Date: 20 October 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Spravato

International non-proprietary name: esketamine as esketamine hydrochloride

Pharmaceutical form: nasal spray, solution

Dosage strength: 28 mg/0.2 mL

Route(s) of administration: nasal

Marketing Authorisation Holder: Janssen-Cilag AG

Marketing Authorisation No.: 67103

Decision and Decision date: extension of therapeutic indication approved on 27 August 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CADSS	Clinician-administered dissociative states scale
CGI-SS-R	Clinical global impression – severity of suicidality - revised
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DSM-5	Diagnostic and statistical manual of mental disorders, 5th edition
ER	Exposure-response
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MADRS	Montgomery-Asberg depression rating scale
MAH	Marketing Authorisation Holder
Max	Maximum
MDD	Major depressive disorder
MDSI	Patients with major depressive disorder assessed to be at imminent risk of suicide
Min	Minimum
M.I.N.I.	Mini-International neuropsychiatric interview
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SOC	Standard of care
SwissPAR	Swiss Public Assessment Report
TEAEs	Treatment emergent adverse events
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
TRD	Treatment-resistant depression

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested to add or change the indication in accordance with Article 23 TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

Spravato is indicated, in conjunction with oral antidepressant therapy, for the rapid reduction of depressive symptoms in adult patients with severe Major Depressive Disorder for whom urgent symptom control is necessary.

2.2.2 Approved Indication

Spravato in combination with an oral antidepressant therapy is indicated as acute short-term treatment for the rapid reduction of depressive symptoms in adult patients with a severe episode of major depression (without psychotic symptoms) when the symptoms are classified as a psychiatric emergency according to clinical evaluation.

2.2.3 Requested Dosage

The recommended dosage for Spravato for patients with severe Major Depressive Disorder for whom urgent symptom control is necessary is 84 mg twice a week for 4 weeks. A dosage reduction to 56 mg should be made depending on tolerability. After a 4-week treatment with Spravato, oral antidepressant therapy should be continued according to clinical judgement.
Patients who also have treatment-resistant depression (TRD) should be evaluated to determine whether further treatment with Spravato beyond 4 weeks is necessary.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	3 July 2020
Formal control completed	8 July 2020
List of Questions (LoQ)	13 October 2020
Answers to LoQ	18 January 2021
Predecision	26 March 2021
Answers to Predecision	24 May 2021
Labelling corrections	29 June 2021
Answers to Labelling corrections:	23 July 2021
Final Decision	27 August 2021
Decision	approval

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3 Medical Context

Major depressive disorder (MDD) is one of the leading causes of disability worldwide, affecting about 300 million individuals globally, including 40 million patients in Europe (WHO 2017). Patients with MDD and suicidal ideation usually have more severe depressive symptoms, as well as greater psychiatric comorbidity, poor social support, worse functioning and quality of life, and more prior suicide attempts, compared to MDD patients without suicidal ideation. The risk of suicide is around 30 times higher in depressed patients than in the general population. Around 9% of all patients who have been hospitalised for suicidality and 4% of all patients who have been hospitalised for a depressive disorder (without distinct suicidality) eventually die as a result of suicide. In Germany, every year around 10,000 people commit suicide, while in Switzerland, around 1000 persons die due to suicide per year (rates of around 13/100,000 population). In around 90% of suicide cases, a mental disorder is present, with depressive disorders (MDD and bipolar disorder) being the most common psychological causes of suicides.
While many studies for pharmacological treatments in MDD or bipolar disorder have been conducted, patients with acute suicidality have been typically excluded from such studies in the past, and no pharmacological products for treatment of acute or long-term suicidality are authorised. Since, for currently approved antidepressants the onset of antidepressant effects is delayed, there is a high need for rapidly effective treatments, reducing or even interrupting MDD symptoms in general as well as suicidal symptoms specifically. Once patients restore their perspectives and initiative, their motivation and ability to engage in psychotherapy and/or other psychosomatic interventions is expected to increase.

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4 Nonclinical Aspects

No new nonclinical data were provided to support the applied extension of the indication. This was accepted since there are no major changes in the recommended dosage and there is sufficient clinical experience/data.
The requested indication was already considered in the original ERA submitted for the new active substance application; a risk for the environment by the prescribed use of Spravato is not expected.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

Pharmacokinetics
There were no clinically relevant pharmacokinetic differences between treatment-resistant depression (TRD) and patients with major depressive disorder assessed to be at imminent risk of suicide (MDSI).

Pharmacodynamics
Exposure–Response Relationships for Efficacy
There was a linear relationship between esketamine AUCinf and ΔMADRS (Montgomery-Asberg Depression Rating Scale). The only factor with a statistically significant impact on this exposure-response (ER) relationship was the baseline MADRS score. The data also indicated that the drug effect might be higher in subjects with a prior suicidal attempt. In fact, it seemed that the drug effect was mainly driven by these subjects. The overall ΔMADRS was lower in subjects with a prior suicidal attempt compared to subjects without such an attempt.

There was no statistically significant relationship between esketamine exposure and **CGI-SS-R** (Clinical Global Impression – Severity of Suicidality – Revised) score. Descriptive analyses of the data indicated overlapping effects for esketamine and placebo, but numerically higher values for esketamine. Corresponding to the results for ΔMADRS, subjects who had a previous suicide attempt showed a lower placebo + standard of care (SOC) response compared to those who had no previous suicide attempt.

