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ECHO IDAHO: BEHAVIORAL HEALTH IN PRIMARY CARE

Esketamine

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DISCLOSURES

- Dr. Carlson, in the past, has provided consulting services for Alkermes & Heron Therapeutics.



LEARNING OBJECTIVES

- Review Treatment-Resistant Depression (TRD) treatment strategies
- Describe basic medication profile information regarding intranasal esketamine
- Briefly describe the risk evaluation and mitigation strategy mandates for clinics planning to administer esketamine
- Highlight the appropriate monitoring and documentation steps for a patient administered intranasal esketamine

TREATMENT-RESISTANT DEPRESSION (TRD)

DEFINITION

- Major depressive disorder in individuals who have not responded adequately to at least two different antidepressants of adequate dose and duration



TREATMENT-RESISTANT DEPRESSION (TRD)

CURRENT PHARMACOLOGIC TREATMENT STRATEGIES

- **Optimization:** Maximize dose and duration of antidepressant
- **Switching:** Changing to a similar or different class of antidepressant
- **Combination:** Adding another antidepressant from a different class
- **Augmentation:** Adding a second agent that is not an antidepressant
- **Other therapies:** Intravenous ketamine, intranasal esketamine



AVAILABLE TRD TREATMENTS*

*TREATMENT OPTIONS ARE NOT LISTED IN ANY ORDER OF PREFERENCE/EVIDENCE.

Pharmacologic

- Fluoxetine + Olanzapine
- Agents within/or of differing Antidepressant classes
- Other off-label

Augmentation

- Cognitive Behavioral Therapy
- Other Psychotherapy

Device-Related

- Electroconvulsive Therapy (ECT)
- Transcranial Magnetic Stimulation (TMS)
- Vagus Nerve Stimulator (VNS)



INTRANASAL ESKETAMINE

PROFILE

- **Mechanism of action** – Esketamine (S-enantiomer of racemic ketamine) is a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist, which is a novel mechanism of action. The mechanism by which it exerts its antidepressant effect is unknown. The major circulating metabolite noresketamine demonstrated activity at the same receptor with less affinity.
- **Indication** – Treatment-resistant depression (TRD), with oral antidepressant, in adults
- **Controlled substance** - Schedule III



PHARMACOKINETICS

Absorption

- Bioavailability: 48%
- T_{max}: 20 to 40 min
- C_{max}: 27% to 66%
- AUC_∞: 18% to 45%

Distribution

- Volume of distribution (IV): 709 L
- Protein binding: 43% to 45%

Metabolism

- Metabolite: Noresketamine
- Via CYP2B6 and CYP3A4, to lesser extent CYP2C9 and CYP2C19

Excretion

- Unchanged in urine: less than 1%



INTRANASAL ESKETAMINE

PROFILE BOXED WARNING

- **Sedation and dissociation:** Patients are at risk for sedation and for dissociative or perceptual changes after administration of esketamine. Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours following each treatment, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the health care setting.
- **Abuse and misuse:** Esketamine has the potential to be abused and misused. Consider the risks and benefits of prescribing esketamine prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse.
- **Suicidal thoughts and behaviors:** Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. Esketamine is not approved in pediatric patients.
- **REMS**



INTRANASAL ESKETAMINE

PROFILE

Drug interactions

- CNS depressants: Increase sedation
- Psychostimulants: Increase blood pressure
- Monoamine oxidase inhibitors (MAOIs): Increased blood pressure
- Esketamine has modest induction effects on CYP2B6 and CYP3A4

Contraindications/warnings

- Aneurysmal vascular disease or arteriovenous malformation, intracerebral hemorrhage, medication hypersensitivity, pregnancy/lactation

Storage and Disposal

- Store at 68° to 77° F
- Store per facility procedure for Schedule III drug product, to ensure adequate security and accountability per applicable federal, state and local regulations

