



INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: Esketamine
-August 2021-



Background:

In August 2021, the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug review of esketamine. The evaluation covered an overview of treatment resistant depression (TRD), currently available treatment options for TRD, current standards of care and guidelines for TRD, available literature for esketamine, and a pharmacoeconomic analysis to determine if changes were needed to the National Core Formulary (NCF). Following the clinical and pharmacoeconomic analyses of esketamine in TRD, the NPTC **made no modifications** to the NCF.

Discussion:

Depression is one of the most common mental disorders nationwide with roughly 7% of adults in the United States experiencing at least one depressive episode in their lifetime.^{1,2} These depressive episodes are 60% more likely in American Indians and Alaska Natives.³ The results of depression also have a significant impact on the healthcare system with an annual cost of over \$210 billion.⁴ Recent challenges, including the COVID-19 and opioid pandemics, have increased depressive disorders four times in 2020 compared to 2019.¹

Defined as depression that is refractory to at least two trials of antidepressants from differing pharmacological classes, TRD affects up to 33% of patients suffering from depression.⁵ The overall goal is to return the patient to a functional status, help them engage in social and family roles, and have a customized treatment plan for increased adherence and long-term success.⁶ Proper treatment of TRD includes both non-pharmacological (psychotherapies) and pharmacological (antidepressants) options. Common treatment options include switching antidepressants, adding psychotherapies to medication therapies, augmentation with a combination of antidepressants or antipsychotics or lithium or liothyronine (T3) or psychotherapy, electroconvulsive therapy, vagal nerve stimulation, or transcranial magnetic stimulation.^{5,6}

Esketamine, the S enantiomer of ketamine, is an NMDA receptor antagonist affecting the glutamate pathway.⁷ Esketamine is FDA approved to treat TRD and recently received an additional indication in July 2020 for the treatment of major depressive disorder with suicidal thoughts or actions (MDD-SI) in adults. Esketamine is available as a nasal spray and must be administered by the patient under the supervision of a healthcare provider. Dosing varies based on indication and response and esketamine must always be used in conjunction with an oral antidepressant. Both the pharmacy and healthcare facility must register to order, dispense, and administer esketamine through the FDA REMS program. Common side effects include sedation, dissociation, hypertension, cognitive impairment, ulcerative/interstitial cystitis, and embryo-fetal toxicity. Numerous black box warnings exist including CNS depression, sedation/dissociation, potential for abuse, and suicidal thoughts/behaviors. Concomitant use with psychostimulants (amphetamines, modafinil) and MAIOs (isocarboxazid, phenelzine, selegiline, tranylcypromine) may increase blood pressure and use with CNS depressants (benzodiazepines, opioids, alcohol) may increase sedation. Esketamine should not be used in pregnant/lactating women or in severe hepatic impairment. Patients should have their blood pressure assessed prior to esketamine administration and should be monitored for 2 hours after administration (blood pressure, CNS depression, abuse/misuse, suicidal thoughts/behaviors).⁷

Clinical guidelines for the American Psychiatric Association (APA), Canada, and Department of Veterans Affairs/Department of Defense (VA/DoD) do not specially address the use of esketamine in the treatment of TRD or MDD-SI.^{6,8,9} Both the APA and Canadian guidelines list augmentation therapy, such as esketamine, as a third line option.^{6,8} The 2016 VA/DoD Clinical Practice Guidelines for the Management of MDD does not include esketamine and give a "Strong Against" recommendation for ketamine outside the research setting due to safety and duration of effect.⁹ The 2019 VA/DoD Clinical Practice Guidelines for the Assessment and Management of Patients at Risk for Suicide give a "Weak For" recommendation for ketamine (not esketamine) for those with MDD-SI.⁹

Five, phase 3, randomized, placebo-controlled trials were used to determine the clinically efficacy and safety of esketamine in adult patients with TRD (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, SUSTAIN-2).¹⁰ The primary endpoint of the short-term TRANSFORM trials was the efficacy of esketamine with oral antidepressant (ESK+AD) measured by changes in MADRS total score from baseline to day 28.¹¹⁻¹³ These studies looked at esketamine efficacy with fixed dosing¹¹, flex dosing¹², and in the geriatric population.¹³ In TRANSFORM-1, ESK+AD showed a clinically meaningful improvement in depressive symptoms from baseline but did not reach statistical significance for the 84 mg ESK+AD dose (LSMD: -3.2; 95% CI: -6.88 to 0.45; $p=0.088$).¹¹ In TRANSFORM-2, ESK+AD resulted in clinically meaningful and statistically significantly greater improvement in depressive symptoms compared with AD+placebo (LSMD: -4.0; 95% CI: -7.3 to -0.6; $p=0.02$).¹² In TRANSFORM-3, a clinically meaningful change in MADRS total score favored ESK+AD but it was not statistically significant (LSMD: -3.6; 95% CI: -7.2 to 0.07; $p=0.059$).¹³ The safety profile was consistent with that observed in a younger adult population.¹³ The primary endpoint of the long-term SUSTAIN trials was the efficacy of ESK+AD in

delaying relapse of depressive symptoms in stable remitters (MADRS score ≤ 12) and a secondary endpoint of relapse delay in stable responder ($\geq 50\%$ reduction in MADRS score at baseline).^{14,15} In SUSTAIN-1, continued treatment with ESK+AD demonstrated a statistically significantly lower rate of relapse compared to treatment with AD+placebo in patients who were in either stable remitters (26.7% vs 45.3%; HR: 0.49; 95% CI: 0.20 to 0.84; $p=0.003$) and/or stable responders (25.8% vs 57.6%; HR: 0.30; 95% CI: 0.16 to 0.55; $p<0.001$).¹⁴ In SUSTAIN-2, long-term treatment with ESK+AD was tolerable in adult patients with TRD including elderly (≥ 65 years) patients.¹⁵

