.</li> </ol>

**Janssen Pharmaceuticals, Inc. must provide training to health care settings that dispense SPRAVATO.**

The training includes the following educational material: [REMS Program Overview](#). The training must be provided online and in hardcopy format by mail or fax.

**To support REMS Program operations, Janssen Pharmaceuticals, Inc. must:**

1. Establish and maintain a REMS Program website, [www.SPRAVATOREMS.com](http://www.SPRAVATOREMS.com). The REMS Program website must include the capability to complete healthcare setting and pharmacy certification online, patient enrollment online, the capability to provide patient monitoring information online, and to print the Prescribing Information, Medication Guide and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS program website. The REMS program website must not link back to the promotional product website(s).
2. Make the REMS program website fully operational and all REMS materials available through the website and coordinating center.
3. Establish and maintain a REMS coordinating center for REMS participants at 1-855-382-6022.

4. Establish and maintain a validated and secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
5. Ensure healthcare settings and pharmacies are able to enroll and certify in the REMS Program online or by fax.
6. Ensure healthcare providers in outpatient healthcare settings are able to enroll patients by fax and online.
7. Ensure outpatient healthcare settings are able to submit the [Patient Monitoring Form](#) by fax and online.
8. Notify healthcare settings and pharmacies within 7 calendar days after they become certified in the REMS.
9. Provide the [Outpatient Healthcare Setting Enrollment Form](#), [Inpatient Healthcare Setting Enrollment Form](#), [Pharmacy Enrollment Form](#), [REMS Program Overview](#) and Prescribing Information to REMS participants who (1) attempt to dispense SPRAVATO and are not yet certified, or (2) inquire about how to become certified.
10. Provide public access to a database of certified healthcare settings and pharmacies.
11. Provide certified pharmacies access to the database of certified healthcare settings.
12. Provide certified healthcare settings access to the database of certified pharmacies and enrolled patients.
13. Provide authorized wholesalers-distributors access to a database of certified pharmacies and healthcare settings.
14. Establish and maintain a registry, which includes a reporting and collection system for all patients treated in outpatient healthcare settings, to provide information on the incidence of adverse outcomes from sedation and dissociation.
15. Ensure that once a report suggestive of adverse outcomes from sedation or dissociation is received, Janssen Pharmaceuticals, Inc. follows up with the healthcare provider to obtain all required data for the registry.

**To ensure REMS participants' compliance with the REMS program, Janssen Pharmaceuticals, Inc. must:**

16. Notify outpatient healthcare settings if [Patient Monitoring Forms](#) have not been received by the REMS Program in the last 60 calendar days from the date of submission of the [Patient Enrollment Form](#).
17. Ensure every 60 calendar days from the date of submission of the [Patient Enrollment Form](#) that all expected monitoring forms are received for each patient.
18. Verify annually that the authorized representative's name and information correspond to the authorized healthcare setting or pharmacy. If the authorized representative changes at any time, the healthcare setting or pharmacy must be required to re-certify with a new authorized representative.
19. Maintain adequate records to demonstrate that REMS requirements have been met, including but not limited to records of: drug distribution and dispensing; certification of healthcare settings and pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
20. Establish a plan for addressing non-compliance with the REMS Program requirements.

21. Monitor pharmacies, healthcare settings, and wholesalers/distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
22. Audit 15% or 50 healthcare settings (whichever is greater), 15% or 50 pharmacies (whichever is greater), and data from all wholesalers-distributors that have ordered/dispensed SPRAVATO at 12 months from date of first commercial distribution and annually thereafter to ensure that all REMS processes are in place, functioning and support the REMS requirements. To be audited, healthcare setting must have received at least one shipment of SPRAVATO in the past 12 months and not have been previously audited in the past 3 years.
23. Take reasonable steps to improve implementation of and compliance with the requirements in the SPRAVATO REMS Program based on monitoring and evaluation of the SPRAVATO REMS Program.

## **IV. REMS Assessment Timetable**

Janssen Pharmaceuticals, Inc. must submit REMS assessments at 6 months and 12 months from the date of initial approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Janssen Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

## **V. REMS Materials**

The following materials are part of the SPRAVATO REMS:

### **Enrollment Forms**

Healthcare Setting:

1. [Outpatient Healthcare Setting Enrollment Form](#)
2. [Inpatient Healthcare Setting Enrollment Form](#)

Patient:

3. [Patient Enrollment Form](#)

Pharmacy:

4. [Pharmacy Enrollment Form](#)

### **Training and Educational Materials**

Healthcare Setting:

5. [REMS Program Overview](#)

Pharmacy:

6. [REMS Program Overview](#)

### **Patient Care Forms**

7. [Patient Monitoring Form](#)

### **Other Materials**

8. [REMS Program Website](#)