Esketamine (Spravato) Fact Sheet

FDA Indications:
Treatment-resistant major depression, in conjunction with an oral antidepressant.

Off-Label Uses:
Pain, migraine headache.

Dosage Forms:
- Esketamine is the s-isomer of ketamine (which is a mixture of both s-ketamine and r-ketamine).
- Each nasal spray device contains 28 mg of esketamine to be given in two sprays (one spray in each nostril).

Dosage Guidance:
- Induction phase (weeks 1 to 4): 56 mg on day one, then 56 mg or 84 mg twice a week.
- Maintenance phase (weeks 5 on): 56 or 84 mg weekly or every two weeks, depending on response.
- Use two devices (each 28 mg) for 56 mg dose and three devices for 84 mg dose with 5-minute rest period after using each device to allow medication to absorb.

Drug administration:
- Patients must be observed by a healthcare provider when they take the medication and for at least two hours after administration.
- Patients cannot take the device home; patients must come into the office every time they need to take a dose.
- In order to provide esketamine to patients, your clinic must become a “certified Spravato treatment center.” (online certification: www.spravatorems.com)
- Patient should avoid food for 2 hours before administration and liquids 30 minutes prior, because of the risk of nausea and vomiting.
- Check patient’s blood pressure both before and 40 minutes after dose.

Cost: $$$$$

Side Effects:
- Most common: Sedation, dissociation (including depersonalization and derealization), increased blood pressure (transient, lasts about 4 hours), cognitive impairment, impaired ability to drive.
- Serious but rare: Hypertensive crisis. Contraindicated in aneurysmal vascular disease and history of intracerebral hemorrhage.
- Potential to be abused/misused.

Mechanism, Pharmacokinetics, and Drug Interactions:
- NMDA receptor antagonist.
- Time to maximum concentration: 20-40 minutes.
- Metabolized primarily by CYP2B6 and CYP3A4; t½: 7-12 hours.
- Avoid use with CNS depressants (eg, benzodiazepines, opioids, alcohol), MAOIs, and psychostimulants.

Clinical Pearls:
- Efficacy: In 3 four-week trials, patients with treatment-resistant depression 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.
- One rationale for the development of esketamine is that the s-isomer is a more potent NMDA antagonist than the r-isomer of ketamine.
- Only available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS).
- Controlled schedule III substance due to potential for misuse. It is used recreationally as a club drug under the name “Special K”.

Fun Fact:
Esketamine was granted “breakthrough status” by the FDA. The FDA concedes that this designation is misleading and provides a marketing advantage for drugs which may not really be “breakthroughs”. According to the FDA, "Not all products designated as breakthrough therapies ultimately will be shown to have the substantial improvement over available therapies suggested by the preliminary clinical evidence at the time of designation. If the designation is no longer supported by subsequent data, FDA may rescind the designation”.

Bottom Line:
Esketamine appears to be modestly effective for treatment resistant depression, and it should be offered to patients who have not responded to other agents or for whom ECT is less appealing or appropriate. While it offers greater ease of use compared to the unapproved use of intravenous ketamine infusion, the inconvenience of frequent office visits and onerous monitoring and regulatory requirements are disadvantages but help to manage concerns about safety and abuse.