Spravato® (esketamine) CIII
28 mg nasal spray

Drug-specific S Code Issued for SPRAVATO® on Non-Medicare Claims

S0013 | Esketamine nasal spray, 1 mg

The Centers for Medicare and Medicaid Services (CMS) has issued a temporary, drug-specific HCPCS Level II code to identify SPRAVATO® for non-Medicare payers, on or after January 1, 2021[1]

This document is presented for informational purposes only and is not intended to provide reimbursement or legal advice, nor does it promise or guarantee coverage, levels of reimbursement, payment, or charge. Similarly, all CPT and HCPCS codes are supplied for informational purposes only and represent no statement, promise, or guarantee by Janssen Pharmaceuticals, Inc., that these codes will be appropriate or that reimbursement will be made. It is not intended to increase or maximize reimbursement by any payer. Laws, regulations, and policies concerning reimbursement are complex and are 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. We strongly recommend you consult the payer organization for its reimbursement policies.

Indications:

SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Limitations of Use:

- The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.
- 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).**

HCPCS=Healthcare Common Procedure Coding System.
CPT® - Current Procedural Terminology. CPT® is a registered trademark of the American Medical Association.

Please see additional Important Safety Information, including Boxed WARNINGS, on pages 9-12.

Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Considerations for Reporting Drug-specific S Codes

To avoid potential delays, underpayments, or denials, it may be helpful to perform a review prior to submitting claims for S0013 to a payer.

The following may be considered:

- The payer is NOT Medicare*
- Insurance was verified
- This is a covered service
- If required, prior authorization was obtained
- The payer accepts the S Code†
- Billed units are accurate and consistent with the code descriptor
- Medical necessity is documented‡
- Specific payer requirements were followed

*For Medicare, the drug is packaged in a G Code to report the drug/service combination and S0013 would not be included on the claim.
†Requirements can vary by payer. Some payers may accept the new S Code; others may require the G Codes (G2082, G2083) or the miscellaneous drug code, J3490.
‡A sample letter of medical necessity is available at JanssenCarePath.com.

Consult local payers for coding policies or call a Janssen CarePath Care Coordinator at 877-CarePath (877-227-3728) Monday–Friday, 8:00 AM to 8:00 PM ET

Reminder: Healthcare providers (HCPs) must consult with each patient's payer since coverage will vary. Please note that HCPs are responsible for selecting appropriate codes for any particular claim based on the patient's condition, the items and services that are furnished, and any specific payer requirements. It is advisable to contact your local payer with regard to local payment policies.

SPRAVATO® REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential risks associated with a drug and is required by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks

SPRAVATO® is available only through a restricted distribution program called the SPRAVATO® REMS because of the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO® administration, and abuse and misuse of SPRAVATO®. SPRAVATO® is intended for use only in a certified healthcare setting.

SPRAVATO® is intended for patient administration under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours. SPRAVATO® must never be dispensed directly to a patient for home use[2].

What are the REMS requirements?

1. **Healthcare setting certification**
   All healthcare settings must be certified in the REMS in order to receive, dispense, and/or treat patients with SPRAVATO®.
2. **Pharmacy certification**
   All pharmacies must be certified in the REMS in order to receive and dispense SPRAVATO®.
3. **Patient enrollment**
   Patients in an **outpatient** setting must be enrolled in the REMS with their prescriber in order to receive SPRAVATO® treatment.

Healthcare Settings Type*

All REMS-certified Inpatient and Outpatient Healthcare Settings must have a healthcare provider counsel patients on the safety risk of SPRAVATO® and monitor patients post-dose.

