Spravato™ (esketamine) CIII nasal spray

Healthcare Provider Exceptions & Appeals Resource

Indication

SPRAVATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.

SPRAVATO™ is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO™ as an anesthetic agent have not been established.

Important Safety Information

WARNING: SEDATION, DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration (5.1, 5.2).**
- **Potential for abuse and misuse. Consider the risks and benefits of using SPRAVATO™ prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.3).**
- **SPRAVATO™ is only available through a restricted program called the SPRAVATO™ REMS (5.4).**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO™ is not approved for use in pediatric patients (5.5).**

Please see Important Safety Information, including Boxed WARNINGS, on pages 12-15.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO™.

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Introduction

Janssen Pharmaceuticals, Inc., is pleased to provide educational information to support you through the process of gaining access for your patient for SPRAVATO™ (esketamine) Nasal Spray. As a healthcare provider (HCP), you will be responsible for requesting prior authorization, exceptions, or appeals, depending on plan requirements when prescribing SPRAVATO™. This educational resource may provide you with general information or considerations to help appropriate adult patients gain access to SPRAVATO™.

Refer to the educational information and sample letters contained within this resource when completing the required coverage documentation. It is important to note that some health plans will have specific coverage authorization forms that must be used when requesting SPRAVATO™. These forms may be found on each plan's website. Janssen CarePath may also be able to obtain payer-required forms through the benefits investigation process. Be sure to follow the plan's requirements when requesting SPRAVATO™.

Contained within this resource, you will find:

- Sample Letter of Medical Necessity
- Sample Letter to Request a Formulary Exception
- Sample Medicare Part D Optional Model Form

You may also reach out to your Patient Access Specialist or Janssen representative for more information regarding these resources.

More information on SPRAVATO™ access and reimbursement is also available through **www.spravatotreatmentcenter.com**.

Please see the contact information below.

Sample letters may be downloaded at www.JanssenCarePath.com

Janssen CarePath

Janssen CarePath helps verify insurance coverage for patients, provides reimbursement information, helps find financial assistance options for eligible patients, and provides ongoing support to help patients start and stay on prescribed SPRAVATO™ treatment.

Call a Janssen CarePath Care Coordinator at 844-777-2828, Monday-Friday, 8:00 AM to 8:00 PM ET

Visit **www.JanssenCarePath.com/hcp/Spravato**.

This document is presented for informational purposes only and is not intended to provide reimbursement or legal advice. Laws, regulations, and policies concerning reimbursement are complex and updated frequently. While we have made an effort to be current as of the issue date of this document, the information may not be as current or comprehensive when you view it. In addition, this information does not represent any statement, promise, or guarantee by Janssen Pharmaceuticals, Inc., about coverage, levels of reimbursement, payment, or charge. Please consult with your payer organization(s) for local or actual coverage and reimbursement policies and determination processes. Please consult with your counsel or reimbursement specialist for any reimbursement or billing questions specific to your institution.

Considerations for Developing a Letter of Medical Necessity

A Letter of Medical Necessity is used to support why you believe treatment of your patient with SPRAVATO™ (esketamine) Nasal Spray is medically necessary. This template contains examples of information that payers may require from a healthcare provider to request coverage of SPRAVATO™.

Check with the payer to confirm whether there are specific coverage requirements or information needed as part of the request. Below are some considerations for submitting a Letter of Medical Necessity:

- Check with the payer to see if there is a specific form to use
- Be as specific as possible regarding your request, including the need for treatment, diagnosis information, the specific treatment being requested, treatment start date, etc
- Submit the Letter of Medical Necessity on your practice letterhead
- Consider requesting that the payer provide a psychiatrist to review the patient's case
- For expedited requests, assemble adequate information to support the urgency of the request
- Include additional information with the Letter of Medical Necessity that may assist the payer with making an appropriate decision for the patient. Examples of documentation that may be sent with the Letter of Medical Necessity include:
    - Patient diagnosis; please see Appendix C on page 18 for the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) major depressive disorder diagnosis codes
    - A list of the patient's previous treatments for MDD, the length of treatment, and the results of those treatments
        - SPRAVATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults*
    - Notes from the patient's medical record
        - Treatment history
        - Medication history
        - Relevant allergies or previous adverse reactions
        - Comorbidities
- Sign and date the Letter of Medical Necessity

*Based on the approved US Prescribing Information.

