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November 11, 2020

STATE OF WEST VIRGINIA
DEPARTMENT OF HEALTH AND HUMAN RESOURCES
Bureau for Medical Services
Drug Utilization Review Board

To Whom It May Concern:

Please see the attached information for SPRAVATO® (esketamine), marketed by Janssen Pharmaceuticals, Inc., submitted on behalf of Kayleen Gwyn, PharmD, in preparation for the upcoming Drug Utilization Review Board Meeting on November 18, 2020.

Full contact information for Dr. Gwyn is as follows:

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The enclosed information has been supplied to you in response to your unsolicited request and is not intended as an endorsement of any usage not contained in the prescribing information. For complete information, please refer to the attached Full Prescribing Information, including the following sections: BOXED WARNING(S), INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS AND ADVERSE REACTIONS.

If you require further information, please feel free to contact me directly Monday through Friday, 9:00 a.m. to 5:00 p.m. EST.

Sincerely,

Michelle Han, PharmD
Associate Director, Payer & Health Systems
Medical Information & Knowledge Integration

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Case #: 01883510

West Virginia Pharmaceutical and Therapeutics Committee

Submitted by Janssen Scientific Affairs, LLC, on behalf of Kayleen Gwyn, PharmD, Senior Scientific Account Lead Value & Evidence Scientific Engagement - Field

SPRAVATO® (esketamine)

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning

Indication: Esketamine (ESK) is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant (AD), for the treatment of

- Treatment-resistant depression (TRD) in adults.[1] In clinical trials,[2-6] TRD was defined as a DSM-5 diagnosis of major depressive disorder (MDD) in patients who have not responded adequately to at least 2 different ADs of adequate dose and duration in the current depressive episode
- Depressive symptoms in adults with MDD with acute suicidal ideation or behavior (MDSI).[1]

Limitations of Use:

- The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO.
- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

Dosage and Administration for MDSI: Administer SPRAVATO in conjunction with an oral AD. The recommended dosage of SPRAVATO for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior is 84 mg twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. After 4 weeks of treatment with SPRAVATO, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. The use of SPRAVATO, in conjunction with an oral AD, beyond 4 weeks has not been systematically evaluated.

Dosing and Administration for TRD: Please see full prescribing information for complete dosing and administration instructions.

Safety: The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral AD):

- TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.
- MDSI: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

Risk Evaluation and Mitigation Strategy (REMS): SPRAVATO is a Schedule III (CIII) controlled substance under the Controlled Substances Act with a potential for abuse and misuse. Due to the risks of serious adverse outcomes from abuse or misuse, sedation, and dissociation, SPRAVATO is available only through a restricted program called SPRAVATO REMS. Further information is available at http://www.SPRAVATOrems.com or 1-855-382-6022.

Place in Therapy: ESK is a first-in-class AD with a MOA involving the NMDA receptor, an ionotropic glutamate receptor, indicated for the management of TRD and MDSI in adults.[1] Unlike existing pharmacotherapies for depression, ESK's primary AD activity is not believed to directly involve inhibition of serotonin, norepinephrine, or dopamine reuptake.[7-9] Major depression is the second leading cause of disability in the United States.[10] In 2017, ~17.3 million adults aged 18 or older had a past year MDD episode.[11, 12]

- Approximately 1/3 of patients with MDD may go on to develop TRD,[13] often defined as a failure of patients to respond or go into remission after ≥2 treatment attempts of adequate dose and duration.[14] This would be equivalent to Step 3 as studied in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[13] A substantial number of patients either do not respond adequately to current standard therapies or are unable to tolerate side effects.[15, 16] Comparative clinical trials to somatic treatments (e.g., ECT or TMS) or augmentation therapy (e.g., AD + antipsychotic agent) have not been conducted. ESK + AD has been shown to be effective in moderate to severely depressed TRD patients in clinical trials, with relatively low discontinuation rates due to adverse events.[2-6] A meta-analysis comparing MADRS total score reductions of ESK + AD compared with second generation antipsychotic (SGA) augmentation therapy reported higher mean difference (vs PBO) for the pooled ESK trials than for the pooled SGA augmentation trials.[17]
- Two identically designed phase 3, randomized, double-blind, PBO-controlled studies found that ESK + standard of care (SOC) statistically significantly improved depressive symptoms based on the MADRS total score at 24 hours post first dose compared with PBO + SOC in adults with MDSI.[18, 19] The treatment difference numerically favoring ESK + SOC on depressive symptoms was observed at 4 hours after initial dose and at all time points during the double-blind treatment phases.