Inpatient healthcare settings

- Covers inpatient units, inpatient pharmacy, and emergency departments
- Before prescribing SPRAVATO® treatment, complete and submit the ***inpatient healthcare setting enrollment form***
- Before starting SPRAVATO® treatment, inpatient settings are not required to enroll the patient in the SPRAVATO® REMS
- During SPRAVATO® treatment, inpatient settings do not require the ***patient monitoring form***. Report all suspected adverse events to SPRAVATO® REMS

Outpatient healthcare settings

- Covers outpatient medical offices and clinics
- Before prescribing SPRAVATO® treatment, complete and submit the ***outpatient healthcare setting enrollment form***
- Before starting SPRAVATO® treatment, enroll the patient by completing and submitting the ***patient enrollment form*** to the SPRAVATO® REMS
- During SPRAVATO® treatment, submit the ***patient monitoring form*** and report all suspected adverse events to the SPRAVATO® REMS

*To get started, find more information on how to certify as a healthcare setting and/or pharmacy, and view all REMS requirements and attestations by type of REMS stakeholder **visit SPRAVATOrems.com or call 1-855-382-6022 (8AM to 8PM ET).**

Please see Important Safety Information, including Boxed WARNINGS, on pages 9-12.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Spravato® (esketamine) CIII
28 mg nasal spray

Sample CMS-1500 Claim Form: Coding for Non-Medicare Payers That Accept the S Code

SPRAVATO® (esketamine): 2021 Physician Office Sample Claim

1 Item 21

Indicate diagnosis using appropriate ICD-10-CM codes. Use diagnosis codes to the highest level of specificity for the date of service and enter the diagnoses in priority order.

2 Item 24D

Indicate appropriate CPT®, HCPCS codes, and modifiers, if required.

SPRAVATO®

S0013 – Esketamine, nasal spray, 1 mg[1]

Observation and Monitoring* for SPRAVATO® Administration[3]

99202-99205 – Office or other outpatient visit for the evaluation and management of a new patient

99212-99215 – Office or other outpatient visit for the evaluation and management of an established patient

Payer requirements for observation and monitoring coding may vary.*

3 Item 24E

Refer to the diagnosis for this service (see Item 21). Enter only 1 diagnosis pointer per line.

4 Item 24G

Drug

S0013 – Enter number of HCPCS units based on dose administered (1 mg = 1 unit)

56 mg = 56 units

84 mg = 84 units

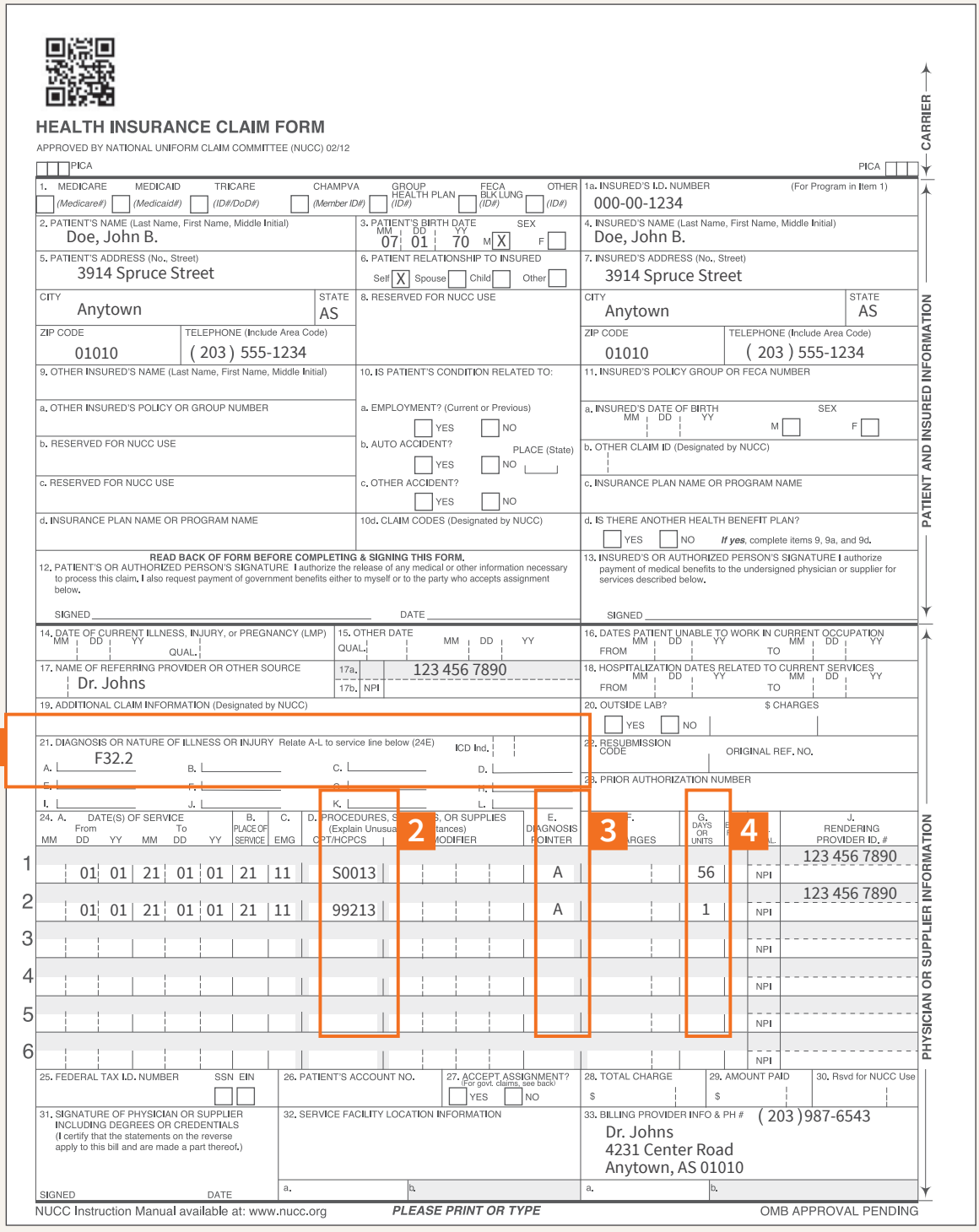
Observation and Monitoring for SPRAVATO® Administration

