

## **PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN**

### **Summary of Risk Management Plan for SPRAVATO (esketamine nasal spray)**

This is a summary of the Risk Management Plan (RMP) for SPRAVATO (esketamine nasal spray). The RMP details important risks of SPRAVATO, how these risks can be minimized, and how more information will be obtained about SPRAVATO's risks and uncertainties (missing information).

SPRAVATO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals (HCPs) and patients on how SPRAVATO should be used.

This summary of the RMP for SPRAVATO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SPRAVATO's RMP.

#### **I. The Medicine and What it is Used For**

SPRAVATO is authorized for use as an antidepressant in adults with treatment-resistant major depressive disorder (TRD) or acute short-term treatment of psychiatric emergency due to major depressive disorder (see SmPC for the full indications). It contains an aqueous solution of esketamine hydrochloride as the active substance within a single-use nasal spray device that delivers two sprays, one spray to each nostril.

Further information about the evaluation of SPRAVATO's benefits can be found in SPRAVATO's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: <https://www.ema.europa.eu/en/medicines/human/EPAR/spravato>.

#### **II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks**

Important risks of SPRAVATO, together with measures to minimize such risks and the proposed studies for learning more about SPRAVATO's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of SPRAVATO, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of SPRAVATO is not yet available, it is listed under 'missing information' below.

## **II.A. List of Important Risks and Missing Information**

Important risks of SPRAVATO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SPRAVATO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

<b>List of Important Risks and Missing Information</b>	
Important identified risks	Drug abuse Transient dissociative states and perception disorders Disturbances in consciousness Blood pressure increased
Important potential risks	Cognitive disorders and memory impairment (long-term use) Interstitial cystitis (long-term use)
Missing information	Use during pregnancy

## II.B. Summary of Important Risks

<b>Important Identified Risk: Drug abuse</b>	
Evidence for linking the risk to the medicine	Evidence from an esketamine abuse potential trial (Trial 54135419TRD1015) suggests that the potential for abuse is similar to that of ketamine, a known drug of abuse recreationally. No evidence of drug-seeking behavior was observed, and no confirmed cases of diversion were reported in clinical trials of esketamine nasal spray.
Risk factors and risk groups	<p>Risk factors and groups for substance abuse include mental health disorders (eg, depression, anxiety, and bipolar disorder), stressful environmental factors, taking addictive prescription medication, alcohol consumption, and family history of drug abuse and addiction.</p> <p>Dependence and attenuation to SPRAVATO may develop, particularly when not used as prescribed (eg, taking high doses on a daily basis over an extended period of time) or in individuals with a history of drug abuse or dependence.</p>
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> <li>• SmPC Section 4.4;</li> <li>• PL Section 2.</li> <li>• Administration under the direct supervision of a healthcare professional (SmPC Sections 4.2 and 4.4, PL Section 3, and Instructions for Use);</li> <li>• Limited pack sizes;</li> <li>• Legal status: Special and restricted medical prescription with categorization at the Member State level.</li> </ul> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> <li>• Healthcare Professional Guide;</li> <li>• Patient Guide;</li> <li>• Controlled Access Program.</li> </ul>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>• Survey to assess effectiveness of the additional risk minimization materials.</li> </ul> <p>See section II.C of this summary for an overview of the postauthorization development plan.</p>

Key: PL = Package Leaflet; SmPC = Summary of Product Characteristics.

<b>Important Identified Risk: Transient dissociative states and perception disorders</b>	
Evidence for linking the risk to the medicine	Transient dissociative states and perception disorders are expected effects of SPRAVATO based on esketamine's mechanism of action, and have been observed in all phases of the clinical development program.
Risk factors and risk groups	<p>Risk factors for transient dissociative states and perception disorders are unknown.</p> <p>There is a dose-response relationship between the esketamine dose and the severity of transient dissociative states/perception disorders, which is attenuated with repeated doses.</p>
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> <li>• SmPC Sections 4.4, 4.7, and 4.8;</li> <li>• PL Sections 2 and 4;</li> <li>• Recommendations for dose adjustment are included in SmPC Section 4.2;</li> <li>• Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2;</li> <li>• Recommendation for postadministration observation is included in SmPC Section 4.2;</li> <li>• As described in SmPC Sections 4.2 and 4.4 and PL Section 3, administration and postadministration monitoring take place under the supervision of a healthcare professional.</li> <li>• Legal status: Special and restricted medical prescription with categorization at the Member State level.</li> </ul> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> <li>• Healthcare Professional Guide;</li> <li>• Patient Guide;</li> <li>• Healthcare Professional Checklist.</li> </ul>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>• Survey to assess effectiveness of the additional risk minimization materials.</li> </ul> <p>See section II.C of this summary for an overview of the postauthorization development plan.</p>