Clinical Trial Summaries (Published October 2019 – Present)

Fedgchin et al (2019)[2] conducted a randomized, DB, multinational study comparing the efficacy and safety of switching patients with TRD from a prior AD treatment to fixed-dose 56 mg or 84 mg ESK + AD or to AD + PBO.

- Primary Endpoint: Both the ESK + AD (56 mg and 84 mg) groups showed a clinically meaningful[20, 21] and numerically greater change from baseline to day 28 in mean MADRS total score compared to AD + PBO (-19.0 vs -18.8 vs -14.8, respectively; LSMD [median unbiased estimate] from PBO: -4.1 vs -3.2, respectively). Statistical significance was not demonstrated with 84 mg ESK + AD (95% CI: -6.88, 0.45; *P*=0.088); therefore, 56 mg ESK + AD could not be formally evaluated (nominal *P*=0.027).
- Secondary Endpoints: Response and remission rates showed greater numerical improvement in both ESK + AD (56 mg and 84 mg) groups over AD + PBO. At day 28, 54.1%, 53.1%, and 38.9% of patients in the ESK 56 mg + AD, ESK 84 mg + AD, and AD + PBO groups, respectively, were responders, and 36.0%, 38.8%, and 30.6%, respectively, were remitters. The NNT to achieve response based on MADRS total score at day 28 for both ESK 56 mg and 84 mg was 7; the NNT to achieve remission was 18 and 12, respectively.
- Safety: Dissociative symptoms and perceptual effects, via CADSS, were observed shortly after each ESK dose administration, with total scores peaking at 40 minutes, and resolving by 1.5 hours postdose.

Fu et al (2020)[18] conducted a DB, randomized, PBO-controlled study to evaluate the efficacy of ESK compared with PBO in addition to SOC in reducing the symptoms of depression in patients with MDD with active suicidal ideation with intent.

- Primary Endpoint: The mean (SD) change in MADRS total score from baseline to 24 hours post–first dose was −16.4 (11.95) in the ESK + SOC group and −12.8 (10.73) in the SOC + PBO group. Treatment with ESK + SOC showed statistically significant improvement in depressive symptoms (reduction from baseline in MADRS total score) versus SOC + PBO (LSMD [SE]: −3.8 [1.39], 95% CI, -6.56 to -1.09; *P*=0.006) at 24 hours post–first dose. Treatment differences assessed by subgroup (based on gender, race, age group, region, baseline MADRS total score, standard of care AD medication at baseline, prior suicide attempt, and suicide attempt in last month) were consistent with the primary analysis for most subgroups, particularly in patients with prior suicide attempt (mean between-group difference [95% CI]: -5.53 [-9.11, -1.95]) and patients with more severe depressive symptoms (-6.53 [-10.88, -2.18]).
- Key Secondary Endpoint: Patients in both treatment groups demonstrated improvements in severity of suicidality at 24 hours post–first dose, with a median (range) change from baseline Clinical Global Impression – Severity of Suicidality – Revised (CGI-SS-R) score of −1.0 (−6; 2) in the ESK + SOC group and −1.0 (−5; 1) in the SOC + PBO group; however, the treatment difference was not statistically significant (LSMD [95% CI]: -0.26 [-0.59, 0.08]; *P*=0.107).
- Safety: 100 (88.5%) patients in the ESK + SOC group and 83 (74.1%) patients in the SOC + PBO group experienced ≥1 TEAE during the DB phase. Most events occurred on dosing days (ESK + SOC, 91%; PBO + SOC, 70.3%) and resolved on the same day (ESK + SOC, 94.9%; PBO + SOC, 85.7%) in both treatment groups.

Dold et al (2020)[17] conducted a meta-analysis to evaluate the efficacy of ESK nasal spray or second-generation antipsychotics (SGAs) compared to PBO as add-on treatment to oral ADs in patients with non-psychotic MDD with inadequate response to prior AD treatment (N=25 trials included).