Report appropriate E&M code; enter 1 unit

HCPCS=Healthcare Common Procedure Coding System.
CPT® - Current Procedural Terminology. CPT® is a registered trademark of the American Medical Association.
*Contact Janssen CarePath at 877-227-3728, Monday to Friday, 8:00 AM to 8:00 PM ET.
E-mail: Submit questions via our askjanssenmedinfo.com site.

Coding for Non-Medicare Payers That Accept the S Code

Sample CMS-1500 Claim Form: **56-mg Dose of SPRAVATO®**



HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

PICA

1. MEDICARE (Medicare#) MEDICAID (Medicaid#) TRICARE (ID#/DoD#) CHAMPVA (Member ID#) GROUP HEALTH PLAN (ID#) FECA BLK LUNG (ID#) OTHER (ID#)

1a. INSURED'S I.D. NUMBER (For Program in Item 1): 000-00-1234

2. PATIENT'S NAME (Last Name, First Name, Middle Initial): Doe, John B.

3. PATIENT'S BIRTH DATE MM DD YY: 07 01 70 SEX M [X] F [ ]

4. INSURED'S NAME (Last Name, First Name, Middle Initial): Doe, John B.

5. PATIENT'S ADDRESS (No., Street): 3914 Spruce Street

6. PATIENT RELATIONSHIP TO INSURED: Self [X] Spouse [ ] Child [ ] Other [ ]

7. INSURED'S ADDRESS (No., Street): 3914 Spruce Street

CITY: Anytown STATE: AS

8. RESERVED FOR NUCC USE

CITY: Anytown STATE: AS

ZIP CODE: 01010 TELEPHONE (Include Area Code): (203) 555-1234

ZIP CODE: 01010 TELEPHONE (Include Area Code): (203) 555-1234

9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)