Availability/cost* – 56 mg (~\$650) and 84 mg (~\$975) dose kits

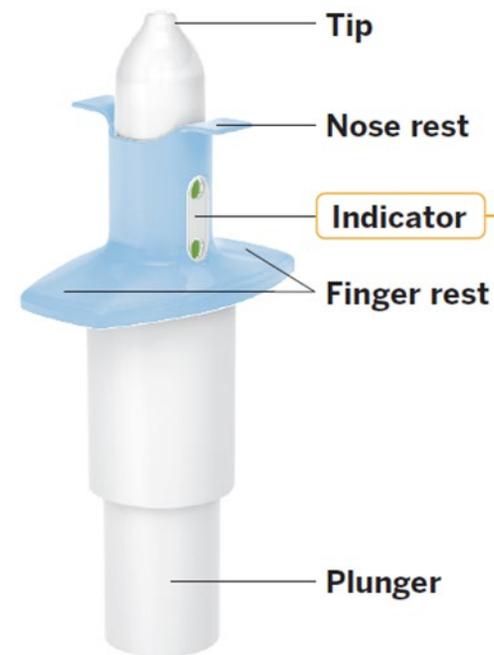
- *Specialty Pharmaceutical Product see REMS requirements



INTRANASAL ESKETAMINE

PRODUCT

Nasal Spray Device

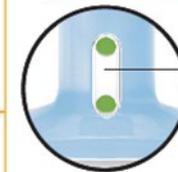


Each device delivers two sprays containing a total of 28 mg of esketamine.

Indicator

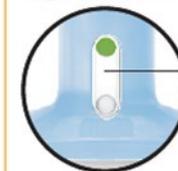
One device contains 2 sprays.
(1 spray for each nostril)

2 green dots (0 mg delivered)



Device full

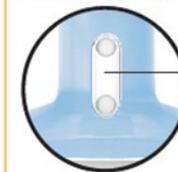
1 green dot



One spray delivered

No green dots

Two sprays (28 mg) delivered



Device empty



INTRANASAL ESKETAMINE

DOSING SCHEDULE

SPRAVATO™ (esketamine) nasal spray, CIII

Table 1: Recommended Dosage for SPRAVATO

		Adults
Induction Phase	<u>Weeks 1 to 4:</u>	Day 1 starting dose: 56 mg
	Administer twice per week	Subsequent doses: 56 mg or 84 mg
Maintenance Phase	<u>Weeks 5 to 8:</u>	
	Administer once weekly	56 mg or 84 mg
	<u>Week 9 and after:</u>	
	Administer every 2 weeks or once weekly*	56 mg or 84 mg

* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.



INTRANASAL ESKETAMINE

MONITORING

- Sedation PI: 49% to 61%
- Dissociation PI: 61% to 75%
- Elevated Blood Pressure PI: 8% to 17%



INTRANASAL ESKETAMINE

REMS REQUIREMENTS

REMS program enrollment for each healthcare setting

- Enrolled by the healthcare setting prior to product administration

Provide consent for treatment

- Review medication guide
- Counseled risks associated with the product
- Must work with prescriber to complete patient enrollment form

Self-administer medication at each visit

Remain at healthcare setting for at least 2 hours

- Adhere to any other facility-specific policies/procedures



KEY POINTS

ESKETAMINE

- Esketamine is now an option in the treatment strategies for Treatment-Resistant Depression (TRD), but has Risk Evaluation and Mitigation Strategy (REMS) requirements that include post administration monitoring
- Esketamine is considered a Schedule III controlled substance
- Sedation, dissociation, and elevated blood pressure need to be monitored prior to patient leaving treatment site.



REFERENCES

- American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. November 2010.
- Spravato (esketamine) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; February 2020.
- Am Fam Physician. 2009;80(2):167-172.
- www.Spravatorems.com



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RESOURCES FROM TODAY'S SESSION AND PAST SESSIONS CAN BE FOUND IN OUR ONGOING RESOURCE LIST.

<https://iecho.unm.edu/sites/uidaho/download.hns?i=85>

<https://www.spravatorems.com/>

<https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=386#tabs-2>