GLUTAMATERGIC ANTIDEPRESSANT | C-III

Esketamine

Spravato

Intranasal NMDA receptor antagonist for treatment-resistant depression, given only in certified REMS settings with 2 hours of observation.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
56-84 mg intranasal	7-12 h; Tmax 20-40 min	CYP2B6, CYP3A4	Hours to days; 2-4 wks full

⚠ FDA BOXED WARNING

Sedation, dissociation, and respiratory depression after administration; abuse and misuse; and increased suicidal thoughts and behaviors in pediatric and young adult patients. Monitor patients for at least 2 hours after each dose. Available only through the restricted SPRAVATO REMS program.

INDICATIONS

- FDA-approved for treatment-resistant depression in adults, defined as inadequate response to at least two adequate antidepressant trials.
- Approved in January 2025 as monotherapy for treatment-resistant depression, in addition to the original combination indication.
- FDA-approved with an oral antidepressant for depressive symptoms in adults with major depressive disorder and acute suicidal ideation or behavior.
- Effectiveness in preventing suicide or in reducing suicidal ideation itself has not been demonstrated, so it does not replace hospitalization.
- Not approved as an anesthetic and not approved for pediatric patients; safety and effectiveness under 18 years are not established.
- Off-label use outside a certified REMS treatment center is not permitted, and the drug is never dispensed for use at home.

DOSING & TITRATION

- Each device delivers **28 mg** as two sprays, one per nostril; give devices 5 minutes apart with a 5-minute rest between them.
- For treatment-resistant depression, give **56 mg on day 1**, then 56 or 84 mg twice weekly for weeks 1 through 4 of induction.
- Maintenance is **56 or 84 mg once weekly** for weeks 5 through 8, then every 2 weeks or weekly thereafter based on response.
- For depression with acute suicidal ideation, give **84 mg twice weekly for 4 weeks**, reducing to 56 mg only for tolerability.
- Start at **28 mg** in adults 65 years and older, and self-administration is never permitted outside direct clinician observation.
- Patients must avoid food for 2 hours and liquids for 30 minutes before dosing to reduce the risk of nausea and vomiting.

MECHANISM OF ACTION

- The S-enantiomer of ketamine, acting as a noncompetitive antagonist at the NMDA glutamate receptor with higher affinity than the R-enantiomer.
- NMDA blockade on GABAergic interneurons disinhibits pyramidal cells, producing a glutamate surge and AMPA receptor activation.
- Downstream AMPA signaling triggers BDNF release and mTORC1 activation, driving rapid synaptogenesis in prefrontal cortex.
- This synaptic mechanism explains an antidepressant onset within hours to days rather than the weeks required by monoamine agents.
- Dissociation and sedation arise from the same NMDA antagonism and are expected transient effects rather than idiosyncratic reactions.

PHARMACOKINETICS

- Intranasal bioavailability is approximately 48 percent, with peak plasma concentrations reached 20 to 40 minutes after the last spray.
- Terminal half-life is roughly 7 to 12 hours, and dissociative and sedative effects generally resolve within 1.5 hours of dosing.
- Metabolized primarily by CYP2B6 and CYP3A4 to noresketamine, an active metabolite with substantially lower NMDA affinity.
- Clearance is high and the drug is largely eliminated as metabolites in urine, with less than 1 percent excreted unchanged.
- Nasal corticosteroids or decongestants should be given at least 1 hour before dosing so that absorption is not altered.

ADVERSE EFFECTS

- Dissociation occurs in roughly 41 percent of patients, dizziness in about 29 percent, and nausea in about 28 percent.
- Sedation affects roughly 23 percent; vertigo, hypoesthesia, anxiety, and lethargy are also common during the observation period.
- Respiratory depression can occur, and sedation combined with a central nervous system depressant raises that risk during observation.
- Transient blood pressure elevation peaks about 40 minutes after dosing and can exceed 180 systolic or 110 diastolic in some patients.
- Abuse and misuse potential led to Schedule III control, and dependence has been reported with recreational ketamine use.
- Cognitive impairment and impaired driving persist for hours; patients must not drive until the next day after restful sleep.

MONITORING

- Measure blood pressure before dosing, again about 40 minutes after dosing, and thereafter until values are clinically acceptable.
- Observe every patient for at least **2 hours** after each dose for sedation, dissociation, and hemodynamic changes before discharge.
- Do not dose if baseline blood pressure is elevated enough to make an acute rise unsafe, generally above 140 over 90 in most protocols.
- Assess depression severity and suicidality with a standardized scale before each session and reassess the need for continued treatment.
- Confirm the patient has arranged transportation home, since driving after a session is prohibited until the following day.

INTERACTIONS & CAUTIONS

- Central nervous system depressants including benzodiazepines, opioids, and alcohol increase sedation and prolong recovery time.
- Psychostimulants and monoamine oxidase inhibitors can compound the blood pressure rise and should generally be avoided.
- Strong CYP3A4 or CYP2B6 inducers such as rifampin may lower exposure, though dose adjustment is not formally recommended.
- Contraindicated in aneurysmal vascular disease, arteriovenous malformation, or any history of intracerebral hemorrhage.
- Contraindicated in patients with hypersensitivity to esketamine, ketamine, or any component of the nasal spray formulation.

SPECIAL POPULATIONS

- Esketamine may cause fetal harm and is not recommended in pregnancy; there is a national pregnancy exposure registry for the drug.
- Breastfeeding is not recommended during treatment because esketamine is present in human milk and infant effects are unknown.
- Not approved under 18 years of age, and pediatric use carries the antidepressant class suicidality concern without efficacy data.
- In adults 65 and older start at **28 mg**, since exposure is higher and sedation, falls, and confusion are more likely.
- Use caution in moderate hepatic impairment and avoid in severe impairment, since exposure and recovery time both increase.

PRESCRIBING PEARLS

- Never dispensed for home use; every dose is observed for **2 hours** in a certified REMS site.
- Blood pressure peaks about 40 minutes after dosing, so check it then, not just at baseline.
- No driving until the next day after restful sleep, regardless of how well the patient feels.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.