10. IS PATIENT'S CONDITION RELATED TO:

11. INSURED'S POLICY GROUP OR FECA NUMBER

a. OTHER INSURED'S POLICY OR GROUP NUMBER

a. EMPLOYMENT? (Current or Previous) YES [ ] NO [ ]

a. INSURED'S DATE OF BIRTH MM DD YY SEX M [ ] F [ ]

b. RESERVED FOR NUCC USE

b. AUTO ACCIDENT? YES [ ] NO [ ] PLACE (State)

b. OTHER CLAIM ID (Designated by NUCC)

c. RESERVED FOR NUCC USE

c. OTHER ACCIDENT? YES [ ] NO [ ]

c. INSURANCE PLAN NAME OR PROGRAM NAME

d. INSURANCE PLAN NAME OR PROGRAM NAME

10d. CLAIM CODES (Designated by NUCC)

d. IS THERE ANOTHER HEALTH BENEFIT PLAN? YES [ ] NO [ ] *If yes*, complete items 9, 9a, and 9d.

READ BACK OF FORM BEFORE COMPLETING & SIGNING THIS FORM.

12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below.

SIGNED _____ DATE _____

13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below.

SIGNED _____

14. DATE OF CURRENT ILLNESS, INJURY, or PREGNANCY (LMP) MM DD YY QUAL.

15. OTHER DATE QUAL. MM DD YY

16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION MM DD YY FROM TO MM DD YY

17. NAME OF REFERRING PROVIDER OR OTHER SOURCE: Dr. Johns

17a. 123 456 7890

17b. NPI

18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES MM DD YY FROM TO MM DD YY

19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC)

20. OUTSIDE LAB? YES [ ] NO [ ] $ CHARGES

21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind.

A. F32.2 B. C. D.

E. F. G. H.

I. J. K. L.

22. RESUBMISSION CODE ORIGINAL REF. NO.

23. PRIOR AUTHORIZATION NUMBER

24. A. DATE(S) OF SERVICE From MM DD YY	To MM DD YY	B. PLACE OF SERVICE	C. EMG	D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS	MODIFIER	E. DIAGNOSIS POINTER	F. $ CHARGES	G. DAYS OR UNITS	H. EPSDT Family Plan	I. ID. QUAL.	J. RENDERING PROVIDER ID. #
1	01 01 21	01 01 21	11	S0013		A		56		NPI	123 456 7890
2	01 01 21	01 01 21	11	99213		A		1		NPI	123 456 7890
3										NPI	
4										NPI	
5										NPI	
6										NPI	

25. FEDERAL TAX I.D. NUMBER SSN EIN

26. PATIENT'S ACCOUNT NO.

27. ACCEPT ASSIGNMENT? (For govt. claims, see back) YES [ ] NO [ ]

28. TOTAL CHARGE $

29. AMOUNT PAID $

30. Rsvd for NUCC Use

31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)

SIGNED DATE

32. SERVICE FACILITY LOCATION INFORMATION

a. b.

33. BILLING PROVIDER INFO & PH # (203)987-6543

Dr. Johns
4231 Center Road
Anytown, AS 01010

a. b.

NUCC Instruction Manual available at: www.nucc.org **PLEASE PRINT OR TYPE** OMB APPROVAL PENDING

CARRIER

PATIENT AND INSURED INFORMATION

PHYSICIAN OR SUPPLIER INFORMATION

1 2 3 4

Please see Important Safety Information, including Boxed WARNINGS, on pages 9-12.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Spravato® (esketamine) CII
28 mg nasal spray

Sample CMS-1450 Claim Form: Coding for Non-Medicare Payers That Accept the S Code

SPRAVATO® (esketamine): 2021 Hospital Outpatient Department (HOPD) Sample Claim

1 Locator Box 42

List revenue codes in ascending order.

2 Locator Box 43

Enter narrative description for corresponding revenue code.

3 Locator Box 44

SPRAVATO®

S0013 – Esketamine, nasal spray, 1 mg[1]

Observation and Monitoring* for SPRAVATO® Administration[4]

99202-99205 – Office or other outpatient visit for the evaluation and management of a new patient

99212-99215 – Office or other outpatient visit for the evaluation and management of an established patient

Payer requirements for observation and monitoring coding may vary.*

4 Locator Box 46

Enter the number of HCPCS units.