However, for subjects who had a previous suicide attempt, the proportion of subjects who achieved a CGI-SS-R score <2 was consistently higher in the esketamine + SOC treatment group, which was not the case for subjects without a previous suicide attempt.

Exposure–Response Relationships for Safety
The relationship between esketamine exposure and blood pressure was similar in TRD and MDSI patients, while the probability of experiencing a clinician-administered dissociative states scale (CADSS) score > 4 at 40 minutes postdose occasionally appeared to be higher in the latter population.

5.2 Efficacy

Efficacy in patients with major depressive disorder and acute suicidal ideation or behaviour was investigated in two identically designed studies, SUI3001 and SUI3002.

Study SUI3001
SUI3001 was a double-blind, randomised, placebo-controlled, multicentre study performed from June 2017 to December 2018 (North America, Europe, Asia) to evaluate the efficacy, safety, and tolerability of esketamine nasal spray 84 mg compared with placebo nasal spray in the treatment of subjects with major depressive disorder, and judged to be at imminent risk for suicide. Eligible patients were dosed twice weekly for 4 weeks and afterwards followed up without intranasal medication (but with standard of care, SOC) until day 90. Subjects were treated in the context of SOC, consisting of initial inpatient psychiatric hospitalisation for a recommended 5 days, initiation and optimisation of antidepressant therapy, concomitant medications, psychotherapy, and twice-weekly study visits with clinical contact. After the first dose, a one-time dose reduction to esketamine 56 mg was allowed if a subject was unable to tolerate the 84 mg. Patients were included if they were 18-64 years of age, met DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) diagnostic criteria for MDD (of at least moderate severity), had current suicidal ideation (confirmed by certain responses in the Mini-International Neuropsychiatric Interview (M.I.N.I.)); if acute psychiatric hospitalisation was clinically warranted due to a subject's imminent risk of suicide, subjects agreed to a recommended 5-day

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inpatient stay and had a MADRS total score of >28 predose on day 1. Adequate rater training documentation was available for both pivotal studies.
The mean age was 39 years, and the majority of subjects were female (62%). The majority of subjects (67%) were White, 25% were Asian, and 5% were Black or African American. For 51% of patients the enrolment region was in Europe, for 25% in North America and for 24% in Asia. Prior to entering the study, 92% of the patients had received antidepressant therapy (including antidepressants, mood stabilisers, atypical antipsychotics and typical antipsychotics). The mean baseline MADRS total score was 41 overall, ranging from 29 to 58, which corresponds to depression of moderate to very high severity. The median duration of the current depressive episode was 14 months. The majority of subjects (90%) were rated by the clinician to be moderately to extremely suicidal, as measured by the CGI-SS-R scale. All subjects (100%) responded “Yes” to the M.I.N.I. Questions B3 and B10 within 24 hours prior to randomisation (confirming active suicidal ideation and intent). The majority of subjects (60%) reported any prior suicide attempt, and 28% reported a suicide attempt within the last month. Most demographics, depression characteristics and psychiatric history were similar across treatment groups. At randomisation, 55% of subjects were to receive antidepressant monotherapy as SOC treatment, and 45% of subjects were to receive antidepressant plus augmentation therapy.

Efficacy results in study SUI3001:
A statistically significant effect was shown, with a -3.8 point difference vs. placebo vs. baseline in the primary endpoint MADRS score at 24h, which is a quite rapid and clinically relevant effect on the MADRS scale.
The decrease from 41 points on the MADRS at baseline to around 28 in the placebo group and 25 under esketamine also shows a very high placebo response (probably due to the comprehensive standard of care treatment). Differences in the MADRS score vs. placebo predose on the following drug administration days (day 4, 8, 11, 15, 18, 22, 25) ranged between -1.5 and -4.6 in favour of the esketamine group.
For the key secondary endpoint of CGI-SS-R score, a positive trend for esketamine was documented in several subgroups, but without a statistically significant difference. Several other secondary endpoints, mainly associated with suicidality symptoms (e.g. SIBAT (suicide ideation and behaviour assessment tool), which was newly developed for these studies), were assessed in an exploratory way, and showed some differences in favour of esketamine, but were not evaluated statistically.
Responder analyses in MADRS showed differences of 5-15% between treatment groups. Higher efficacy was noted in male (vs. female) patients, in patients from North America (vs. Europe or Asia), in patients with higher than median MADRS score at baseline (vs. lower than median MADRS score), and in patients with prior suicide attempt (vs. no prior attempt).)

Study SUI3002
The study design was identical to SUI3001.
The mean age was 41 years, and the majority of subjects were female (60%). The majority of subjects (78%) were White, 13% were Asian, and 7% were Black or African American. For 48% of the included patients, the enrolment region was in Europe, for 29% in North America and for 23% in South America. The mean baseline MADRS total score was 40 overall, ranging from 29 to 54. The median duration of the current depressive episode was 17 months. The majority of subjects (92%) were rated by the clinician to be moderately to extremely suicidal, as measured by the CGI-SS-R scale. The majority of subjects (66%) reported any prior suicide attempt, and 26% reported a suicide attempt within the last month. Most demographics, depression characteristics and psychiatric history were similar across treatment groups. A higher proportion of subjects in the esketamine + SOC group had a recent suicide attempt compared to the placebo + SOC group (30% versus 24%).

