

אוגוסט 2021

רוקח/ת יקר/ה,
רופא/ה יקר/ה,

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא ועלון לצרכן בעקבות תוספת התוויה ועדכונים
נוספים בתכשיר:

SPRAVATO®
Esketamine 28 mg
תרסיס לאף

התוויה טרם העדכון:

Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode

התוויה מאושרת עדכנית:

Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

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.

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

1. Therapeutic indications

Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

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.

See section 5.1 for a description of the populations studied.

4.2 Posology and method of administration

Posology

Treatment-resistant Major Depressive Disorder

The dose recommendations for Spravato for treatment-resistant Major Depressive Disorder are shown in Table 1 and Table 2 (adults ≥ 65 years)...

Table 1: Recommended dosing for Spravato in adults <65 years with treatment-resistant Major Depressive Disorder

...

Table 2: Recommended dosing for Spravato in adults ≥ 65 years with treatment-resistant Major Depressive Disorder

...

Acute short-term treatment of psychiatric emergency due to Major Depressive Disorder
The recommended dosage of Spravato for adult patients (<65 years) is 84 mg twice per week for 4 weeks. Dosage reduction to 56 mg should be made based on tolerability. After 4 weeks of treatment with Spravato, the oral antidepressant (AD) therapy should be continued, per clinical judgement.

In these patients, treatment with Spravato should be part of the comprehensive clinical care plan.

There is limited data on the use of esketamine in patients between 18 to 24 years.
A subgroup analysis of patients with or without at least one previous suicidal experience for the primary endpoint "Change from baseline (day 1, predose) to 24 hours after the first dose (day 2) in MARDS" of the pivotal studies, demonstrated no statistically significant efficacy for the group of patients without at least one previous suicidal experience (See section 5.1).

...

Missed treatment session(s)

Patients who have missed treatment session(s) during the first 4 weeks of treatment should continue with their current dosing schedule.

For patients with treatment-resistant Major Depressive Disorder who miss treatment session(s) during maintenance phase and have worsening of depression symptoms, per clinical judgement, consider returning to the previous dosing schedule (see Tables 1 and 2).

Special populations

Elderly (65 years of age and older)

In elderly patients the initial Spravato dose for treatment-resistant Major Depressive Disorder is 28 mg esketamine (day 1, starting dose, see Table 2 above) ...

Spravato has not been studied in elderly patients as acute short-term treatment of psychiatric emergency due to Major Depressive Disorder.

...

4.4 Special warnings and precautions for use

... The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated (see section 5.1). Use of Spravato does not preclude the need for hospitalisation if clinically warranted, even if patients experience improvement after an initial dose of Spravato.

...

4.8 Undesirable effects

...

System Organ Class	Adverse Drug Reaction		
	Frequency		
	Very common	Common	Uncommon
Psychiatric disorders	...	...confusional state...	psychomotor retardation, emotional distress, dysphoria
Nervous system disorders	...	... disturbance in attention	nystagmus, psychomotor hyperactivity
...	...	...	...
Respiratory, thoracic and mediastinal disorders	...	... throat irritation, oropharyngeal pain...	...
...	...	...	...
Skin and subcutaneous tissue disorders	...	...	cold sweat
...	...	...	...
General disorders and administration site conditions	...	...	gait disturbance
Investigations	blood pressure increased	...	...

5.1 Pharmacodynamic properties

...

Clinical efficacy and safety

...

The efficacy and safety of Spravato nasal spray was investigated in two Phase 3 clinical studies in adult patients (18 to 64 years) with moderate to severe MDD (MADRS total score >28) who had affirmative responses to Mini International Neuropsychiatric Interview (MINI) questions B3 ("Think [even momentarily] about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide [i.e., about killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?"). 456 adult patients were enrolled, of which 227 patients were exposed to Spravato.

...

Dosing frequency

Acute short-term treatment of psychiatric emergency due to Major Depressive Disorder

Spravato was investigated in two identical Phase 3 short-term (4-week) randomised, double-blind, multicentre, placebo-controlled studies, Aspire I (SUI3001) and Aspire II (SUI3002) in adult patients with moderate to severe MDD (MADRS total score >28) who had affirmative responses to MINI questions B3 (“Think [even momentarily] about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide [i.e., about killing yourself]?”) and B10 (“Intend to act on thoughts of killing yourself in the past 24 hours?”). In these studies, patients received treatment with Spravato 84 mg or placebo nasal spray twice-weekly for 4 weeks. All patients received comprehensive standard of care (SOC) treatment, including an initial inpatient hospitalisation and a newly initiated or optimised oral antidepressant (AD) therapy (AD monotherapy or AD plus augmentation) as determined by the investigator. In the physician’s opinion, acute psychiatric hospitalisation was clinically warranted due to the subject’s immediate risk of suicide. After the first dose, a one-time dose reduction to Spravato 56 mg was allowed for patients unable to tolerate the 84 mg dose.