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Spravato™ (esketamine) CIII nasal spray

Sample Format: Letter of Medical Necessity

[Insert Physician Letterhead]

[Insert Name of Medical Director]
[Insert Payer Name]
[Insert Address]
[Insert City, State Zip]

RE: Member Name: [Insert Member Name]
Member Number: [Insert Member Number]
Group Number: [Insert Group Number]

REQUEST: Authorization for treatment with SPRAVATO™ (esketamine) Nasal Spray CIII

DIAGNOSIS: [Insert Diagnosis] [Insert ICD]

DOSE AND FREQUENCY: [Insert Dose & Frequency]

REQUEST TYPE: ☐ Standard ☐ EXPEDITED

Dear [Insert name of Medical Director or name of individual responsible for prior authorization]:

I am writing to support my request for an **authorization** for the above-mentioned patient to receive treatment with SPRAVATO™ for [Insert Indication], dosed concomitant with [insert oral antidepressant]. My request is supported by the following:

Summary of Patient's Diagnosis

[Insert patient's diagnosis, date of diagnosis, lab results and date, current condition]

Summary of Patient's History

[Insert:

- Previous therapies/procedures, including dose and duration, response to those interventions
- Description of patient's recent symptoms/condition
- Site of medical service—include appropriate site type: inpatient, hospital outpatient, outpatient clinic, private practice, or other
- Rationale for not using drugs that are on the plan's formulary
- Summary of your professional opinion of the patient's likely prognosis or disease progression without treatment with SPRAVATO™

Note: Exercise your medical judgment and discretion when providing a diagnosis and characterization of the patient's medical condition.]

Rationale for Treatment

[Insert summary statement for rationale for treatment such as: Considering the patient's history, condition, and the full Prescribing Information supporting uses of SPRAVATO™, I believe treatment with SPRAVATO™ at this time is medically necessary, and should be a covered and reimbursed service.]

[You may consider including documents that provide additional clinical information to support the recommendation for SPRAVATO™ for this patient, such as the full Prescribing Information, peer-reviewed journal articles, or clinical guidelines.]

[Given the urgent nature of this request,] please provide a timely authorization. Contact my office at [Insert Phone Number] if I can provide you with any additional information.

Sincerely,

[Insert Physician Name and Participating Provider Number]

Enclosures [Include full Prescribing Information and the additional support noted above]

Download an editable Sample Letter of Medical Necessity template at **JanssenCarePath.com/hcp/Spravato**.

Considerations for Developing an Exception Request

Consider using a Letter of Exception with commercial payers or Medicaid payers without a formal exception form to request SPRAVATO™ (esketamine) Nasal Spray if it is not on formulary, if the plan requires a step through other treatments, or if it has a National Drug Code (NDC) block. This template contains examples of information that payers may require to request an exception for SPRAVATO™.

Check with the payer to confirm whether there are specific requirements or information needed as part of the request. Below is some helpful information for submitting a Letter of Exception:

- Check with the payer to see if there is a specific form that should be used to request an exception
- Be as specific as possible regarding your request, including the need for treatment, why other alternatives on the formulary would not be appropriate for this patient, the results of other treatments that the patient has tried, etc
- Submit the Letter of Exception on your practice letterhead
- Consider requesting that the payer provide a psychiatrist to review the patient's case
- Include additional information that may assist the payer with making an appropriate decision for the patient. Examples of documentation that may be sent with the Letter of Exception include:
    - Patient diagnosis; please see Appendix C on page 18 for the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) major depressive disorder diagnosis codes
- Previous treatments for selected diagnosis with date and duration of therapy
    - SPRAVATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults*
- Contraindications, warnings/precautions, and adverse events, if applicable
- Notes from the patient's medical record
    - Treatment history
    - Medication overview
    - Relevant allergies or previous adverse reactions
    - Comorbidities
- Sign and date the exception letter
- Verify the time frame to make a decision on your request with the payer

*Based on the approved US Prescribing Information.