Drug

S0013 – Enter number of HCPCS units based on dose administered (1 mg = 1 unit)

56 mg = 56 units

84 mg = 84 units

Observation and Monitoring for SPRAVATO® Administration

Report appropriate E&M code; enter 1 unit.

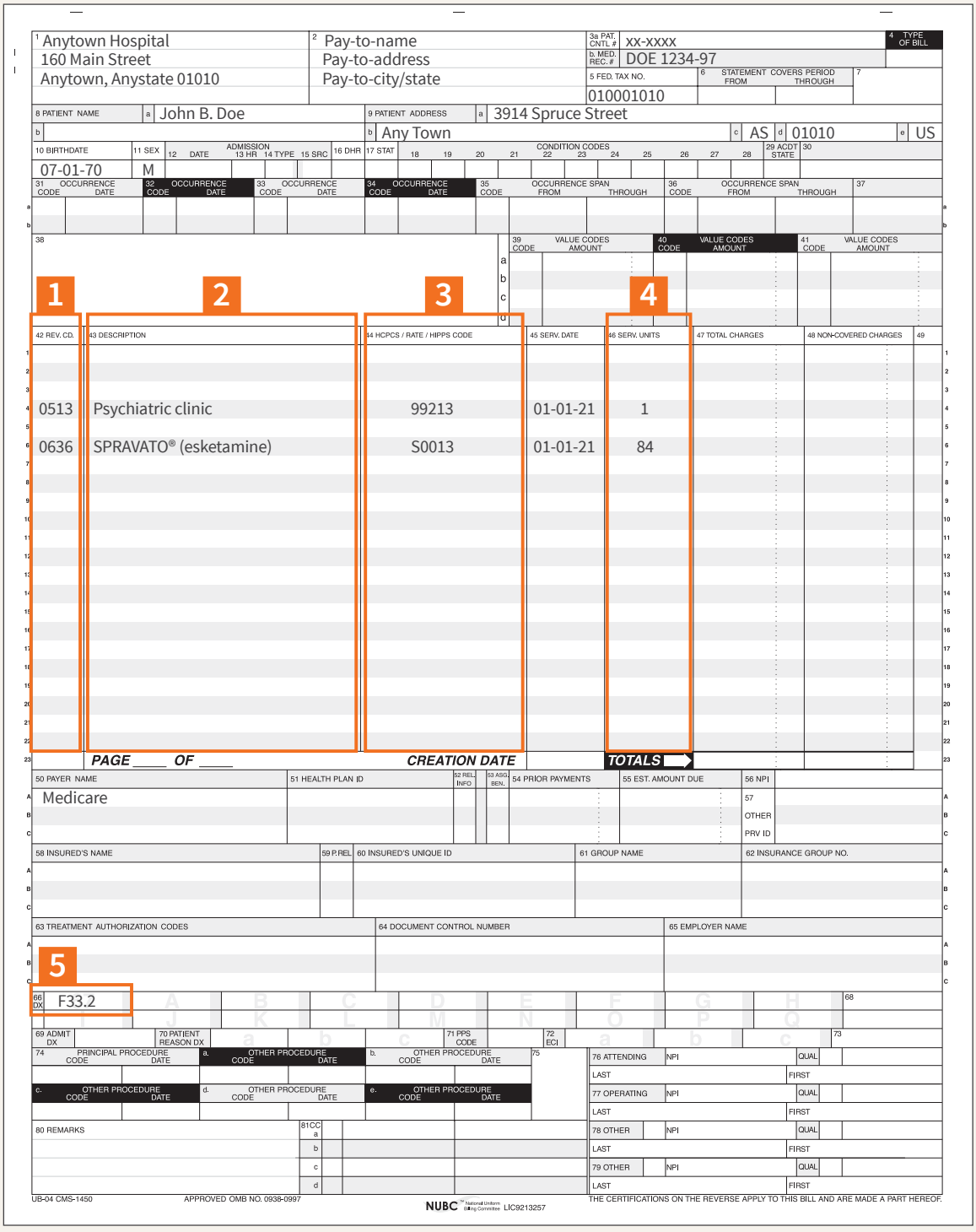
5 Locator Box 66

Indicate diagnosis using appropriate ICD-10-CM codes. Code to the highest level of specificity for the date of service and enter diagnoses in priority order.

