Esketamine Nasal Spray (Spravato®)

FDA approved March 2019 (initial ketamine approval: 1970)
Janssen Pharmaceuticals Inc., Schedule III Controlled Substance

Indication: To be used in conjunction with an oral antidepressant for the treatment of treatment-resistant depression (TRD) in adults. Not approved as an anesthetic agent.

Mechanism of Action: Esketamine, the S-enantiomer of racemic ketamine, is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist that enhances glutamine release in the brain. The mechanism by which esketamine exerts its antidepressant effect is not fully understood. Esketamine has greater affinity for the NMDA receptor & greater dopamine transporter inhibition compared to the R-enantiomer or racemic ketamine

Dosage & Administration

Phase	Frequency of administration	Dose
Induction Phase	Weeks 1 to 4: Twice a week	Initial dose: 56 mg Subsequent doses: 56 or 84 mg
Maintenance Phase	Weeks 5 to 8: Once weekly	56 or 84 mg
	Week 9 & after: Every 2 weeks or once weekly ▪ individualize to the least frequent dosing to maintain remission/response	

Prior to administration	▪ Avoid food for at least 2 hours & liquids for 30 minutes prior to administration ▪ Clts on nasal corticosteroid/decongestant should use these medications at least 1 hour prior to esketamine administration ▪ BP assessment
Administration	▪ Administer intranasally under the supervision of a healthcare provider (HCP)
Post-administration	▪ BP assessment ▪ Do not drive/operate machinery until the next day after a restful sleep
Moderate or severe hepatic impairment	▪ Moderate impairment: may need to monitor for ARs for a longer period of time ▪ Severe impairment: not recommended (not studied)
How Supplied	Each device delivers 2 sprays containing a total of 28 mg of esketamine

Drug Drug Interactions

Concomitant Medication	Effect
Benzodiazepines & other CNS depressants	Additive effects. Closely monitor for sedation
Psychostimulants or Monoamine Oxidase Inhibitors	May increase BP. Closely monitor

Adverse Effects (see attached tables 3 & 6)

Most frequently reported AEs (≥5% & at least twice of placebo plus oral antidepressant)	Dissociation, dizziness, N/V, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased BP, & feeling drunk

Warnings & Precautions

- **Black Box warnings**
  - Sedation: Monitor for at least 2 hours after administration
  - Dissociation: Monitor for at least 2 hours after administration
  - Potential for abuse & misuse. Available through Spravato REMS program only
  - Increased risk of suicidal thoughts & behaviors in pediatric & young adults taking antidepressants. Not approved for use in pediatric patients
- **Contraindications**
  - Aneurysmal vascular disease or arteriovenous malformation

References available upon request

    - Intracerebral hemorrhage or hypersensitivity to esketamine/ketamine/excipients
- **Other warnings**
    - Increases in BP: Pts with CV/cerebrovascular conditions & risk factors may be at an increased risk
    - Cognitive Impairment
    - Do not drive/operate machinery until the next day after a restful sleep
    - Embryo-fetal toxicity

Pharmacokinetics

Bioavailability (F)	Nasal spray: 48%
Cmax	20 to 40 minutes (after the last spray) Inter-subject variability: 27% to 66% Intra-subject variability: 15%
Metabolism	Primarily hepatic via CYP450 & glucuronidation
Half-life (mean terminal $t_{1/2}$)	▪ Esketamine: 7 to 12 hours ▪ Noresketamine (major metabolite): ~ 8 hours ▪ Biphasic decline in plasma esketamine & noresketamine concentration
Excretion	Urine < 1% of nasal esketamine dose excreted as unchanged drug

Role in Therapy
Esketamine nasal spray when used in combination with an oral antidepressant appears to be associated with relatively faster reduction of depressive symptoms and delayed time to relapse compared with placebo plus an oral antidepressant

- Not a replacement drug – to be given in conjunction with an oral antidepressant
- faster relief of depression symptoms compared to traditional antidepressants
- Intranasal formulation
    - less invasive, easier to use
    - potent S-enantiomer (lower dose possibly fewer side effects)
    - granted Fast Track and Breakthrough Therapy designations by FDA

- Restricted Distribution System
    - To be administered at certified physician's office or clinic
    - Esketamine's high cost & restricted access could divert demand to inexpensive street ketamine for rapid symptom relief (may worsen ketamine addiction problem)
    - Prescribers & clts will need to sign a Patient Enrollment Form indicating the clt understands they should
        - make arrangements to get home post-treatment
        - not drive or use heavy machinery for the rest of the day
    - To be dispensed with a Medication Guide

- Esketamine compared to other treatment options for TRD
    - please contact BHRS Pharmacy Services for a comparison table
- Unidentified potential risks associated with longer-term exposure in real life settings
- Lack of published evidence for prolonged efficacy with continued use
- Abuse potential
    - Esketamine has similar PK profile to ketamine - popular recreational drug used for "out of body" experiences
    - Risk of addiction with long term use
- Ketamine cannot be patented
    - Approved in 1970 as an anesthetic
    - Pharmaceutical companies have no incentive to conduct trials for a new indication

