
ESKETAMINE (Spravato) Fact Sheet

Note: See ketamine fact sheet in this chapter for information on off-label ketamine treatment.

Bottom Line:

Esketamine is the *s*-enantiomer of ketamine, given as a nasal spray. It is only modestly effective for treatment-resistant depression and suicidality; its main advantage is its speed of onset, which is typically 24 hours. FDA requirements mandate that it be given in a health care facility and that patients be monitored for two hours after each treatment. Most clinicians consider it less effective than the unapproved intravenous use of ketamine.

FDA Indications:

Treatment-resistant major depression (TRD) or major depression with acute suicidal ideation or behavior (MDSI), to be used in conjunction with an oral antidepressant.

Off-Label Uses:

Pain, migraine headache.

Dosage Forms:

Nasal spray device: 28 mg per device, to be given in two sprays (one 14 mg spray in each nostril).

Dosage Guidance:

- TRD:
 - Induction phase (weeks one to four): 56 mg on day one, then 56 mg or 84 mg twice a week.
 - Maintenance phase (subsequent weeks): 56 or 84 mg weekly or every two weeks, depending on response.
- MDSI:
 - Start and continue 84 mg twice weekly for four weeks.
- Use two devices (each 28 mg) for a 56 mg dose and three devices for an 84 mg dose, with a five-minute rest period after using each device to allow medication to be absorbed.
- Patients must be observed by a health care provider when they take the medication and for at least two hours after administration, and they will require transportation after treatment.
- Patients cannot take the nasal spray device home; they must come into the office for all doses.
- Patients should avoid food for two hours before administration and liquids 30 minutes prior, because of the risk of nausea and vomiting.
- Check patients' blood pressure (for possible hypertension) both before dose and 40 minutes after dose.

Monitoring: BP (see Spravato REMS, mentioned in Clinical Pearls below).

Cost: \$\$\$\$\$

Side Effects:

- Most common: Sedation, dissociation (including depersonalization and derealization), increased blood pressure (transient, lasts about four hours), cognitive impairment, impaired ability to drive.
- Serious but rare: Hypertensive crisis. Contraindicated in aneurysmal vascular disease and history of intracerebral hemorrhage. Treatment-emergent suicidality may be more common than with standard antidepressants.
- Pregnancy/breastfeeding: Not enough data to recommend.

Mechanism, Pharmacokinetics, and Drug Interactions:

- N-methyl-D-aspartate (NMDA) receptor antagonist.
- Time to maximum concentration: 20–40 minutes.
- Metabolized primarily by CYP2B6 and CYP3A4; $t_{1/2}$: 7–12 hours.
- Avoid use with CNS depressants (eg, benzodiazepines, opioids, alcohol), MAOIs, and psychostimulants.

Clinical Pearls:

- Esketamine is the *s*-isomer of ketamine (which is a mixture of *s*-ketamine and *r*-ketamine). One rationale for the development of esketamine is that the *s*-isomer is a more potent NMDA antagonist than the *r*-isomer of ketamine.
- Efficacy: In three four-week trials, patients with TRD were randomly assigned to an oral antidepressant plus either esketamine or placebo nasal spray. Esketamine outperformed placebo in one of these trials. In a longer-term maintenance trial, patients were less likely to relapse when continuing on esketamine than placebo.
- Efficacy may be seen as early as 24 hours after first dose. Appropriate duration of treatment remains unknown.
- Only available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS) program. In order to provide esketamine to patients, your clinic must become a “certified Spravato treatment center” (online certification: www.spravatorems.com).
- Controlled substance (Schedule III) due to potential for misuse.

Fun Fact:

Esketamine was granted “breakthrough status” by the FDA. This designation is given to agents intended to treat a serious disease if preliminary evidence suggests they provide substantial improvement over existing treatments.