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Spravato™ (esketamine) CIII nasal spray

Sample Format: Letter to Request a Formulary Exception

[Insert Physician Letterhead]

[Insert Name of Medical Director]
[Insert Payer Name]
[Insert Address]
[Insert City, State Zip]

RE: Member Name: [Insert Member Name]
Member Number: [Insert Member Number]
Group Number: [Insert Group Number]

REQUEST: Authorization for treatment with SPRAVATO™ (esketamine) Nasal Spray CIII
DIAGNOSIS: [Insert Diagnosis] [Insert ICD]
DOSE AND FREQUENCY: [Insert Dose & Frequency]
REQUEST TYPE: ☐ Standard ☐ EXPEDITED

Dear [Insert Name of Medical Director]:

I am writing to request a **formulary exception** for the above-mentioned patient to receive treatment with SPRAVATO™ for [insert indication], dosed concomitant with [insert oral antidepressant]. My request is supported by the following:

Summary of Patient's Diagnosis
[Insert patient's diagnosis, date of diagnosis, lab results and date, current condition]

Summary of Patient's History
[Insert:

- Previous therapies/procedures, including dose and duration, response to those interventions
- Description of patient's recent symptoms/condition
- Site of medical service—include appropriate site type: Inpatient, hospital outpatient, outpatient clinic, private practice, or other
- Rationale for not using drugs that are on the plan's formulary
- Summary of your professional opinion of the patient's likely prognosis or disease progression without treatment with SPRAVATO™

Note: Exercise your medical judgment and discretion when providing a diagnosis and characterization of the patient's medical condition.]

Rationale for Treatment
[Insert summary statement for rationale for treatment such as: Considering the patient's history, condition, and the full Prescribing Information supporting uses of SPRAVATO™, I believe treatment with SPRAVATO™ at this time is medically necessary, and should be a covered and reimbursed service.]

[You may consider including documents that provide additional clinical information to support the recommendation for SPRAVATO™ for this patient, such as the full Prescribing Information, peer-reviewed journal articles, or clinical guidelines.]

[Given the urgent nature of this request,] please provide a timely authorization. Contact my office at [Insert Phone Number] if I can provide you with any additional information.

Sincerely,
[Insert Physician Name and Participating Provider Number]

Enclosures [Include full Prescribing Information and the additional support noted above]

Download an editable Sample Exception Letter template at **JanssenCarePath.com/hcp/Spravato**.

Medicare Part D Coverage Determination (Exception)

Medicare provides an optional model form that may be used to initiate the exceptions request with Part D payers and allow the prescriber to provide supporting information. This optional model form was developed in response to requests from outside parties to provide guidance to enrollees and prescribers on requesting coverage determinations (including exception requests) from Part D payers. There are 2 components to the model form:

- The request (may be completed by the enrollee, appointed representative, or prescriber)
- Supporting information (completed and signed by the prescriber)

Under the Medicare Part D prescription drug benefit program, a Part D plan enrollee, the enrollee's representative, or the enrollee's doctor/prescriber can request a coverage determination, including a tiering or formulary exception. A request for a coverage determination can be made verbally or in writing. Use of this form is optional. An enrollee, the enrollee's representative, or the enrollee's prescriber may submit a written request for a coverage determination in any format and cannot be required to use this or any other form.

When requesting a coverage determination from a non-Medicare payer, prescribers may be required to use that payer's specific forms. It is important to clarify with each payer the accepted process and format for submitting coverage determination requests. If the payer does not provide specific forms, this model may help organize what is likely to be needed. For all payers, both Medicare and non-Medicare, it may be necessary to submit additional information or documentation to support the request.

Note: Formulary and tiering exception requests must include a prescriber's supporting statement.

Sample Format: Medicare Part D Optional Model Form

Medicare Part D Form (page 1 of 3)*

REQUEST FOR MEDICARE PRESCRIPTION DRUG COVERAGE DETERMINATION

This form may be sent to us by mail or fax:

Address:	Fax Number:
[Insert plan address(es)]	[Insert plan fax number(s)]

You may also ask us for a coverage determination by phone at [insert plan telephone number] or through our website at [insert plan web address].