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<b>Important Identified Risk: Disturbances in consciousness</b>	
Evidence for linking the risk to the medicine	Disturbances in consciousness such as sedation and somnolence are expected effects of SPRAVATO based on esketamine's mechanism of action, and have been observed in all phases of the clinical development program.
Risk factors and risk groups	Risk factors for sedation include old age (elderly patients) and use of concomitant sedatives.
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> <li>• SmPC Sections 4.4, 4.7, and 4.8;</li> <li>• PL Sections 2 and 4;</li> <li>• Recommendations for dose adjustment are included in SmPC Section 4.2;</li> <li>• Recommendation regarding driving a motor vehicle or operating machinery is included in SmPC Section 4.7 and PL Section 2;</li> <li>• Recommendation for postadministration observation is included in SmPC Section 4.2;</li> <li>• As described in SmPC Sections 4.2 and 4.4 and PL Section 2, administration and postadministration monitoring take place under the supervision of a healthcare professional.</li> <li>• Recommendation that administration and postadministration observation of SPRAVATO should be carried out in an appropriate clinical setting (SmPC Section 4.2).</li> <li>• Legal status: Special and restricted medical prescription with categorization at the Member State level.</li> </ul> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> <li>• Healthcare Professional Guide;</li> <li>• Patient Guide;</li> <li>• Healthcare Professional Checklist.</li> </ul>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>• Survey to assess effectiveness of the additional risk minimization materials.</li> </ul> <p>See section II.C of this summary for an overview of the postauthorization development plan.</p>

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<b>Important Identified Risk: Blood pressure increased</b>	
Evidence for linking the risk to the medicine	Cardiovascular effects due to increased blood pressure are expected for SPRAVATO based on esketamine's mechanism of action (sympathomimetic effect; direct stimulation of the CNS that leads to increased sympathetic nervous system outflow). Transient increases in blood pressure, as well as cardiovascular and blood pressure-related events, in association with esketamine nasal spray have been reported in the completed randomized, double-blind, controlled and open-label clinical trials. In clinical trials, elevations of blood pressure were transient, generally self-limiting, and did not require intervention.
Risk factors and risk groups	The risk of cardiovascular effects is greater in patients for whom an increase in blood pressure poses a serious risk, for example: <ul style="list-style-type: none"> <li>• Patients who recently experienced a cardiovascular event, including myocardial infarction;</li> <li>• Patients with aneurysmal vascular disease (including intracranial, thoracic aorta, abdominal aorta, or peripheral arterial vessels);</li> <li>• Patients with history of intracerebral hemorrhage.</li> </ul>
Risk minimization measures	Routine risk minimization measures: <ul style="list-style-type: none"> <li>• SmPC Sections 4.2, 4.3, 4.4, and 4.8;</li> <li>• PL Sections 2 and 4.</li> <li>• Recommendations regarding blood pressure assessment (before and after treatment), monitoring, and actions to manage blood pressure elevation are provided in SmPC Sections 4.2 and 4.4;</li> <li>• Recommendation regarding treatment in patients whose blood pressure is elevated prior to administration is provided in SmPC Section 4.4;</li> <li>• Recommendation not to administer SPRAVATO to patients in whom an elevation of blood pressure would present a serious risk is provided in SmPC Sections 4.2 and 4.3 and PL Section 2.</li> <li>• As described in SmPC Section 4.2, administration and postadministration monitoring take place under the supervision of a healthcare professionals with training in blood pressure monitoring.</li> <li>• Legal status: Special and restricted medical prescription with categorization at the Member State level.</li> </ul> Additional risk minimization measures: <ul style="list-style-type: none"> <li>• Healthcare Professional Guide;</li> <li>• Patient Guide;</li> <li>• Healthcare Professional Checklist.</li> </ul>
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none"> <li>• Survey to assess effectiveness of the additional risk minimization materials.</li> </ul> See section II.C of this summary for an overview of the postauthorization development plan.

Key: CNS = central nervous system; PL = Package Leaflet; SmPC = Summary of Product Characteristics.

<b>Important Potential Risk: Cognitive disorders and memory impairment (long-term use)</b>	
Evidence for linking the risk to the medicine	Long-term cognitive disorders and memory impairment have been reported with long-term ketamine use or drug abuse. These effects did not increase over time and were reversible after ketamine discontinuation. The effect of esketamine nasal spray on cognitive functioning was evaluated in long-term clinical trials, and results generally showed that performance on cognitive tests was slightly improved or remained stable.
Risk factors and risk groups	Patients at risk for cognitive disorders and memory impairment are those who use SPRAVATO for an extended period. A study that evaluated the long-term cognitive consequences of ketamine use found that frequent ketamine users (>4 times per week) were impaired on cognitive testing after long-term use (12 months) while infrequent ketamine users (<4 times a week, but at least once a month) and ex-users did not show any long-term cognitive impairment.
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> <li>• SmPC Section 4.8;</li> <li>• PL Section 2.</li> <li>• Legal status: Special and restricted medical prescription with categorization at the Member State level.</li> </ul> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> <li>• None</li> </ul>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>• Long-term safety study 54135419TRD3008 (ongoing).</li> </ul> <p>See section II.C of this summary for an overview of the postauthorization development plan.</p>

Key: PL = Package Leaflet; SmPC = Summary of Product Characteristics.