- Meta-analysis outcome: Calculations for all outcomes were separately performed for the pooled SGA and pooled ESK add-on treatment group, in comparison with placebo group. Compared to AD/PBO, the pooled add-on ESK trials (mean difference [MD]=4.09, 95% CI: 2.01 to 6.17; n [number of subjects]=641) had a higher mean difference than the pooled SGA augmentation trials (MD=2.05, 95% CI:1.51 to 2.59; n=8363).
    - Individual SGA/AD itemization demonstrated superiority over AD/PBO for aripiprazole (MD=2.51, 95% CI: 1.81 to 3.21; n=2284), brexpiprazole (MD=1.46, 95% CI: 0.18 to 2.74; n=2393), cariprazine (MD=1.02, 95% CI: 0.12 to 1.91; n=1563), olanzapine (MD=3.19, 95% CI: 0.45 to 5.92; n=1012), and quetiapine (MD=1.89, 95% CI: 0.31 to 3.47; n=1088). Risperidone did not significantly differentiate from AD/PBO (n=23). No significant heterogeneity was identified in the study comparisons.

- Descriptive analysis showed a higher pooled mean reduction in the MADRS total score for ESK /AD (-18.08) than for SGA/AD treatment (-10.72) when the intervention and control group was analyzed separately. A higher mean MADRS reduction was reported in the control AD/PBO groups of the ESK trials (-13.72, n=268) compared to the SGA studies (-8.45 points).

- Limitations: The authors noted that the methodological differences of the studies make direct comparisons of mean reductions in MADRS for SGA augmentation and ESK studies difficult. The lack of safety considerations, exclusion of the 5 RCTS without MADRS assessments, change in the MADRS rating scale, and exclusion of RCTs with MDD patients with psychotic symptoms were identified as additional limitations to this meta-analysis.

Ionescu et al (2020)[19] conducted another DB, randomized, PBO-controlled study to evaluate the efficacy of ESK compared with PBO in addition to SOC in reducing the symptoms of depression in patients with MDD with active suicidal ideation with intent.

- Primary Endpoint: At 24 hours, the mean (SD) change from baseline in MADRS total score was −15.7 (11.56) in the ESK + SOC group and −12.4 (10.43) in the SOC + PBO group. Treatment with ESK + SOC showed statistically significant improvement (reduction from baseline in MADRS total scores) in depressive symptoms versus SOC + PBO (LSMD [SE]: −3.9 [1.39]; *P*=0.006) at 24 hours post–first dose. Treatment differences assessed by subgroup (based on gender, race, age group, region, baseline MADRS total score, standard of care AD medication at baseline, prior suicide attempt, and suicide attempt within the last month) were generally consistent with the primary analysis.
- Key Secondary Endpoint: Both treatment groups demonstrated improvements in severity of suicidality scores at 24 hours post–first dose, with a median (range) change from baseline in CGI-SS-R score of −1.0 (−6; 2) in the ESK + SOC group and −1.0 (−5; 2) in the SOC + PBO group; however, the treatment difference was not significant (*P*=0.379).
- Safety: 104 (91.2%) patients in the ESK + SOC group and 87 (77.0%) patients in the SOC + PBO group experienced ≥1 TEAE during the DB phase. The majority of events occurred on dosing days (ESK + SOC, 89.1%; PBO + SOC, 68%) and resolved on the same day (ESK + SOC, 94.9%; PBO + SOC, 84.9%) in both treatment groups.

Ochs-Ross et al (2020)[4] conducted a randomized, DB, multicenter study in elderly patients (≥65 years) with TRD to assess the efficacy and safety of flexible doses of ESK + AD compared with AD + PBO:

- Primary Endpoint: While not statistically significant, the ESK + AD group showed a clinically meaningful improvement,[20, 21] and a numerically greater decrease in the MADRS total score from baseline to day 28, compared to the AD + PBO group (-10.0 vs -6.3; LSMD [median unbiased estimate]: -3.6; 95% CI: -7.2, 0.07; *P*=0.059).
- Secondary Endpoints: Overall response (27.0% vs 13.3%) and remission (17.5% vs 6.7%) rates at Day 28 favored the ESK + AD vs AD + PBO group, respectively. The NNT to achieve response and remission at day 28 was 8 and 10, respectively.
- Safety: The most common TEAEs (≥10% in any treatment group) included: dizziness, nausea, blood pressure increased, fatigue, headache, dissociation, and vertigo. Dissociation symptoms typically resolved by 1.5 hours post dose and the severity tended to reduce over time with repeated treatments. Total CADSS score never exceeded 10 on any given dosing day.

