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January 15, 2021

Sarah Servid, PharmD
OSU College of Pharmacy - Drug Use Research & Management
OHA Health Systems Division
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Dear Dr. Servid:

Please see the attached information for SPRAVATO® (esketamine), marketed by Janssen Pharmaceuticals, Inc., submitted on behalf of Stephanie Yamamoto, PharmD, BCPS, in preparation for the upcoming Oregon Pharmacy and Therapeutics (P&T) Committee Meeting on February 4, 2021.

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 #: 01932419

Oregon P&T Committee – February 2021

Submitted by Janssen Scientific Affairs, LLC on behalf of Stephanie Yamamoto, PharmD, BCPS, West Field Director, Major Markets/Institutional Business Group, 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: SPRAVATO 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.

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

New Clinical Data Publications (2020 – present)

Dold et al (2020)[7] conducted a meta-analysis to evaluate the efficacy of esketamine (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. The analysis included trials with an adult study population (age ≥18, no restriction in terms of gender, ethnicity, and comorbidities) with non-psychotic MDD and at least one failed treatment with antidepressants prior to randomization (N=25 trials).

- Meta-analysis outcome: Calculations for all outcomes were separately performed for the pooled SGA and pooled ESK add-on treatment group, in comparison with PBO 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.

Fu et al (2020)[8] 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 (LSM difference [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.

Ionescu et al (2020)[9] 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 double-blind 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 (TRANSFORM-3) 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,[10, 11] 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. There was also a clinically meaningful treatment difference, though not formally statistically tested, for improvement in the overall severity of depressive illness based on Clinical Global Impression–Severity (CGI-S) scores for ESK + AD over AD + PBO (median change from baseline to endpoint, -1.0 vs. 0). Patients in the ESK + AD arm were 5.3 times more likely than those in the AD + PBO arm to have an improved CGI-S score at the end of the DB phase.
- 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 Clinician-Administered Dissociative States (CADSS) score never exceeded 10 on any given dosing day.

Papakostas et al (2020)[12] 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, 13, 14]).

- 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)[15] conducted a systematic review of randomized DB, PBO-controlled studies to evaluate the effectiveness 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, 13, 14]).

- 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 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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Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

December 27, 2020

Oregon Drug Use Research and Management Program (DURM)
Drug Use Research & Management Program Oregon State University
500 Summer Street NE, E35
Salem, Oregon 97301-1079
Re: Duchenne Therapies

To Whom It May Concern,

On behalf of the Americans who live with the devastating diagnosis of Duchenne muscular dystrophy, we are writing today to urge you to support coverage for access to FDA approved therapies aimed at treating Duchenne muscular dystrophy, including EXONDYS 51, VYONDYS 53, VILTEPSO, and Emflaza. Patients should be afforded the right to start treatment following consultation and prescription from their medical provider. **PPMD believes that EXONDYS 51, VYONDYS 53, Emflaza, and VILTEPSO should never be restricted for access based on age, function, or stage of disease progression.** PPMD would like to thank the committee for your thoughtful engagement with the Duchenne community, we greatly appreciates your past coverage of EXONDYS 51, VYONDYS 53, Emflaza. **We believe VILTEPSO should fall under similar coverage rationale for patients who are amenable to this treatment**.

Parent Project Muscular Dystrophy (PPMD) is the nation's leading patient advocacy organization dedicated to ending Duchenne. As you may know, Duchenne muscular dystrophy is a universally fatal, genetic disorder that affects approximately 1 in 5,000 live male births. People with Duchenne face a relentless deterioration of muscle strength leading to loss of mobility followed by severe cardiac and respiratory compromise in early adulthood. There is no escape.

Notwithstanding rising investments in research and development following the 1986 discovery of the Duchenne gene and the protein it specifies, there had been no FDA approved therapy to treat the underlying cause of Duchenne prior to September 2016 when the FDA approved market authorization for EXONDYS 51[1]. Following that, the Duchenne community enthusiastically celebrated FDA approvals of Emflaza[2] (February 9, 2017), VYONDYS 53[3] (December 12, 2019) and more recently VILTEPSO[4] (August 2020). The fact that all dystrophin restoration therapies were advanced under the agency's accelerated approval pathway is a clear indication of the **high unmet medical need** in Duchenne.