Efficacy results in study SUI3002:
The results for the primary endpoint were quite similar to the ones from study 3001, with a -3.9 point difference vs. placebo vs. baseline in the MADRS total score at 24h (decrease from 40 points on MADRS at baseline to around 28 points in the placebo group and 24 points under esketamine). These

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results also show a high placebo response, which could be due to the comprehensive standard of care measures. Differences on MADRS vs. placebo predose on the following drug administration days (day 4, 8, 11, 15, 18, 22, 25) ranged between -1.2 and -3.7 in favour of the esketamine group. For the key secondary endpoint of CGI-SS-R score, a positive trend for esketamine was documented in several subgroups, but without a statistically significant difference. Several other secondary endpoints mainly in association with suicidality symptoms were assessed in an exploratory way, and showed some differences in favour of esketamine, but were not evaluated statistically, and overall these differences were smaller compared to the differences in study 3001.

For further details, please see the “Properties/effects” and “Clinical efficacy” sections of the information for healthcare professionals.

5.3 Safety

A total of 262 subjects with major depressive disorder with imminent risk for suicide (MDSI) received at least one dose of esketamine in the three completed phase 2 and 3 studies, resulting in a combined cumulative exposure to esketamine of 15.8 patient years (13.8 patient-years in the phase 3 studies). The combined cumulative exposure to placebo nasal spray was 15.7 patient-years based on 256 subjects who received at least one dose. During the double-blind treatment phase of the pooled Phase 3 studies, 227 subjects in the esketamine + SOC group received at least one esketamine dose of 84 mg, and 45 subjects (19.8%) received at least one esketamine dose of 56 mg or less because of a protocol-permitted one-time reduction to 56 mg for tolerability reasons or due to an administration/device error.
The most frequent treatment emergent adverse events (TEAEs) in patients treated with esketamine with clear differences in frequency vs. placebo were dizziness (38% vs. 14%), dissociation (34% vs. 6%), sedation (10% vs. 2%), somnolence (21% vs. 10%), nausea (27% vs. 14%), dysgeusia (20% vs. 13%), blurred vision (12% vs. 5%), oral paraesthesia (7% vs. 1%) and increased blood pressure (12% vs. 5%). The TEAEs that are closely related to esketamine administration, such as dissociative symptoms, sedation and blood pressure increases, typically started shortly after dosing, peaked by 40 minutes postdose and mostly resolved by 1.5 to 2 hours. Based on the rather small data set from the studies in patients with imminent risk of suicide, the safety profile appears similar to the known profile from the TRD studies.

For further details, please see the “Undesirable effects” and the “Warnings and precautions” sections of the information for healthcare professionals.

5.4 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Patients with MDD and acute suicidal symptoms are very difficult to treat, with a lower response to conventional antidepressants and a higher risk for unfavourable outcomes, including suicide. To date, Spravato is indicated for patients with treatment-resistant depression. The currently requested extension of indication aims at treating patients “with severe major depression who require urgent symptom control.”
The two pivotal clinical studies for this application were performed in patients with “moderate to severe major depression with imminent risk of suicide”, comparing 84 mg intranasal esketamine + standard of care vs. placebo + standard of care. Statistically significant differences of almost -4 points in favour of the esketamine 84 mg + SOC groups were documented for the primary endpoint, change in MADRS total score at 24h postdose vs. baseline. At other timepoints during the 4-week double-blind treatment phase with study treatment twice weekly, differences of around 2-3 points in total MADRS score were noted. Such effect sizes are usually considered as clinically relevant. Even higher effects were shown in patients with a high baseline MADRS score (≥35) and in patients with prior suicide attempts (post-hoc analyses), whereas no significant effect vs. placebo was documented in patients with a MADRS score <35 (moderate severity). MADRS single-item analyses showed that esketamine is effective on a broad spectrum of depressive symptoms, such as reported sadness,

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apparent sadness, inner tension, concentration difficulties, inability to feel, pessimistic thoughts. However, no statistically significant results were demonstrated for the key secondary endpoint of CGI-SS-R score assessing suicidal symptoms.
Regarding safety and tolerability, the already known profile of side effects with sedation, dissociation, nausea, blood pressure increase was also documented in this subpopulation of suicidal patients, and confirms the necessary measures for safe administration. Based on small numbers, and also on imbalanced baseline risks, intentional self injury TEAEs were noted with higher frequency under esketamine compared to placebo.
Overall, esketamine's rapid effect on depressive symptoms in highly depressed patients offer a new treatment option, even without specifically reducing suicidality symptoms. However, a broad indication for treatment of patients with moderate to severe depression is not considered adequate due to the inherent risks and side effects of the treatment, and also due to the restricted study population. A positive benefit-risk ratio can be established only with a clearly limited and tailored indication to address the right target population. Without effects shown on suicidality, the indication wording should not be aimed at patients with "suicidal ideation or behaviour", but focus on psychiatric emergency situations in patients with a severe depressive episode, without psychotic symptoms.

5.5 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Spravato was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the *Undesirable effects* section for advice on the reporting of adverse reactions.

Spravato®

Composition

Active substances

Esketamine (as esketamine hydrochloride).

Excipients

Citric acid monohydrate (E330), sodium edetate, sodium hydroxide, water for injection.