Who May Make a Request: Your prescriber may ask us for a coverage determination on your behalf. If you want another individual (such as a family member or friend) to make a request for you, that individual must be your representative. Contact us to learn how to name a representative.

Enrollee's Information

Enrollee's Name		Date of Birth
Enrollee's Address		
City	State	Zip Code
Phone	Enrollee's Member ID #	

Complete the following section ONLY if the person making this request is not the enrollee or prescriber:

Requester's Name		
Requester's Relationship to Enrollee		
Address		
City	State	Zip Code
Phone		

Representation documentation for requests made by someone other than enrollee or the enrollee's prescriber:

Attach documentation showing the authority to represent the enrollee (a completed Authorization of Representation Form CMS-1696 or a written equivalent). For more information on appointing a representative, contact your plan or 1-800-Medicare.

Name of prescription drug you are requesting (if known, include strength and quantity requested per month):

*Model coverage determination request form and instructions available at: https://www.cms.gov/Medicare/Appeals-and-Grievances/MedPrescriptDrugApplGriev/CoverageDeterminationsandExceptions.html

Note: Some payers require specific forms, depending on the route of administration. Please check with the participating payer for any specific requirements.

Considerations for Developing a Letter of Appeal

Use a Letter of Appeal to request that the payer review a claim or denied coverage determination for SPRAVATO™ (esketamine) Nasal Spray if the member or provider disagrees with the decision. An appeal may be submitted when the payer has adjudicated the claim for SPRAVATO™ and there is an explanation of benefits for the claim documenting the reason for the denial. Below are some reasons payers may deny a claim that can be appealed:

- Medical policy does not specify coverage
- The rationale to prescribe the drug does not meet the payer's medical necessity criteria

The template contains examples of information that payers may be required to reconsider a claim for coverage of SPRAVATO™. Check with the payer to confirm if there are specific coverage requirements or information needed as part of the request. Below are some helpful tips for submitting a Letter of Appeal:

- Check with the payer to see if there is a specific appeal form to use
- Verify the reason for the denial to be sure the decision can be appealed, and specifically address the reason the payer denied the claim in the appeal
- Submit the appeal within the time frame specified by the payer
- Indicate the type and/or level of appeal being requested (internal, external, first-level, etc)
- Write the Letter of Appeal on your practice letterhead
- Consider requesting that the payer provide a psychiatrist's review of the patient's case
- Include additional information with the Letter of Appeal that may assist the payer with making an appropriate decision for the patient. Examples of documentation that may be sent with the Letter of Appeal include:
    - Published studies
    - Notes from the patient's medical record
    - Notes from psychiatric evaluation
    - A copy of the explanation of benefits
- Sign and date the Letter of Appeal

Tools and Resources

Resource	Access
CMS Exceptions and Appeals Processes CMS website applicable to Part D exceptions and appeals processes; offers links to resources	http://www.cms.gov/MedPrescriptDrugApplGriev
How Medicare Drug Plans Use Pharmacies, Formularies, and Common Coverage Rules CMS beneficiary publication providing overview of Medicare Part D; specifically reviews coverage rules	https://www.medicare.gov/Pubs/pdf/11136-Pharmacies-Formularies-Coverage-Rules.pdf
Forms Website with links to forms applicable to Part D grievances, coverage determinations and exceptions, and appeals processes	https://www.cms.gov/Medicare/Appeals-and-Grievances/MedPrescriptDrugApplGriev/Forms.html
Medicare Appeals CMS beneficiary publication for all types of Medicare appeals; contains Part D-specific information	http://www.medicare.gov/Pubs/pdf/11525.pdf
Medicare Exceptions and Appeals Processes Access contact information by state	http://www.medicare.gov/contacts
Sponsor Grievance, Coverage Determination, and Appeals Contacts Download files: contact information for exceptions and appeals responsibility at Medicare Part D plans	www.cms.gov/Medicare/Appeals-and-Grievances/MedPrescriptDrugApplGriev/Exceptions.html
State Health Insurance Assistance Program (SHIP) Obtain state-specific contact numbers	https://www.medicare.gov/contacts/#resources/ships

Important Safety Information for SPRAVATO™ (esketamine) CIII Nasal Spray

Indication

SPRAVATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.