The baseline demographic and disease characteristics of patients in SUI3001 and SUI3002 were similar between the Spravato plus SOC or placebo nasal spray plus SOC groups. The median patient age was 40 years (range 18 to 64 years), 61% were female; 73% Caucasian and 6% Black; and 63% of patients had at least one prior suicide attempt. Prior to entering the study, 92% of the patients were receiving antidepressant therapy. During the study, as part of standard of care treatment, 40% of patients received AD monotherapy, 54% of patients received AD plus augmentation regimen, and 6% received both AD monotherapy/AD plus augmentation regimen.

The primary efficacy measure was the reduction of symptoms of MDD as measured by the change from baseline MADRS total score at 24 hours after first dose (Day 2).

In SUI3001 and SUI3002, Spravato plus SOC demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus SOC (see Table 8).

Table 8: Primary Efficacy Results for Change from Baseline in MADRS Total Score at 24 Hours After First Dose (Studies SUI3001 and SUI3002) (ANCOVA BOCF*)					
Study No.	Treatment Group[‡]	Number of Patient	Mean Baseline Score	LS Mean Change from Baseline to 24 hr Post First Dose (SE)	LS Mean Difference (95% CI)[§]
Study 1 (SUI3001)	Spravato 84 mg + SOC	112	41.2 (5.87)	-15.7 (1.05)	-3.7 (-6.41; -0.92)¶
	Placebo nasal spray + SOC	112	41.0 (6.29)	-12.1 (1.03)	–
Study 2 (SUI3002)	Spravato 84 mg + SOC	114	39.5 (5.19)	-15.9 (1.02)	-3.9 (-6.65; -1.12)¶
	Placebo nasal spray + SOC	113	39.9 (5.76)	-12.0 (1.06)	–

Pooled Studies 1	Spravato 84 mg + SOC	226	40.3 (5.60)	-15.8 (0.73)	-3.8 (-5.69; -1.82)
	Placebo nasal spray + SOC	225	40.4 (6.04)	-12.1 (0.73)	—

SD=standard deviation; SE=standard error; LS Mean=least-squares mean; CI=confidence interval;
SOC=standard of care

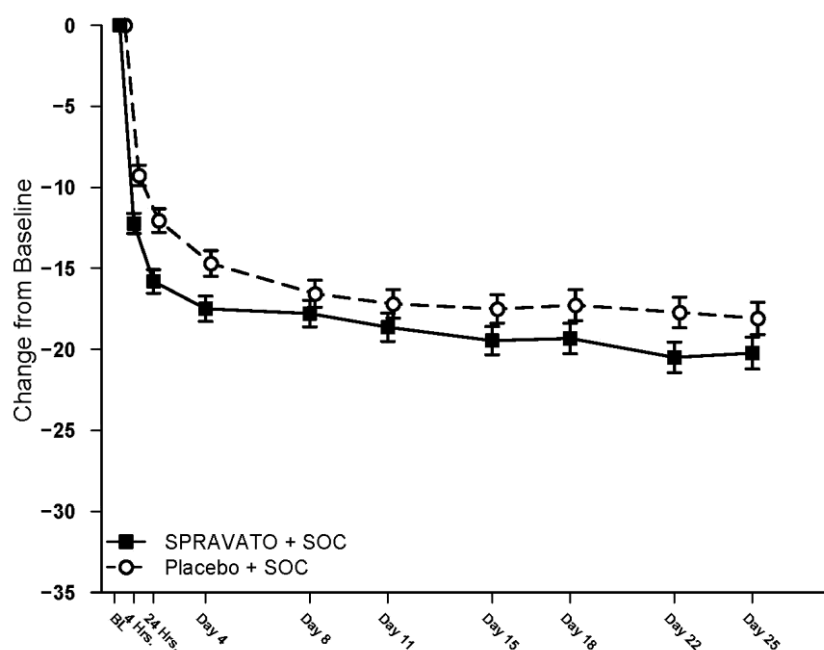
- * ANCOVA analysis using Baseline Observation Carried Forward: In SUI3001, 2 subjects (1 subject in each group) did not have the Day 2 (24 hours post first dose) MADRS total score and in SUI3002, 6 subjects (4 subjects in Esketamine and 2 subjects in Placebo) did not have the Day 2 (24 hours post first dose) MADRS total score. For these subjects, it is assumed that the depression level returns to the baseline level (i.e. the depression level is the same as the start of treatment) and the MADRS total scores from baseline were carried forward for the analysis
- ‡ Nasally administered esketamine or placebo
- § Difference (Spravato + SOC minus placebo nasal spray + SOC) in least-squares mean change from baseline
- ¶ Treatment groups that were statistically significantly superior to placebo nasal spray + SOC.

The treatment differences (95% CI) in change from baseline in MADRS total score at Day 2 (24 hours post first dose) between Spravato + SOC and placebo + SOC were -4.70 (-7.16; -2.24) for the subpopulation that reported a prior suicide attempt (N=284) and -2.34 (-5.59; 0.91) for the subpopulation that did not report a prior suicide attempt (N=166).