Pharmaceutical form and active substance quantity per unit

Nasal spray for single use containing 28 mg esketamine (as esketamine hydrochloride) in two sprays. Clear, colorless, aqueous solution.

Indications/Uses

Spravato in combination with an oral antidepressant is indicated for the treatment of treatment-resistant episodes of major depression in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.
Spravato in combination with an oral antidepressant therapy is indicated as acute short-term treatment for the rapid reduction of depressive symptoms in adult patients with a severe episode of major depression (without psychotic symptoms) when the symptoms are classified as a psychiatric emergency according to clinical evaluation.
Spravato must only be administered in a treatment setting in which the necessary safety measures (including cardiopulmonary resuscitation measures) can be ensured before, during and after administration of the medicinal product (see *Dosage/Administration* and *Warnings and precautions*).

Dosage/Administration

The decision to prescribe Spravato should be determined by a psychiatrist. Spravato must be administered concomitantly with a therapy of an oral antidepressant (AD). Spravato is intended to be self-administered by the patient under the direct supervision of a physician.

Spravato must be administered in a treatment setting in which the appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation measures are available. In particular, this includes measures for active ventilation and management of blood pressure crises.
A treatment session consists of nasal administration of Spravato and an at least two hours post-administration observation period.

Important instructions before and after treatment

Blood pressure assessment before and after treatment

Assess blood pressure prior to dosing with Spravato (see *Warnings and precautions*).
If baseline blood pressure is elevated (>140 mmHg systolic, >90 mmHg diastolic), consider the risks of increases in blood pressure and benefit of Spravato treatment (see *Warnings and precautions*) and use should be postponed, as required. Do not administer Spravato if an increase in blood pressure or intracranial pressure poses a serious risk (see *Contraindications*).
After dosing with Spravato, reassess blood pressure at approximately 40 minutes and subsequently as clinically warranted. If necessary, monitoring of the patient should be continued beyond the 2-hour observation period (see *Warnings and precautions*).
If blood pressure is decreasing and the patient appears clinically stable, the patient may leave at the end of the post-dose monitoring period; if not, continue to monitor (see *Warnings and precautions*).

Food and drink intake prior to use of Spravato

After administration of Spravato, nausea and vomiting may occur. Patients should be advised not to eat for at least 2 hours before administration and not to drink liquids at least 30 minutes prior to administration.

Nasal corticoid treatment and nasal decongestants

Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should be advised not to use these medications within 1 hour before administration of Spravato. For instructions to prepare the patient and for use of the nasal spray device, see Instructions for Use.

Usual dosage

Spravato is to be used in combination with an oral antidepressant.

Adults

Treatment-resistant depression (TRD)
The dosage recommendations for Spravato for TRD are shown in Table 1. Dose adjustments should be made based on efficacy and tolerability to the previous dose.

Table 1: Recommended Dosing for Spravato for TRD

Induction Phase	Maintenance Phase
Weeks 1-4 (two treatment sessions/week): Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg	*Weeks 5-8:* 56 mg or 84 mg once weekly *From Week 9:* 56 mg or 84 mg every 2 weeks or once weekly **
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.	Periodically reexamine the need for continued treatment.

* For patients ≥65 years Day 1 starting dose is 28 mg (see *Special dosage instructions*)

** Dosing frequency should be individualized to the lowest frequency to maintain remission/response.

Acute short-term treatment of a psychiatric emergency in the context of major depression

The recommended dosage for Spravato is 84 mg twice per week for 4 weeks. Dosage reduction to 56 mg should be made based on tolerability. Therapeutic benefit should be assessed at the end of 4 weeks of treatment to determine the need for continued treatment.

Treatment beyond 4 weeks was not investigated in controlled trials in this indication.

Patients who also have TRD should be evaluated to determine need for continued treatment with Spravato beyond 4 weeks.

Mode of administration

Spravato is for nasal use only. The nasal spray is intended for single-use and delivers a total of 28 mg of esketamine in two sprays (one spray per nostril). To prevent loss of medication, the nasal spray should not be primed before use. It is intended for self-administration by the patient under the direct supervision of a physician, using 1 nasal spray (for a 28 mg dose), 2 nasal sprays (for a 56 mg dose) or 3 nasal sprays (for an 84 mg dose), with a 5-minute rest between use of each nasal spray.

Post-administration observation

After dosing with Spravato, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted (see *Warnings and precautions*).

Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored for at least 2 hours under the supervision of a physician until the patient is considered clinically stable and ready to leave the healthcare setting (see *Warnings and precautions*).

Missed treatment session(s)

If a patient misses treatment session(s) during the first 4 weeks of treatment, patients should continue their current dosing schedule.

For patients with TRD 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 Table 1).

Special dosage instructions

Patients with impaired hepatic function

No dosage adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. In patients with moderate hepatic impairment, extended monitoring time following administration of Spravato may be required (see *Pharmacokinetics – Kinetics in specific patient groups, Hepatic impairment*).
Spravato has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended (see *Pharmacokinetics – Kinetics in specific patient groups, Hepatic impairment*).

Patients with impaired renal function

No dose adjustment is necessary in patients with mild to severe renal impairment. Patients on dialysis were not studied.

Elderly patients

Treatment-resistant depression (TRD)
In patients 65 years of age and older the initial Spravato dose is 28 mg (Day 1, Starting Dose, see Table 1). Subsequent doses should be increased in increments of 28 mg up to 56 mg or 84 mg, based on efficacy and tolerability.
Acute short-term treatment of a psychiatric emergency in the context of major depression
No data are available for this indication in patients aged 65 years and older.