SPRAVATO™ is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO™ as an anesthetic agent have not been established.

Important Safety Information

WARNING: SEDATION, DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration (5.1, 5.2).**
- **Potential for abuse and misuse. Consider the risks and benefits of using SPRAVATO™ prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.3).**
- **SPRAVATO™ is only available through a restricted program called the SPRAVATO™ REMS (5.4).**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO™ is not approved for use in pediatric patients (5.5).**

CONTRAINDICATIONS

SPRAVATO™ is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage
- Hypersensitivity to esketamine, ketamine, or any of the excipients

WARNINGS AND PRECAUTIONS

Sedation: In clinical trials, 49% to 61% of SPRAVATO™-treated patients developed sedation and 0.3% of SPRAVATO™-treated patients experienced loss of consciousness.

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Closely monitor for sedation with concomitant use of SPRAVATO™ with CNS depressants *[see Drug Interaction (7.1)]*.

SPRAVATO™ is available only through a restricted program under a REMS.

Dissociation: The most common psychological effects of SPRAVATO™ were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 75% of SPRAVATO™-treated patients developed dissociative or perceptual changes). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO™; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

SPRAVATO™ is available only through a restricted program under a REMS.

Abuse and Misuse: SPRAVATO™ contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing and monitor all patients for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence.

SPRAVATO™ is available only through a restricted program under a REMS.

SPRAVATO™ Risk Evaluation and Mitigation Strategy (REMS): SPRAVATO™ is available only through a restricted program called the SPRAVATO™ REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.

Important requirements of the SPRAVATO™ REMS include the following:

- Healthcare settings must be certified in the program and ensure that SPRAVATO™ is:
  - Only dispensed in healthcare settings and administered to patients who are enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO™.

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Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO™.

Spravato™ (esketamine) CIII nasal spray

Important Safety Information for SPRAVATO™ (esketamine) CIII Nasal Spray (continued)

- Pharmacies must be certified in the REMS and must only dispense SPRAVATO™ to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies, is available at www.SPRAVATOrems.com or 1-855-382-6022.

Suicidal Thoughts and Behaviors in Adolescents and Young Adults: In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included adult and pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. SPRAVATO™ is not approved in pediatric (<18 years of age) patients.

There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO™ and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Increase in Blood Pressure: SPRAVATO™ causes increases in systolic and/or diastolic blood pressure (BP) at all recommended dosages. Increases in BP peak approximately 40 minutes after SPRAVATO™ administration and last approximately 4 hours.

Approximately 8% to 17% of SPRAVATO™-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. SPRAVATO™ is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Before prescribing, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO™ outweigh its risk.

Assess BP prior to administration of SPRAVATO™. In patients whose BP is elevated prior to SPRAVATO™ administration (as a general guide: >140/90 mmHg), a decision to delay SPRAVATO™ therapy should be taken into account to balance the benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO™ administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO™ with psychostimulants or monoamine oxidase inhibitors (MAOIs) *[see Drug Interactions (7.2, 7.3)]*.

In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Cognitive Impairment

Short-Term Cognitive Impairment: In a study in healthy volunteers, a single dose of SPRAVATO™ caused cognitive performance decline 40 minutes post-dose. SPRAVATO™-treated subjects required a greater effort to complete the cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO™ and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment: Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO™ nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO™ have not been evaluated beyond one year.

Impaired Ability to Drive and Operate Machinery: Before SPRAVATO™ administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO™.

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Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO™.

Spravato™ (esketamine) CIII nasal spray

Important Safety Information for SPRAVATO™ (esketamine) CIII Nasal Spray (continued)

Ulcerative or Interstitial Cystitis: Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO™ nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO™-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which involved treatment for up to a year.

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO™ and refer to an appropriate healthcare provider as clinically warranted.

Embryo-fetal Toxicity: SPRAVATO™ may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO™ *in utero*. Advise women of reproductive potential to consider pregnancy planning and prevention.

DRUG INTERACTIONS

CNS depressants (e.g., benzodiazepines, opioids, alcohol): Concomitant use may increase sedation. Closely monitor for sedation with concomitant use of CNS depressants.

Psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil): Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of psychostimulants.