Similar to EXONDYS 51[5] and VYONDYS 53[6], the FDA package label insert for VILTEPSO[7] provided no restriction on administrating this therapy based on age or disease progression. As with EXONDYS 51 and VYONDYS 53, we strongly recommend coverage for VILTEPSO for all patients who have a confirmed genetic mutation amenable to this therapy who have been issued a prescription by a treating physician. This would be in agreement with the Medicaid Drug Rebate Program Notice - For State Technical Contacts (Release No. 185)[8] which states "as with any other drug, if the drug is labeled by a manufacturer that has signed a Medicaid National Drug Rebate Agreement, and the drug meets the definition of covered outpatient drug, then the drug

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is covered by the Medicaid Drug Rebate Program (MDRP) and is to be covered by state Medicaid programs".

PPMD supports all therapy development in an independent and objective manner as our mission dictates. Our work has included an emphasis in recent years on patient-focused drug development strategies as the Duchenne therapy pipeline has become more robust. One of our efforts included a rigorous study[9] on community preferences where our team, supported by Dr. John Bridges of Johns Hopkins, found that caregivers are willing to accept risk and uncertainty when balanced with non-curative slowing or stopping of the progression of muscle weakness, even absent improvement in lifespan. Protection of muscle function, including muscle for pulmonary and cardiac function[10] are the highest priorities for patients. These preference findings are important both for regulatory review and for determining the value of a treatment for a health plan beneficiary.

We recommend you carefully consider all this information in evaluating coverage of all Duchenne therapies approved by FDA.

About Duchenne

Duchenne muscular dystrophy is a fatal genetic disorder caused by mutations in the dystrophin gene and characterized by the progressive loss of skeletal muscle and degeneration, primarily in boys. It affects one out of 5000 live male births in the US [11,12.] The primary symptoms of Duchenne muscular dystrophy are caused by a lack of dystrophin in the muscle. Children with Duchenne lose the ability to walk independently and most become reliant on wheelchairs for mobility by the age of 13[13]. Most individuals with Duchenne experience serious respiratory, orthopedic, and cardiac complications. By the age of 18, the majority of patients require ventilation support at night[14]. The average life expectancy is approximately 25 years of age, with respiratory complications and cardiomyopathy being common causes of death[14]. Dystrophin is located beneath the sarcolemma, and functions to connect the subsarcolemmal cytoskeleton to the sarcolemma. A loss of dystrophin in muscle results in inflammation, muscle degeneration and replacement of muscle with fibroadipose (fat and fibrotic) tissue[15].

EXONDYS 51, VYONDYS 53, and VILTEPSO

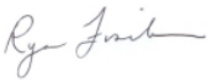
The data contained in the NDA submissions for **EXONDYS 51[16], VYONDYS 53[17], and VILTEPSO[18]** have met the standard for accelerated approval under 21 CFR 314.510 based on the surrogate endpoint of increased dystrophin protein production, with the FDA concluding that this surrogate is reasonably likely to predict clinical benefit. The goal of these therapies is to slow the progression of the disease, which can be monitored through regular outcome and functional testing. We believe the totality of evidence presented by all sponsors to the FDA provide enough reason to believe these therapies are likely to benefit the majority of amenable patients, and through their own health care providers the ability to assess the potential effect and exercise judgment based on the benefit-risk profile.

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

Given the high unmet medical need and identified preferences in the Duchenne community, PPMD strongly believes that the data supporting approvals of **EXONDYS 51, VYONDYS 53, and VILTEPSO** are sufficient to warrant coverage for all amendable patients as the post-approval studies are conducted to further confirm the clinical benefit in real world settings.

We thank you for your dedication to the wellbeing of patients and for all you do.

Sincerely,



Pat Furlong
President & CEO
Parent Project Muscular Dystrophy

Ryan Fischer
Chief Advocacy Officer
Parent Project Muscular Dystrophy

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[2] FDA approves drug to treat Duchenne muscular dystrophy (Emflaza) https://www.fda.gov/news-events/press-announcements/fda-approves-drug-treat-duchenne-muscular-dystrophy

[3] FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation (VYONDYS 53)https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation

[4] FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation (VILTEPSO) https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation

[5] EXONDYS 51 FDA Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf

[6] VYONDYS 53 FDA Label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211970s000lbl.pdf

[7] VILTEPSO FDA Label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212154s000lbl.pdf

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