Children and adolescents

Spravato is not indicated for use in patients under 18 years of age. The safety and efficacy of Spravato have not been established in patients aged 17 years and younger.

Contraindications

Spravato is contraindicated in:

- Patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see *Warnings and precautions – Effect on blood pressure*):
    - Patients with known aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels)
    - Patients with known history of intracerebral hemorrhage
    - Patients who have had a recent (within the past 6 weeks) cardiovascular event, including myocardial infarction (MI)

- Patients with a known hypersensitivity to esketamine, ketamine, or to any of the excipients.

Warnings and precautions

Suicide/suicidal thoughts or clinical worsening

The efficacy of Spravato in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated.
Use of Spravato for the acute short-term treatment of a psychiatric emergency in the context of major depression does not preclude the need for hospitalization, if clinically warranted, even if patients experience improvement after an initial dose of Spravato.
Closely monitor all antidepressant-treated patients including patients treated with Spravato for clinical worsening or emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). This increased risk persists until significant remission occurs, therefore, patients should be closely monitored. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.
In the pooled pivotal studies of adult patients with a major depressive disorder (MDD) having active suicidal ideation with intent, intentional self-injury (confirmed not to be suicide attempt) occurred in 3.1% of patients in the Spravato plus standard of care (SOC) group and in 1.3% of patients in the placebo plus SOC group during the double-blind treatment phase. During the follow-up phase while patients were receiving only SOC, suicide attempts were observed in 3.7% and 1.6% of patients who were treated previously with Spravato and placebo, respectively.
A meta-analysis of placebo-controlled clinical trials of oral antidepressants in adults with psychiatric disorders revealed an increased risk of suicidal behavior in comparison with placebo in patients under 25 years who were taking antidepressants.
Consider changing the therapeutic regimen, including possibly discontinuing Spravato and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Respiratory depression

No case of respiratory depression was observed in clinical trials with esketamine nasal spray (Spravato); rare cases of deep sedation have been reported. Respiratory depression may occur at high

doses following rapid intravenous injection of esketamine or ketamine, when used for anesthesia. Concomitant use of Spravato with central nervous system depressants may increase the risk for sedation (see *Interactions*). Close monitoring of patient is required for sedation and respiratory depression.

Effect on blood pressure

Spravato can cause transient increases in systolic and/or diastolic blood pressure, which peak at approximately 40 minutes after drug administration and last approximately 1-2 hours (see *Undesirable effects*). A substantial increase in blood pressure could occur after any treatment session. Spravato is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see *Contraindications*). Before prescribing Spravato, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of Spravato outweigh its risks.

In patients whose blood pressures prior to dose administration of Spravato is judged to be elevated (as a general guide: >140/90 mmHg for patients <65 years of age and >150/90 mmHg for patients ≥65 years of age), it is appropriate to consider a change in lifestyle and/or pharmacologic therapies to reduce blood pressure before starting treatment with Spravato. The decision whether or not to delay Spravato therapy should take into account the balance of benefit and risk in individual patients.

Blood pressure should be monitored after dose administration until blood pressure returns to starting values prior to Spravato administration. If blood pressure remains elevated, the requirement for blood pressure treatment should be urgently reviewed and if appropriate, the necessary steps should be initiated immediately, if necessary.

In the clinical marketing authorisation studies, 8% to 17% of patients treated with Spravato experienced an elevation in systolic blood pressure of >40 mmHg and in diastolic blood pressure of >25 mmHg in comparison to 1% to 3% under placebo.

In patients ≥65 years of age, an elevated incidence of acute blood pressure elevation (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg) was demonstrated in comparison to patients under 65 years of age (see *Warnings and precautions - patients ≥65 years of age*). For patients with symptoms of a hypertensive crisis, emergency treatment should be initiated immediately.

Close monitoring of blood pressure is required in patients who are being treated with psychostimulants or monoamine oxidase inhibitors (MAOIs) (see *Interactions*).

Patients with clinically significant or unstable cardiovascular or respiratory conditions

Only initiate treatment with Spravato in patients with clinically significant or unstable cardiovascular or respiratory conditions if the benefit outweighs the risk. Examples of conditions which should be considered include, but are not limited to:

- Significant pulmonary insufficiency, including COPD;
- Sleep apnea with morbid obesity (BMI ≥35);

- Patients with uncontrolled brady- or tachyarrhythmias that lead to hemodynamic instability;
- Patients with a history of a MI. These patients should be clinically stable and cardiac symptom free prior to administration;
- Hemodynamically significant valvular heart disease or heart failure (NYHA Class III-IV).

Dissociation

The most common psychological effects of Spravato were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (see *Undesirable effects*). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering Spravato; treatment should be initiated only if the benefit outweighs the risk.
Because of the risks of dissociation, patients must be monitored for at least 2 hours under the supervision of a physician at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the practice or clinic.

Sedation

Because of the possibility of delayed or prolonged sedation, patients must be monitored for at least 2 hours under the supervision of a physician at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the practice or clinic.
Closely monitor for sedation with concomitant use of Spravato and central nervous system depressants (see *Interactions*).