Monoamine oxidase inhibitors (MAOIs): Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of MAOIs.

USE IN SPECIFIC POPULATIONS

Pregnancy: SPRAVATO™ is not recommended during pregnancy. SPRAVATO™ may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO™ *in utero*. There are risks to the mother associated with untreated depression in pregnancy. If a woman becomes pregnant while being treated with SPRAVATO™, treatment with SPRAVATO™ should be discontinued and the patient should be counseled about the potential risk to the fetus.

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO™, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at *https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/*.

Lactation: SPRAVATO™ is present in human milk. Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with SPRAVATO™.

Females and Males of Reproductive Potential: SPRAVATO™ may cause embryo-fetal harm when administered to a pregnant woman. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO™.

Pediatric Use: The safety and effectiveness of SPRAVATO™ in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO™, 12% were 65 years of age and older, and 2% were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.

The mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients.

The treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO™ plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥65 years of age. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Åsberg Depression Rating Scale (MADRS).

Hepatic Impairment: SPRAVATO™-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO™ has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: SPRAVATO™ contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act.

Abuse: Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO™. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the

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Spravato™ (esketamine) CIII nasal spray

Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO™.

Important Safety Information for SPRAVATO™ (esketamine) CIII Nasal Spray (continued)

intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

SPRAVATO™ may produce a variety of symptoms including anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment and to be "spaced out." Monitoring for signs of abuse and misuse is recommended.

ADVERSE REACTIONS

The most common adverse reactions with SPRAVATO™ plus oral AD (incidence ≥5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

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Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO™.

Spravato™ (esketamine) CIII nasal spray

Appendix A

Considerations for HCPs When Submitting Exceptions and Appeals

The list below is not an exhaustive list but includes considerations. The HCP's experience, research of the patient's payer requirements, and clinical judgment need to be followed.

Resource	✓	Notes
I have developed a clear and simple statement about what my patient needs and why		
I have assembled information adequate to support medical necessity for this request		
For expedited requests: I have assembled adequate information to support the urgency of this request		
I have designated a primary contact for interacting with the payer/PBM on this matter		
I have reviewed the payer's/PBM's website or contacted customer service/provider relations for policy/process information, including forms and contacts		
I have a tracking mechanism in place to log date, time, contact person, and outcome of all communications		
I know who the payer/PBM will contact and how they will communicate their decision		