References available upon request

        - Esketamine nasal spray can be patented
            - S-enantiomer, new formulation, new indication
- Potential candidates
    - Clts who may hurt themselves (fast benefit in suicidal clts)
        - Esketamine nasal spray appears to rapidly reduce depression symptoms including suicidal thoughts in depressed patients at elevated risk of suicide
        - Possibly shorten hospital stays or avoid hospitalization
    - Clts experiencing severe, ongoing treatment resistant depression
    - Need to define "treatment resistant depression"
        - FDA – tried/failed 2 traditional antidepressants at adequate doses for an adequate duration in the current episode
- FDA's approval could encourage clients with limited access to treatment to self-medicate depression symptoms with street ketamine
- Potential off-label use
    - Esketamine as a bridge while antidepressants exert their effect

Pricing:

Drug	Dosing	30-day Cost *
Spravato	Induction Phase-week 1-4 56mg or 84mg twice weekly	$5664 to $8496
	Maintenance Phase 56mg or 84mg once weekly	$2832 to $4258
	Maintenance Phase 56mg or 84mg every two weeks	$1416 to $2129
Symbyax Generic	Olanzapine 12mg + Fluoxetine 50mg Once daily	$ 655

*Average Wholesale Price as of 4/3/2019

References available upon request

Table 3: Adverse Reactions Occurring in ≥2% of TRD Patients Treated with SPRAVATO + Oral AD at Any Dose and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD

	SPRAVATO + Oral AD (N=346)	Placebo + Oral AD (N=222)
Cardiac disorders		
Tachycardia*	6 (2%)	1 (0.5%)
Ear and labyrinth disorders		
Vertigo*	78 (23%)	6 (3%)
Gastrointestinal disorders		
Constipation	11 (3%)	3 (1%)
Diarrhea	23 (7%)	13 (6%)
Dry mouth	19 (5%)	7 (3%)
Nausea	98 (28%)	19 (9%)
Vomiting	32 (9%)	4 (2%)
General disorders and administration site conditions		
Feeling abnormal	12 (3%)	0 (0%)
Feeling drunk	19 (5%)	1 (0.5%)
Investigations		
Blood pressure increased*	36 (10%)	6 (3%)
Nervous system disorders		
Dizziness*	101 (29%)	17 (8%)
Dysarthria*	15 (4%)	0 (0%)
Dysgeusia*	66 (19%)	30 (14%)
Headache*	70 (20%)	38 (17%)
Hypoesthesia*	63 (18%)	5 (2%)
Lethargy*	37 (11%)	12 (5%)
Mental impairment	11 (3%)	2 (1%)
Sedation*	79 (23%)	21 (9%)
Tremor	12 (3%)	2 (1%)
Psychiatric disorders		
Anxiety*	45 (13%)	14 (6%)
Dissociation*	142 (41%)	21 (9%)
Euphoric mood	15 (4%)	2 (1%)
Insomnia	29 (8%)	16 (7%)
Renal and urinary disorders		
Pollakiuria	11 (3%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders		
Nasal discomfort*	23 (7%)	11 (5%)
Oropharyngeal pain	9 (3%)	5 (2%)
Throat irritation	23 (7%)	9 (4%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	14 (4%)	5 (2%)

Table 6: Increases in Blood Pressure in Double-blind, Randomized-controlled, Short-term Trials of SPRAVATO + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD

	Patients <65 years		Patients ≥65 years	
	SPRAVATO + Oral AD N=346	Placebo + Oral AD N=222	SPRAVATO + Oral AD N =72	Placebo + Oral AD N=65
Systolic blood pressure				
≥180 mmHg	9 (3%)	---	2 (3%)	1 (2%)
≥40 mmHg increase	29 (8%)	1 (0.5%)	12 (17%)	1 (2%)
Diastolic blood pressure				
≥110 mmHg	13 (4%)	1 (0.5%)	---	---
≥25 mmHg increase	46 (13%)	6 (3%)	10 (14%)	2 (3%)

References available upon request

Formulary Recommendation from BHRS P&T

Formulary Update (CMC only):

- SPRAVATO added w/ PA, QL since it is a protected class drug and requires formulary placement. Quantity limit to prevent fraud, waste, and abuse.

Formulary Update (BHRS, HealthWorx, Healthy Kids, Medi-Cal):

- NONFORMULARY

Prior Authorization (CMC)/Approval Criteria (HealthWorx, Healthy Kids, Medi-Cal) Update:

- SPRAVATO prior authorization criteria/approval criteria:

    - **Covered Uses:** All FDA approved indications not otherwise excluded from Part D
    - **Required Medical Information:**

        1. Assessment of baseline symptoms severity
        2. Tried and failed 4 antidepressant trials of adequate dose and duration, must include one augmentation trial with lithium or atypical antipsychotic
        3. Tried and failed ECT or has contraindications to ECT
        4. Use in combination with an antidepressant
        5. Negative urine tox screen
        6. No current or recent substance abuse (within 12 months)
        7. Negative pregnancy test for female of childbearing age
        8. Client does not have the following contraindications to Spravato:

            Aneurysmal vascular disease or arteriovenous malformation

            History of intracerebral hemorrhage

            Hypersensitivity to esketamine/ketamine/excipients
        9. REMS certified health care setting and pharmacy

        Coverage Duration:

        Initial: Approved for 3 month duration

        Renewal: Approved for 6 months with documentation:
        1. Negative urine tox screen
        2. Assessment of symptom improvement post treatment

References available upon request