Cognitive and motor impairment

Spravato has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety during the clinical trials (see *Undesirable effects*). These effects may impair attention, judgment, thinking, reaction speed and motor skills. At each treatment session, patients should be monitored under the supervision of a physician to assess when the patient is considered clinically stable (see *Dosage/Administration - Post-administration observation*).
Long-term cognitive and memory impairment have been reported with long-term ketamine use or drug abuse. These effects did not increase over time and were reversible after discontinuing ketamine. In the clinical trials, the effect of esketamine nasal spray on cognitive functioning was evaluated over time; the cognitive performance remained stable at the end of the study in comparison to the start of the study.

Patients ≥65 years of age

Experience with safety and efficacy of Spravato in patients ≥65 years of age is limited and Spravato must be used with caution in these patients, particularly in the presence of cardiovascular co-morbidities (see *Clinical trials*, *Undesirable effects*).
In the marketing authorisation studies, 194 (12%) patients ≥65 years of age were treated with Spravato. In a 4-week double-blind study, the efficacy and safety of Spravato in combination with an oral AD

(n=72) was compared with intranasally applied placebo in combination with an oral AD (n=66). During the study, 11.1% of patients treated with Spravato experienced an acute elevation in blood pressure (systolic ≥180 mmHg or diastolic ≥110 mmHg) in comparison to 6.2% in the control group. A statistically significant difference was not exhibited in the primary efficacy endpoint (see *Properties/Effects - Clinical efficacy* and *Warnings and precautions - Effect on blood pressure*).

Effect on Driving

Two studies were conducted to assess the effects of Spravato on the ability to drive (see *Pharmacodynamics – Effects on Driving*). Before Spravato administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep (see *Warnings and Precautions - Cognitive and motor impairment*).

Bladder Effects

Cases of interstitial cystitis have been reported in subjects using ketamine for recreational use or for treatment of chronic pain at high doses with long-term use. In clinical studies with esketamine nasal spray, subjects were assessed for symptoms of cystitis, bladder pain and interstitial cystitis. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which involved treatment for up to a year. In clinical studies with Spravato, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in Spravato-treated patients than in placebo-treated patients.
Patients should be monitored for urinary tract and bladder symptoms during treatment with Spravato and referred to a specialist if clinically indicated.

Drug abuse and dependence

Abuse

Assess each patient’s risk for abuse or misuse prior to prescribing Spravato and monitor each patient receiving Spravato for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of Spravato. Prior to treating persons with substance misuse or addiction in the medical history, including alcohol, a careful risk/benefit assessment should be conducted.
Ketamine, the racemic mixture of arketamine and esketamine, has been reported as a drug of abuse. In a study of abuse potential conducted in recreational polydrug users (n=41), single doses of esketamine nasal spray (84 mg and 112 mg) and the positive control drug intravenous ketamine (0.5 mg/kg infused over 40 minutes) produced significantly greater scores than placebo on subjective ratings of “drug liking” and on other measures of subjective drug effects.

Dependence

Dependence and tolerance have been reported with prolonged use of ketamine. Individuals who were dependent on ketamine reported withdrawal symptoms of cravings, anxiety, shaking, sweating and palpitations. Pay attention to signs of dependence during treatment with Spravato.

Other populations at risk

Spravato should be used with caution in patients with the following conditions. These patients should be carefully assessed before prescribing Spravato and treatment initiated only if the benefit outweighs the risk:

- Presence or history of psychosis.
- Presence or history of mania or bipolar disorder.
- Hyperthyroidism that has not been sufficiently treated.
- History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure.

Patients who were not studied in clinical trials

No experience is available on the efficacy and safety of Spravato in the following patient populations: patients with seizures in the medical history, patients with neurodegenerative diseases (e.g. Alzheimer's disease, vascular dementia, Parkinson's disease with clinical signs of cognitive limitations, patients with mild cognitive impairment, as well as patients with uncontrolled hypertension (<65 years: SBP/DBP >140/90 mmHg; ≥65 years: SBP/DBP ≥150/90 mmHg).

Pregnancy

Based on studies conducted in animals with ketamine, taking Spravato during pregnancy may harm the fetus (see *Pregnancy, lactation*).

Interactions

Pharmacodynamic interactions

CNS depressants

Sedation may be enhanced during concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol). Close monitoring for symptoms of sedation is required during concomitant use of Spravato and CNS depressants.

Psychostimulants

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of Spravato with psychostimulants.

Monoamine oxidase inhibitors (MAOIs)

Concomitant use with monoamine oxidase inhibitors (MAOIs) (e.g., tranylcypromine, selegiline, phenelzine) may increase blood pressure. Closely monitor blood pressure with concomitant use of Spravato with MAOIs.

Pharmacokinetic interactions

Esketamine is extensively metabolized in the liver. The primary metabolic pathway of esketamine in human liver microsomes is N-demethylation to form noresketamine. The main cytochrome P450 (CYP) enzymes responsible for esketamine N-demethylation are CYP2B6 and CYP3A4 (see *Pharmacokinetics*).