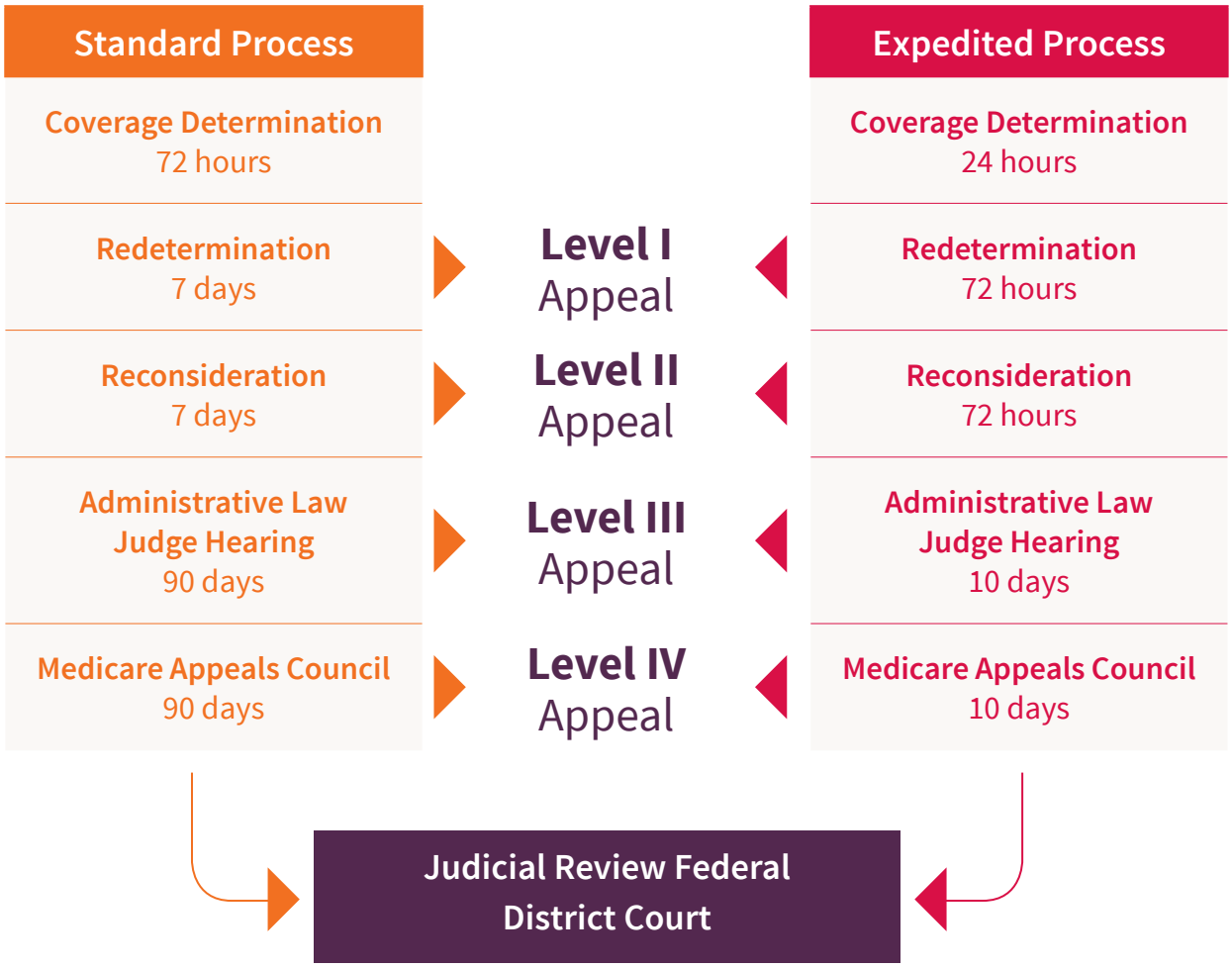
This request is for ☐ Prior authorization ☐ Exception request ☐ Appeal

Primary payer contact: _____

Title: _____Phone:_____E-mail:_____

Appendix B

Medicare Prescription Drug (Part D) Coverage Determination Process[1]



Appendix C

ICD-10-CM Diagnosis Codes

There is no ICD-10-CM code for treatment-resistant depression. The codes below are provided for your consideration, since our clinical trials included patients with Major Depressive Disorder (MDD) who failed at least 2 treatments of adequate dose and duration. Payer requirements for ICD-10 codes will vary. It is essential to verify correct diagnosis coding with each payer.

ICD-10-CM Diagnosis Codes for Consideration*[2]

Code	Description
Code Considerations for Patients New to SPRAVATO™	
F32.0	Major depressive disorder, single episode, mild
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.9	Major depressive disorder, single episode, unspecified
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent, severe without psychotic features
F33.9	Major depressive disorder, recurrent, unspecified
Code Considerations for Patients Already Receiving SPRAVATO™	
F32.4	Major depressive disorder, single episode, in partial remission
F32.5	Major depressive disorder, single episode, in full remission
F33.40	Major depressive disorder, recurrent, in remission, unspecified
F33.41	Major depressive disorder, recurrent, in partial remission
F33.42	Major depressive disorder, recurrent, in full remission

*These codes are not intended to be promotional or to encourage or suggest a use of drug that is inconsistent with FDA-approved use. The codes provided are not exhaustive and additional codes may apply.

Note: SPRAVATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.

Please see Important Safety Information, including Boxed WARNINGS, on pages 12-15. Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO™.

Spravato™ (esketamine) CIII nasal spray

References

1. CMS flow chart: Medicare Part D appeals process. https://www.cms.gov/Medicare/Appeals-and-Grievances/MedPrescriptDrugApplGriev/Downloads/Flowchart-Medicare-Part-D.pdf. Accessed April 5, 2019.
2. American Medical Association. *ICD-10-CM 2019: The Complete Official Code Book*. Chicago, IL: Optum 360 LLC; 2018.

Please see Important Safety Information, including Boxed WARNINGS, on pages 12-15.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO™.

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