<b>Important Potential Risk: Interstitial cystitis (long-term use)</b>	
Evidence for linking the risk to the medicine	Cystitis and lower urinary tract symptoms have been reported with ketamine in long-term street users or with higher doses (>10-fold therapeutic use). In a comprehensive literature review, the reported chronic physical effects of high-dose, near-daily, long-term ketamine use included ulcerative interstitial cystitis. Cases reported in the literature have linked ketamine abuse to cystitis. Similar effects may potentially occur following esketamine abuse. In clinical trials with esketamine nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in esketamine-treated patients than in patients who received placebo. No cases of esketamine nasal spray-related interstitial cystitis have been observed in clinical trials, which involved treatment for up to a year.
Risk factors and risk groups	Patients at risk for cystitis include those who use SPRAVATO for a long period or at higher doses than prescribed.
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> <li>• SmPC Sections 4.4 and 4.8;</li> <li>• PL Section 2.</li> <li>• Legal status: Special and restricted medical prescription with categorization at the Member State level.</li> </ul> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> <li>• None</li> </ul>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>• Long-term safety study 54135419TRD3008 (ongoing).</li> </ul> <p>See section II.C of this summary for an overview of the postauthorization development plan.</p>

Key: PL = Package Leaflet; SmPC = Summary of Product Characteristics.

<b>Missing Information: Use during pregnancy</b>	
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> <li>• SmPC Sections 4.6 and 5.3;</li> <li>• PL Section 2.</li> <li>• Legal status: Special and restricted medical prescription with categorization at the Member State level.</li> </ul> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> <li>• None.</li> </ul>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> <li>• Pregnancy registry for psychiatric medications such as antidepressants including esketamine.</li> </ul> <p>See section II.C of this summary for an overview of the postauthorization development plan.</p>

Key: PL = Package Leaflet; SmPC = Summary of Product Characteristics.

## **II.C. Postauthorization Development Plan**

### **II.C.1. Studies Which are Conditions of the Marketing Authorization**

There are no studies that are conditions of the marketing authorization or specific obligation of SPRAVATO.

### **II.C.2. Other Studies in Postauthorization Development Plan**

#### **54135419TRD3008: An open-label long-term extension safety study of intranasal esketamine in treatment-resistant depression.**

Purpose of the study: Further characterize the impact of the important potential risks of Cognitive disorders and memory impairment (long-term use) and Interstitial cystitis (long-term use) on the safety profile of SPRAVATO.

The primary objective of this trial is to assess the long-term safety (>1 year) of SPRAVATO in subjects with TRD, with special attention to the following: potential long-term effects on cognitive function; treatment-emergent adverse events (TEAEs), including TEAEs of special interest; postdose effects on heart rate, blood pressure, respiratory rate and blood oxygen saturation; potential effects on suicidal ideation/behavior.

#### **PCSNSP002812: Survey to assess the effectiveness of SPRAVATO educational materials for additional risk minimization measures.**

Purpose of the study: To assess the effectiveness of additional risk minimization materials (ie, Healthcare Professional Guide, Patient Guide, Healthcare Professional Checklist) related to the understanding of the important identified risks of Drug abuse, Transient dissociative states and perception disorders, Disturbances in consciousness, and Blood pressure increased.

A survey of HCPs involved in the prescription, administration, and management of SPRAVATO and of patients who use SPRAVATO will be conducted to measure the effectiveness of the educational materials to address the important identified risks associated with SPRAVATO treatment. Sampled HCPs involved in the prescription, administration and management of SPRAVATO treatment and patients who use SPRAVATO will be asked to participate in the survey to assess knowledge and understanding of how to reduce important identified risks, in accordance with the educational materials.

#### **National Pregnancy Registry for Antidepressants (part of the National Pregnancy Registry for Psychiatric Medications).**

Purpose of this study: To characterize the safety profile of SPRAVATO during pregnancy. Periodic safety assessments of data will be conducted from a United States-based pregnancy registry for psychiatric medications, including antidepressants. The aims of review of this registry data are as follows:

- Primary:
  - To prospectively evaluate rates of congenital malformations among infants exposed in utero to psychiatric medications;

- Secondary:
  - To evaluate neonatal outcomes of infants with prenatal exposure to specific psychiatric medications alone or in combination with other psychotropics;
  - To evaluate maternal health outcomes associated with use of psychiatric medications during pregnancy;
  - To evaluate neurobehavioral development of children (1 month and older) with prenatal exposure to psychiatric medications.