Papakostas et al (2020)[22] conducted a meta-analysis of randomized, double-blind, acute-phase clinical trials exclusively comparing adjunctive treatment of oral ADs with ESK in patients with MDD to placebo that used either the Hamilton Depression Rating Scale (HDRS) or the MADRS as the primary outcome measure (N=5 trials included[2-4, 23, 24]).

- Primary Outcome (comparison of standardized mean difference (SMD) in change in primary outcome scores between adjunctive treatment with ESK and PBO at study endpoint): Across the trials, the SMD was 0.36 (95% CI: 0.24, 0.49; *P*<0.0001). In studies where the augmented AD was kept at a fixed dose, the magnitude of the difference was greater (SMD=0.6; RR for response 2.94).
- Secondary outcome (comparison of the risk ratio (RR) for response and remission between ESK + AD and AD + PBO at study endpoint): The RRs for response and remission were 1.40 (95% CI: 1.22, 1.61; *P*<0.0001) and 1.45 (95% CI: 1.20, 1.75; *P*<0.0001), respectively. The corresponding pooled response rates were 53.2% and 36.4% for the ESK and PBO groups, respectively, and remission rates were 38.5% and 24.7%, respectively. The NNT for response was 6 and 7 for remission.

Wajs et al (2020)[6] conducted a long-term, open-label, phase 3 study to evaluate the safety and tolerability of ESK + AD in patients ≥18 years of age with TRD treated with ESK + AD for up to 1 year.

- TEAEs occurred in 723 patients (90.1%), and 55 patients (6.9%) had events that were considered serious. The majority of TEAEs were mild or moderate in intensity, occurred on dosing days, and usually resolved on the same day. Treatment-emergent dissociative symptoms, sedation, and blood pressure increases generally resolved by 1.5 hours postdose. There were no cases of interstitial or ulcerative cystitis. Cognitive performance either improved or remained stable through week 44. New occurrences of suicidal ideation and behavior were reported in 114/784 patients (14.5%) using the C-SSRS assessment. There were 2 deaths: one considered by investigators to be doubtfully related to ESK (60-year-old man who died due to acute cardiac and respiratory failure) and the other not considered by investigators to be related to ESK (suicide-related death in a 55-year-old woman).
- Mean MADRS total score improved throughout the induction phase (mean [SD] change: -16.4 [8.76]) and appeared to be maintained from optimization/maintenance baseline to optimization/maintenance endpoint (mean [SD] change: 0.3 [8.12]). The percentage of responders and remitters increased over time during the induction phase.

Wei et al (2020)[25] conducted a systematic review of randomized DB, PBO-controlled studies to evaluate the effectiveness, tolerability, and safety of ESK in patients with MDD, 18-65 years old, with TRD and/or suicidal ideation (N=4 clinical trials included[2, 3, 23, 24]).

- Significant superiority of ESK vs PBO was identified in the reduction of MADRS total score ≥50% (55.2% vs. 34.2%, RR=1.39, 95%CI: 1.18 to 1.64, *P*<0.0001; NNT=7, 95% CI: 5 to 13). ESK also demonstrated significantly greater study-defined response and remission starting at 2 hours, peaking at 24 hours and maintained for at least 28 days.
- Meta-analysis of depressive symptoms measured by the MADRS and Patient Health Questionnaire-9 (PHQ-9) favored ESK vs PBO.
- ESK was associated with significantly higher discontinuation rate due to intolerability vs PBO (5.8% vs.1.5%, RR=3.50, 95% CI: 1.38 to 8.86, *P*=0.008; NNH=25, 95% CI: 10 to 100). Discontinuation due to any reason and lack of efficacy was similar between ESK and PBO groups.

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