SPRAVATO® (esketamine)
Oregon Pharmacy and Therapeutics (P&T) Committee Meeting - December 2023

Submitted by Janssen Scientific Affairs, LLC on behalf of Nirmal Ghuman, Principal Scientific Account Lead, Value & Evidence Scientific Engagement – Field

PRESCRIBING INFORMATION- UPDATED OCTOBER 2023 – RESPIRATORY DEPRESSION WARNING

- **BOXED WARNING: SEDATION; DISSOCIATION; RESPIRATORY DEPRESSION; ABUSE AND MISUSE; AND SUICIDAL THOUGHTS AND BEHAVIORS. See full prescribing information for complete boxed warnings and Risk Evaluation and Mitigation Strategy (REMS).**[1]
- Indications: 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: **1)** Treatment-resistant depression (TRD) in adults. In clinical trials, 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. **2)** Depressive symptoms in adults with MDD with acute suicidal ideation or behavior (MDSI).[1]
- 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 sedation, dissociation, respiratory depression, and abuse and misuse, 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.[1]

New Pertinent Information

Fu et al (2023) Post hoc analysis of pooled data from ASPIRE I and II[2]

A post hoc analysis of pooled data from two pivotal phase 3 trials, ASPIRE I and ASPIRE II, found that patients with MDSI achieved remission and consistent remission faster when treated with SPRAVATO + standard of care (SOC). The analysis, which included 451 patients, found that the median time to remission (defined as Montgomery-Åsberg Depression Rating Scale [MADRS] ≤12) was 15 days in the SPRAVATO + SOC group, versus 23 days in the placebo + SOC group (*P*=0.005). The median time to consistent remission (defined as MADRS ≤12 on 2 consecutive visits) was 23 days in the SPRAVATO + SOC group, compared with 50 days in the placebo + SOC group (*P*=0.007). A greater proportion of patients in the SPRAVATO + SOC group achieved remission and consistent remission by day 25 compared with the placebo + SOC group (65.2% vs 55.5% and 54.2% vs 39.8%, respectively). The median percent of days in remission during the double-blind treatment phase was also significantly longer in the SPRAVATO + SOC group vs placebo + SOC (27.1% or 5 days vs 8.3% or 2 days, respectively, *P*=0.006).

Canuso et al (2021) Post hoc analysis of pooled data from ASPIRE I and II[3]

Another post-hoc analysis of pooled data from ASPIRE I and II showed that patients receiving SPRAVATO + SOC showed significantly greater improvement in depression scores compared to those receiving placebo + SOC, as measured by MADRS. The least square mean difference in MADRS was -3.8 (95% CI -5.75 to -1.89) at 24 hours after first dose. The difference was also significant at 4 hours after first dose and day 25 time points. There was no significant difference between both groups in terms of reduction in suicidality scores. Common adverse events occurring in ≥20% of patients during SPRAVATO + SOC treatment included dizziness (38.3%), dissociation (33.9%), nausea (26.9%), somnolence (20.7%), and headache (20.3%).

Jamieson et al (2023) Patient reported outcomes from ASPIRE I and II[4]

Patient reported outcomes (PROs) from two pivotal phase 3 studies evaluating the efficacy and safety of SPRAVATO in patients with MDSI were collected. The change from baseline to the end of the double-blind treatment phase (day 25) in PROs are displayed in Table: Change in patient reported outcomes from baseline to Day 25. Additionally, the relative risk (95% CI) of reporting perceived problems in the European QoL Group-5-Dimension-5-Level (EQ-5D-5L) on day 25 was less in the SPRAVATO + SOC vs placebo + SOC in all 5 dimensions: mobility [0.78 (0.50, 1.20)], self-care [0.83 (0.55, 1.27)], usual activities [0.87 (0.72, 1.05)], pain/discomfort [0.85 (0.69, 1.04)], and anxiety/depression [0.90 (0.80, 1.00)].