Two, double-blind, 4-week, multicenter, randomized controlled trials (ASPIRE-1, ASPIRE-2) were used to determine efficacy and safety of esketamine in adult patients with MDD-SI.^{16,17} The primary endpoint was change in MADRS score from baseline to 24 hours and a secondary endpoint of change in symptom severity using the Clinical Global Impression of Severity of Suicidality (CGI-SS). In ASPIRE-1, the MADRS total score decreased from baseline after the first dose in both groups and significant improvement was observed in the ESK group (LSMD [Secondary Endpoint]: -3.8 [1.39]; 95% CI: -6.56 to -1.09; $p=0.006$).¹⁶ The mean group difference in MADRS total score at 24 hours favored ESK in those with prior suicide attempt (-5.53; CI: -9.11 to -1.95) and more severe depressive symptoms (-6.53; 95% CI: -10.88 to -2.18). At the 24-hour endpoint, patients in both treatment groups experienced improvement in the severity of their suicidality but there was no statistically significant difference between treatment groups ($p=0.107$). In ASPIRE-2, the MADRS total score decreased from baseline to 24 hours after the first dose in both groups and significant improvement was observed in depressive symptoms with ESK (LSMD [Secondary Endpoint]: -3.9 [1.39]; 95% CI: -6.60 to -1.11; $p=0.006$).¹⁷ The treatment effect of ESK was observed in patients who have attempted suicide (-4.26; -7.66 to -0.86) and/or those with more severe depressive symptoms (-4.84; -8.85 to -0.83).

A meta-analysis of eight double-blind, randomized controlled trials looked at esketamine effectiveness for TRD and MDD-SI and found that MADRS scores improved significantly and response/remission were noticeable as early as 2 to 4 hours (SMD: -0.67; CI: -1.16 to -0.17, $p=0.008$) after the first ESK dose, and this superior efficacy lasted through 4 weeks (SMD: -0.23; 95% CI: -0.37 to -0.10, $p=0.0007$).¹⁸ When evaluating ESK use in MDD-SI, the analysis showed that ESK had rapid anti-suicidal effects and superior efficacy over placebo between 2 to 4 hours after administration (OR: 2.04; 95% CI: 1.37 to 3.05, $p=0.0005$) but the statistical significance was not maintained at 24 hours (OR: 1.15; 95% CI: 0.80 to 1.65, $p=0.46$) or at 4 weeks (OR: 1.32; 95% CI: 0.91 to 1.90, $p=0.44$).¹⁸

Findings:

Antidepressants (although not specifically indicated for TRD) currently listed on the NCF include amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, nortriptyline, paroxetine, sertraline, and venlafaxine. There are a limited number of randomized controlled trials, meta-analyses and current practice guidelines evaluating esketamine. The effectiveness in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated with esketamine use. Improvement in depressive symptoms was observed for those with higher initial MADRS scores and/or a prior history of suicide attempts.

References:

1. National Institute of Medicine. Health Topics: Depression. Available at: <https://www.nimh.nih.gov/health/topics/depression>.
2. TMS & Brain Health. Alternative Treatments to Depression That Work. Available at: <https://www.tmsbrainhealth.com/>.
3. U.S. Department of Health and Human Services; Office of Minority Health. Available at: <https://www.minorityhealth.hhs.gov>.
4. American Psychiatric Association; Center for Workplace Mental Health. Available at: <https://www.workplacementalhealth.org>.
5. American Academy of Family Physicians. Treatment-Resistant Depression. Available at: <https://www.aafp.org>.
6. American Psychological Association; Treatment-Resistant Depression. Available at: <https://www.apa.org>.
7. SPRAVATO® (esketamine) nasal spray, CIII. **PRODUCT INSERT**. Janssen Pharmaceuticals, Inc. Titusville, NJ 08560. Revised 07/2020.
8. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder. **Section 3. Pharmacological treatments**. *Can J Psychiatry*. 2016; 61:540-560.
9. U.S. Department of Veterans Affairs. VA/DoD Clinical Practice Guidelines: **Management of Major Depressive Disorder** (2016).
10. Ehret MJ. **A novel approach to treatment resistant depression: esketamine**. NAMIcon. July 13-14, 2020.
11. Fedgchin M, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: **Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1)**. *Int J Neuropsychopharmacol*. 2019; 22(10):616-630.
12. Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: **A Randomized Double-Blind Active-Controlled Study**. *Am J Psychiatry*. 2019; 176(6):428-438.
13. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression-**TRANSFORM-3**. *Am J Geriatr Psychiatry*. 2020;28(2):121-141.
14. Daly EJ, Trivedi MH, Janik A, et al. **Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial**. *JAMA Psychiatry*. 2019; 76(9):893-903.
15. Wajs E, Aluisio L, Holder R, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (**SUSTAIN-2**). *J Clin Psychiatry*. 2020;81(3):19m12891.
16. Fu DJ, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (**ASPIRE I**). *J Clin Psychiatry*. 2020;81(3):19m13191.
17. Ionescu DF, Fu DJ, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (**ASPIRE II**). *Int J Neuropsychopharmacol*. 2021;24(1):22-31.
18. Wang SM, Kim NY, Na HR, et al. **Rapid Onset of Intranasal Esketamine in Patients with Treatment Resistant Depression and Major Depression with Suicide Ideation: A Meta-Analysis**. *Clin Psychopharmacol Neurosci*. 2021;19(2):341-354.