In vitro data

Esketamine is not a substrate of transporters P-glycoprotein (P-gp; multidrug resistance protein 1), breast cancer resistance protein (BCRP), or organic anion transporter (OATP) 1B1, or OATP1B3. Noresketamine is not a substrate for these transporters or for organic anion transporter 1 (OAT1), OAT3, organic cation transporter 1 or 2 (OCT1 or OCT2). Esketamine and noresketamine do not inhibit P-gp, or BCRP, or MATE1 (multi-drug and toxin extrusion 1), and MATE2-K, or OAT1, or OAT3. Esketamine is a weak inhibitor of OCT2; the clinical relevance of this inhibition is unknown. Noresketamine does not inhibit OCT2. Esketamine and noresketamine exhibit a low reversible or time-dependent inhibition potential against CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4). CYP3A4 inhibition by noresketamine was substrate-dependent and was evaluated not to be clinically relevant. Esketamine and noresketamine do not inhibit uridine diphosphate glucuronosyltransferases (UGT) 1A1 and 2B7.
Esketamine and its major circulating metabolites had no induction effect on CYP1A2 in human hepatocytes. There were some inducing effects of esketamine on CYP3A4 and CYP2B6 in vitro in human hepatocytes, which did not translate into a clinically relevant drug-drug interaction (see *Effect of Spravato on other medicinal products*).

Effect of Spravato on other medicinal products

Nasal administration of 84 mg esketamine twice a week for 2 weeks reduced the mean plasma AUC_{∞} of oral midazolam (single 6 mg dose), a substrate of hepatic CYP3A4, by approximately 16%.
Nasal administration of 84 mg esketamine twice a week for 2 weeks did not affect the mean plasma AUC_{∞} of oral bupropion (single 150 mg dose), a substrate of hepatic CYP2B6.

Effect of other medicinal products on Spravato

Hepatic enzyme inhibitors

Pretreatment of healthy subjects with oral ticlopidine, an inhibitor of hepatic CYP2B6 activity, (250 mg twice daily for 9 days prior to and on the day of esketamine administration) had no effect on the

maximum plasma concentration (C_{max}) of esketamine administered as a nasal spray. The area under the plasma concentration-time curve (AUC_{∞}) of esketamine was increased by approximately 29%. The terminal half-life of esketamine was not affected by ticlopidine pretreatment.
Pretreatment with oral clarithromycin, an inhibitor of hepatic CYP3A4 activity, (500 mg twice daily for 3 days prior to and on the day of esketamine administration) increased the mean C_{max} and AUC_{∞} of nasally administered esketamine by approximately 11% and 4%, respectively. The terminal half-life of esketamine was not affected by clarithromycin pretreatment.

Hepatic enzyme inducers

Pretreatment with oral rifampicin, a potent inducer of the activity of multiple hepatic CYP enzymes such as CYP3A4 and CYP2B6, (600 mg daily for 5 days prior to esketamine administration) decreased the mean C_{max} and AUC_{∞} values of esketamine administered as a nasal spray by approximately 17% and 28%, respectively.

Other nasal spray products

Concomitant use of Spravato with other nasally administered medicinal products has been evaluated in the following pharmacokinetic interaction studies. Pretreatment of subjects with history of allergic rhinitis and pre-exposed to grass pollen with oxymetazoline administered as a nasal spray (2 sprays of 0.05% solution administered at 1 hour prior to nasal administration of esketamine) had minor effects on the pharmacokinetics of esketamine.
Pretreatment of healthy subjects with nasal administration of mometasone furoate (200 mcg per day for 2 weeks with the last mometasone furoate dose administered at 1 hour prior to nasal administration of esketamine) had minor effects on the pharmacokinetics of esketamine.

Pregnancy, lactation

Pregnancy

Insufficient data available on use in pregnant patients.
In investigational studies in animals with ketamine, teratogenicity and neurotoxic effects in the fetuses were observed (more detailed information in *Preclinical data*). The potential for esketamine to have effects on fetal development cannot be excluded. Spravato should not be used during pregnancy unless it is clearly necessary.
To avoid exposing the fetus to esketamine, women of reproductive potential should be advised to use highly effective contraception during and up to 6 weeks after the last treatment with Spravato. If a woman becomes pregnant while being treated with Spravato, treatment with esketamine should be discontinued and the patient should be counseled about the potential risk to the fetus and clinical/therapeutic options as soon as possible.

Lactation

Spravato is not recommended in women who are breast-feeding. The risks of Spravato during breast-feeding have not been studied in humans. Based on data from studies in animals, the passage of esketamine into human milk is to be expected. A decision must be made either not to undergo therapy with Spravato while breast-feeding or discontinue breast-feeding if treatment with Spravato is initiated, taking into consideration the benefit for the mother and the benefit of breast-feeding for the infant (see *Preclinical data*).

Effects on ability to drive and use machines

Spravato has a major influence on the ability to drive and use machines. In clinical studies, Spravato has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety (see *Undesirable effects*). Before Spravato administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep (see *Warnings and precautions* and *Properties/Effects – Clinical efficacy*).

Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that have been considered to be reasonably associated with the use of esketamine based on the comprehensive assessment of the available adverse event information. A causal relationship with esketamine cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Summary of the safety profile

Undesirable effects from clinical studies in TRD

Spravato was evaluated for safety in 1709 patients diagnosed with TRD (patients with MDD and were non-responders to at least two oral ADs treatments, of adequate dosage and duration, in the current MDD episode) from five Phase 3 studies (3 short-term and 2 long-term studies) and one Phase 2 dose-ranging study. Of all esketamine-treated patients in the completed Phase 3 studies, 479 (29.9%) received at least 6 months of treatment exposure, and 178 (11.1%) received at least 12 months of exposure.