Table: Change in patient reported outcomes from baseline to Day 25

Mean ± SD	SPRAVATO + SOC (n=226)	Placebo + SOC (n=225)
BHS total score*	-7.4 ± 6.7	-6.8 ± 6.5
QLDS score*	-14.4 ± 11.5	-12.2 ± 10.8
Health status index+	0.23 ± 0.21	0.19 ± 0.22
EQ-VAS+	24.0 ± 27.2	19.3 ± 24.4
TSQM-9 scores – effectiveness‡	67.2 ± 25.3	56.2 ± 26.8
TSQM-9 scores – global satisfaction‡	69.9 ± 25.2	56.3 ± 27.8
TSQM-9 scores – convenience‡	74.0 ± 19.4	75.4 ± 18.7

Abbreviations: BHS, Beck Hopelessness Scale; EQ-VAS, European Quality of Life Visual Analogue Scale; QLDS, Quality of Life in Depression Scale; SD, standard deviation; SOC, standard of care; TSQM-9, 9-item Treatment Satisfaction Questionnaire for Medication
*Negative change indicates improvement
+Positive change indicates improvement
‡TSQM scores presented were only recorded on day 25 (higher score indicates greater satisfaction)

Zhdanava et al (2023) Real-world economic analysis[5]

A study was conducted to analyze the real-world access, use, healthcare resource use (HRU), and costs of SPRAVATO among adults with MDSI. The study included patients who had at least one claim for SPRAVATO and evidence of MDSI 12 months before/on the date of SPRAVATO initiation (index date). A total of 269 patients had SPRAVATO pharmacy claims, 46.8% had the first pharmacy claim approved, 38.7% had it rejected, and 14.5% abandoned their claim. Of the 169 patients initiated on SPRAVATO, 45.0% had ≥8 SPRAVATO treatment sessions, and the mean [median] time from index to 8th session was 85.0 [58.5] days. HRU and healthcare costs were described over 6 months pre- and post-index among 115 patients who had at least 6 months post-index data, see Table: Healthcare Resource Use in the 6-month before and after SPRAVATO initiation. All-cause per patient per month total healthcare costs mean ± SD were $8,371 ± $15,792 pre-index and $6,486 ± $7,614 post-index.

Table: Healthcare Resource Use in the 6-month before and after SPRAVATO initiation (index date)[5]

	6-month pre-index	6-month post-index
≥1 all-cause hospitalization	37.4%	19.1%
≥1 all-cause ER visit	42.6%	33.9%
≥1 all-cause outpatient visit	92.2%	81.7%