HCPCS=Healthcare Common Procedure Coding System.
CPT® - Current Procedural Terminology. CPT® is a registered trademark of the American Medical Association.
*Contact Janssen CarePath at 877-227-3728, Monday to Friday, 8:00 AM to 8:00 PM ET.
E-mail: Submit questions via our askjanssenmedinfo.com site.

Coding for Non-Medicare Payers That Accept the S Code

Sample CMS-1450 Claim Form: **84-mg Dose of SPRAVATO®**



1 Anytown Hospital 160 Main Street Anytown, Anystate 01010	2 Pay-to-name Pay-to-address Pay-to-city/state	3a PAT. CNTL # xx-xxxx b. MED. REC. # DOE 1234-97 5 FED. TAX NO. 010001010 6 STATEMENT COVERS PERIOD FROM THROUGH	4 TYPE OF BILL

8 PATIENT NAME	9 PATIENT ADDRESS	10 BIRTHDATE	11 SEX
a John B. Doe	a 3914 Spruce Street	07-01-70	M
b	b Any Town c AS d 01010 e US		

42 REV. CD.	43 DESCRIPTION	44 HCPCS / RATE / HIPPS CODE	45 SERV. DATE	46 SERV. UNITS	47 TOTAL CHARGES	48 NON-COVERED CHARGES
0513	Psychiatric clinic	99213	01-01-21	1		
0636	SPRAVATO® (esketamine)	S0013	01-01-21	84		
	PAGE ____ OF ____	CREATION DATE		TOTALS		

50 PAYER NAME	51 HEALTH PLAN ID	54 PRIOR PAYMENTS	55 EST. AMOUNT DUE	56 NPI
Medicare				

58 INSURED'S NAME	60 INSURED'S UNIQUE ID	61 GROUP NAME	62 INSURANCE GROUP NO.

63 TREATMENT AUTHORIZATION CODES	64 DOCUMENT CONTROL NUMBER	65 EMPLOYER NAME

66 DX	67	68
F33.2		

76 ATTENDING	77 OPERATING	78 OTHER	79 OTHER
NPI / QUAL / LAST / FIRST	NPI / QUAL / LAST / FIRST	NPI / QUAL / LAST / FIRST	NPI / QUAL / LAST / FIRST

UB-04 CMS-1450 APPROVED OMB NO. 0938-0997 NUBC LIC9213257 THE CERTIFICATIONS ON THE REVERSE APPLY TO THIS BILL AND ARE MADE A PART HEREOF.

Please see Important Safety Information, including Boxed WARNINGS, on pages 9-12.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Spravato® (esketamine) CIII
28 mg nasal spray

FAQs

What is an S Code?

S Codes are Level II HCPCS codes that are issued to meet the needs of non-Federal (i.e., commercial) payers to describe products and services for which there are no nationally accepted codes. S Codes are often used to describe items that are not separately billable to Medicare under Part B. The Medicare program does not use, and does not accept claims for, S Codes.

Will CMS be issuing a separate specific J Code?

No. CMS issued a drug-specific S Code in lieu of a J Code. CMS's goal was to address the commercial payers' claims processing needs when they could not use the bundled (drug and service) G Code.[1] CMS also chose the S Code in lieu of a J Code to prevent any confusion with Medicare coding policy; the Medicare program does not accept S Codes.

Will some payers still accept miscellaneous J Code J3490 (Unclassified drugs) to describe SPRAVATO®? If so, under what circumstances?

Yes. Providers will still have the option to use miscellaneous code J3490 to describe the drug on claims submitted to

- Commercial payers and Medicaid plans that do not specify use of bundled G Codes or S Codes
- Medicare when the drug is obtained at no cost to the practice or clinic

The unclassified drug code will still be an option for commercial payers, Medicare, and Medicaid and it will be used only for reimbursement for product. Contact your payer to confirm what codes they accept.[1]

Is the S Code the same as a G Code, but for commercial plans only?