Time course of treatment response

In both SUI3001 and SUI3002, Spravato's treatment difference compared to placebo was observed starting at 4 hours. Between 4 hours and Day 25, the end of the treatment phase, both the Spravato and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 25. Figure 3 depicts time course of the primary efficacy measure of change in MADRS total score using pooled studies SUI3001 and SUI3002.

Figure 3: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in SUI3001 and SUI3002* (Pooled Data, Safety Analysis Set) – ANCOVA BOCF



- * Note: In these studies, after the first dose, a one-time dose reduction to Spravato 56 mg was allowed for patients unable to tolerate the 84 mg dose. Approximately 16% of patients had reduction in Spravato dosage from 84 mg to 56 mg twice weekly.

Remission rates

In the Phase 3 studies, the percentage of patients who achieved remission (MADRS total score ≤ 12 at any given time during the study) was greater in the Spravato + SOC group than in the placebo + SOC group at all timepoints during the 4-week double-blind treatment phase (Table 9).

Table 9: Patients Who Achieved Remission of MDD; Double-blind Treatment Phase; Full Efficacy Analysis Set						
	SUI3001		SUI3002		Pooled Studies (SUI3001 and SUI3002)	
	Placebo n (%)	Spravato n (%)	Placebo n (%)	Spravato n (%)	Placebo n (%)	Spravato n (%)
Day 1, 4 hours post first dose Patients	9 (8.0%)	12	4 (3.5%)	12	13	24
Day 2, 24 hours post first dose Patients	10	21	12	25	22	46
Day 25 (predose) Patients with MADRS ≤ 12	38	46	31	49	69	95
Day 25 (4 hours postdose) Patients	42	60	42	54	84	114

SOC = standard of care

Note: Remission is based on a MADRS total score of ≤ 12 . Subjects who did not meet such criterion or discontinued prior to the time point for any reason are not considered to be in remission.

Effects on suicidality

Overall patients in both treatment groups experienced improvement in the severity of their suicidality as measured by the Clinical Global Impression – Severity of Suicidality - revised (CGI-SS-r) scale at the 24-hour endpoint, though there was no statistically significant difference between treatment groups.

The long-term efficacy of Spravato to prevent suicide has not been established.

השינויים המהותיים בעלון לצרכן מופיעים בסעיפים הבאים:

1. למה מיועדת התרופה?

ספראבטו, בשילוב עם נוגדי דיכאון ממשפחת SSRI או SNRI, מיועדת לטיפול במחלת דיכאון מג'ורי, במטופלים מבוגרים אשר לא

הגיבו לפחות ל-2 סוגי טיפול עם נוגדי דיכאון באפידודת הדיכאון הנוכחית, שדרגת הבינונית עד חמורה.

ספראבטו משמשת גם לטיפול במבוגרים, להפחתת מהירות הסמיני דיכאון, במצבים הדורשים התערבות מיידי (ידוע גם כמצב חירום פסיכיאטרי).

הגבלת שימוש - היעילות של ספראבטו במניעת אובדנות או הפחתת מחשבות אובדניות או התנהגות

אובדנית לא הוכחה.
השימוש בספראבטו אינו מונע את הצורך באשפוז במידה ונדרש קלינית, גם אם המטופל חווה שיפור לאחר תחילת מתן התרופה.

3. כיצד תשתמש בתרופה?

ספראבטו ניתנת פעמיים בשבוע, למשך 4 השבועות הראשונים לטיפול. **במידה והטיפול שלך ממשיך:**
● ספראבטו לרוב ניתנת פעם בשבוע **למשך 4 שבועות.**

4. תופעות לוואי

תופעות לוואי שכיחות מאוד (מופיעות ביותר ממשתמש 1 מתוך 10)

● **עלייה בלחץ דם**

תופעות לוואי שכיחות (מופיעות ב-10-1 משתמשים מתוך 100)

● **תחושת בלבול**

● **קשיי ריכוז**

● **גירוי בגרון**

● **כאב גרון**

● **תחושת חולשה**

● **בכי**

תופעות לוואי שאינן שכיחות (מופיעות ב-10-1 משתמשים מתוך 1,000)

● **האטה במחשבה, בדיבור והאטה בתנועות גוף.**

● **מצוקה רגשית.**

● **תחושת מתיחות וחוסר נוחות**

● **תנועות עיניים מהירות שאינן משלטות**

● **פעילות יתר (היפראקטיביות)**

● **ריור מוגבר**

● **זיעה קרה**

● **הפרעות הליכה.**

העלון לרופא והעלון לצרכן המעודכנים מצורפים בזאת.
העלון לרופא והעלון לצרכן משלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות.

כמו כן, ניתן לקבלם מודפסים בפניה אלינו לטלפון 09-9591111.

בברכה,
אלינה ורמן, רוקחת ממונה