Ochs-Ross et al (2021) SUSTAIN-2 Post-Hoc Analysis[6]
A post hoc analysis of a phase 3 trial compared the efficacy and safety of SPRAVATO in younger (18-64 years) vs older (≥65 years) patients with TRD. Initial doses were 28 mg (≥65 years) or 56 mg (<65 years). The average age in the younger group was 47.2 years and 69.7 years in the older group. Rate of remission and response at the end of the optimization/maintenance phase (week 12) was 56% and 81%, respectively, in younger patients (n=477) and 61% and 79%, respectively, in older patients (n=126). Mean change in MADRS score from baseline to endpoint at the end of the optimization/maintenance phase was similar in both groups (-19.9 [younger] and -22.2 [older], *P*=0.265). Treatment emergent adverse events (TEAEs) were similar between both groups. At the end of the optimization/maintenance phase, 86.8% of younger patients and 81.0% of older patients experienced at least one TEAE, and 6.7% of younger patients and 4.8% of older patients experienced at least one serious TEAE. The most common serious TEAEs during the induction phase in the younger group (depression, suicide attempt, anxiety, suicidal ideation, and gastroenteritis) and older group (depression and suicide attempt) occurred at a rate of <2%.
Reif et al (2023) ESCAPE-TRD[7]
ESCAPE-TRD was a randomized, open-label, rater-blinded phase 3b clinical trial comparing the efficacy and safety of SPRAVATO with quetiapine XR (QUE XR) (both flexibly dosed and in combination with an ongoing SSRI/SNRI) in adult patients (age 18- 74 years) with TRD. The treatment period consisted of an 8-week acute phase followed by a 24-week maintenance phase. Significantly more patients in the SPRAVATO-treated cohort achieved remission (MADRS ≤10 or less) at week 8 than in the QUE XR cohort, 27.1% vs 17.6%, respectively, *P*=0.003 (primary endpoint). Significantly more patients in the SPRAVATO-treated cohort had remission at week 8 and remained relapse free through week 32 than in the QUE XR cohort, 21.7% vs 14.1%, respectively (key secondary endpoint). Adverse events (AEs) were experienced by 91.9% and 78.0% of patients and those leading to treatment discontinuation occurred in 4.2% and 11.0% of patients in the SPRAVATO and QUE XR cohort, respectively.
Zaki et al (2023) SUSTAIN-3 Interim Results[8]
SUSTAIN-3 is a phase 3, open label, single-arm study evaluating the long-term safety and efficacy of flexibly dosed SPRAVATO with an oral AD in patients with TRD. Eligible patients from previous TRD trials including TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, SUSTAIN-2, and TRD-3006 (US only) were included. There were 122 patients (10.6%) who were ≥65 years included in the study. During the open label induction phase (first 4 weeks), patients self-administered SPRAVATO twice weekly under supervision. In the open label optimization/maintenance phase (variable duration), SPRAVATO was administered weekly, every other week, or every 4 weeks based on Clinical Global Impression- Severity Scale (CGI-S) and tolerability. These interim results were analyzed based on a data cutoff date of December 1, 2020. Mean (median) cumulative duration of maintenance SPRAVATO treatment was 31.5 (37.7) months.
The most frequently reported treatment emergent adverse effects (TEAEs; occurring in at least 20% of patients) during the induction phase (n=458) were dissociation (21.8%) and dizziness (20.5%). The most frequently reported TEAEs during the optimization/maintenance phase (n=1,110) were headache (33.2%), dizziness (30.8%), nausea (29.9%), dissociation (23.2%), nasopharyngitis (22.6%), and somnolence (22.2%). Overall, 17.9% of patients experienced a TEAE related to increased BP and 7.8% of patients experienced sedation. Most TEAEs (96.8%) were mild or moderate in severity and led to discontinuation in 5.8% of patients. Improvements in the MADRS total score were observed during the induction phase and decreases in MADRS total score were maintained through the optimization/maintenance (OP/MA) phase (mean [SD] change from baseline to induction phase endpoint, -12.8 [9.73]; to OP/MA phase endpoint, +1.1 [9.93]). During the induction phase, the percent of responders (at least 50% reduction in MADRS total score) increased over time from 15% (66/439) at day 8 to 50.6% (224/443) at day 28. The percent of responders was 49.2% (224/455) at the endpoint of the induction phase. Remission (MADRS total score ≤less than or equal to 12) was reported in 35.6% of patients at the induction phase endpoint and in 46.1% of patients at the OP/MA phase endpoint.

Conclusion

In summary,

- The USPI for SPRAVATO was updated to include an additional warning and revised monitoring recommendations for respiratory depression.[1]
- SPRAVATO has demonstrated efficacy and patient reported satisfaction in patients with MDSI enrolled in two phase 3 pivotal trials.[2] All-cause healthcare costs and healthcare resource use was lower in the period after SPRAVATO initiation than before in patients with MDSI in a real-world claims-based analysis.[5]
- In patients with TRD, SPRAVATO has shown superiority when compared to QUE XR in achieving remission[7] and maintained long-term safety and efficacy consistent with prior studies in a population with over 10% of patients ≥65 years of age.

For these reasons, please consider updating the PA criteria for SPRAVATO to allow coverage for patients with MDSI and patients older than 65 years of age to ensure providers can treat patients with SPRAVATO per USPI in the Medicaid channel. Please refer to the full USPI for complete information.

REFERENCES

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