No. Code S0013 "Esketamine, nasal spray, 1 mg" describes only SPRAVATO® and does not include professional services. It is intended to enable commercial payers to pay separately for the drug, especially when it is billed separately from service claims under Behavioral Health Organization carve-outs.[1]

Will CMS set the rates of reimbursement for S Codes similar to G Codes?

No, S Codes are not used on claims to Medicare. Commercial health plans set the rates, as they do with other codes. It may take time for payers to update their systems with the new code, if they choose to adopt it, and each plan may have different reimbursement rates for the S Code for SPRAVATO®.

If a patient and their HCP determine that it is best to obtain SPRAVATO® under the patient's prescription drug benefit, how may they do so?

Obtaining SPRAVATO® under a prescription benefit involves a pharmacy* and requires:

- A REMS-certified pharmacy that participates in the patient's drug plan
- A physician's statement, prior authorization request, or letter of medical necessity supported by documentation in the patient's medical record
- A drug plan that includes SPRAVATO® on its formulary or approves an exception request for coverage

*The pharmacy will bill the payer for drug covered under a prescription benefit. HCPs will submit claims under the patient's medical benefit and consider using Evaluation and Management (E/M) codes for the administration, monitoring, and observation services. Please consult with your payer organizations for local or actual coverage and reimbursement policies.

HCPCS=Healthcare Common Procedure Coding System.

Indications and Important Safety Information for SPRAVATO® (esketamine) CIII Nasal Spray

Indications:

SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Limitations of Use:

- The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.
- 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, 48% to 61% of SPRAVATO®-treated patients developed sedation and 0.3% to 0.4% 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 (e.g., benzodiazepines, opioids, alcohol).

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 84% 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.

(continued on next page)

Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®. Provide the Medication Guide to your patients and encourage discussion.

Spravato® (esketamine) CIII
28 mg nasal spray

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

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® 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 and administered in healthcare settings.
  - Patients treated in outpatient settings (e.g., medical offices and clinics) must be 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®.
- 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 doses. Increases in BP peak approximately 40 minutes after SPRAVATO® administration and last approximately 4 hours.

Approximately 8% to 19% 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 SPRAVATO®, 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 take into account the balance of benefit and risk in individual patients.

(continued on next page)

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

Increase in Blood Pressure (cont'd)

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).

In patients with a 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. Compared to placebo-treated subjects, 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®.

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.

PREGNANCY, EMBRYO-FETAL TOXICITY, AND LACTATION

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*. Advise women of reproductive potential to consider pregnancy planning and prevention.

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/.

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

(continued on next page)

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

SELECT USE IN SPECIFIC POPULATIONS

Geriatric Use: 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. At the end of a 4-week, randomized, double-blind study, there was no statistically significant difference between groups on the primary efficacy endpoint.

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.

ADVERSE REACTIONS

The most common adverse reactions with SPRAVATO® plus oral antidepressant (incidence ≥5% and at least twice that of placebo nasal spray plus oral antidepressant) were:

TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

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

Provide the Medication Guide to your patients and encourage discussion.

cp-170362v2

References: 1. Centers for Medicare & Medicaid Services (CMS). Healthcare Common Procedure Coding System (HCPCS) Application Summaries and Coding Decisions: Second Quarter, 2021 Coding Cycle for Drug and Biological Products. Accessed August 13, 2021. https://www.cms.gov/files/document/2021-hcpcs-application-summary-quarter-2-2021-drugs-and-biologics-updated-08062021.pdf **2.** SPRAVATO® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; July 2020. **3.** Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 26: Completing and Processing the Form CMS-1500 Data Set. Accessed August 9, 2021. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c26pdf.pdf **4.** Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 25: Completing and Processing the Form CMS-1450 Data Set. Accessed August 9, 2021. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c25.pdf

Janssen Neuroscience

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Spravato® (esketamine) CIII
28 mg nasal spray

 10/21 cp-192251v2