Undesirable effects in patients with MDD with acute suicidal ideation or behavior (Indication "Acute short-term treatment of a psychiatric emergency in the context of MDD")

Spravato was evaluated for safety in 262 patients diagnosed with MDD with suicidal ideation and intent from two Phase 3 studies and one Phase 2 study. Overall, the safety profile of Spravato from this clinical program was generally similar that seen in studies for TRD.

Common Undesirable effects

The most commonly observed undesirable effects in patients treated with Spravato plus oral AD (incidence ≥10% and greater than oral AD plus placebo nasal spray) were dissociation, dizziness, nausea, sedation, headache, dysgeusia, hypoesthesia, vertigo, anxiety, blood pressure increased and vomiting. Most of these undesirable effects were mild or moderate in severity, reported post-dose on the day of administration and resolved the same day.

Adverse events reported as reasons for discontinuation of treatment

In short-term studies in both adult <65 years of age (pooled TRD3001/TRD3002) and patients ≥65 years of age with TRD (TRD3005), the proportion of patients that received Spravato plus oral AD and discontinued treatment because of an adverse event was 4.6% for adult <64 years of age and 5.6% for patients ≥65 years of age, respectively, compared to 1.4% for adults <64 years of age and 3.1% for patients ≥65 years of age receiving oral AD plus placebo nasal spray. In a long-term study, the discontinuation rates because of an adverse event were similar for patients receiving Spravato plus oral AD and oral AD plus placebo nasal spray, 2.6% and 2.1%, respectively. Across all Phase 3 studies, adverse events leading to Spravato discontinuation in more than 2 patients (>0.1%) were (in order of frequency): anxiety (1.2%), depression (0.9%), blood pressure increased (0.6%), dizziness (0.6%), suicidal ideation (0.5%), dissociation (0.4%), nausea (0.4), vomiting (0.4%), headache (0.3%), muscular weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.2%) and sedation (0.2%).
In the pooled Phase 3 studies SUI3001/SUI3002, 6.2% (14/227) of patients diagnosed with MDD with suicidal ideation and intent (Indication “Acute short-term treatment of a psychiatric emergency in the context of major depression”) in the Spravato + SOC group and 3.6% (8/225) of patients in the placebo + SOC group experienced adverse events leading to discontinuation. Adverse events that led to discontinuation in >1 subject in the Spravato + SOC group were: dissociation, blood pressure increased, depersonalization/derealization disorder, and nausea.

Listing of undesirable effects

Undesirable effects are classified by MedDRA system organ class and frequency according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).[a]

Psychiatric disorders
Very common: dissociation (41.7%)[b], anxiety (13.7%)[b].
Common: euphoric mood, emotional distress[b].

Nervous system disorders

Very common: dysgeusia (17.8%)[b], dizziness (37.9%)[b], sedation (25.9%)[b], hypoesthesia (16.3%)[b], headache (23.7%)[b].

Common: mental impairment[b], tremor[b], lethargy[b], dysarthria[b].

Uncommon: nystagmus.

Ear and labyrinth disorders

Very common: vertigo (16.3%)[b].

Cardiac disorders

Common: tachycardia[b].

Respiratory, thoracic and mediastinal disorders

Common: throat irritation[b], nasal discomfort[b].

Gastrointestinal disorders

Very common: nausea (27%), vomiting (10.7%).

Common: dry mouth.

Uncommon: salivary hypersecretion.

Skin and subcutaneous tissue disorders

Common: hyperhidrosis[b].

Renal and urinary disorders

Common: pollakiuria[b], dysuria

General disorders and administration site conditions

Common: feeling abnormal, feeling drunk, asthenia.

Uncommon: gait disturbance.

Investigations

Very Common: blood pressure increased (13.1%)[b].

[a] There were no undesirable effects that met the criteria for the frequencies “rare”, “very rare” and “not known”.

[b] The following terms were combined:
Dissociation includes: dissociation; depersonalization/derealization disorder; derealization; dissociative disorder; flashback; hallucination; hallucination, auditory; hallucination, visual; illusion; somatic hallucination; hallucinations, mixed; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change.
Anxiety includes: anxiety; anticipatory anxiety; anxiety disorder; generalized anxiety disorder; agitation; fear; nervousness; tension; panic attack; panic disorder; panic reaction; feeling jittery; irritability; psychogenic tremor; psychomotor hyperactivity.

Emotional distress includes: emotional distress; crying; dysphoria.
Dizziness includes: dizziness; postural dizziness; procedural dizziness; exertional dizziness.
Sedation includes: sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor.
Headache includes: headache; sinus headache.
Dysgeusia includes: dysgeusia; hypogeusia.
Hypoesthesia includes: hypoesthesia; oral hypoesthesia ; hypoesthesia of the teeth; pharyngeal hypoesthesia; intranasal hypoesthesia.
Lethargy includes: lethargy; fatigue; listless, psychomotor retardation.
Mental impairment includes: mental impairment; confusional state; disturbance in attention.
Dysarthria includes: dysarthria; speech disorder; slow speech.
Tremor includes: tremor; intention tremor.
Vertigo includes: vertigo; positional vertigo.
Tachycardia includes: sinus tachycardia; tachycardia; increased heart rate; extrasystoles.
Nasal discomfort includes: nasal discomfort; nasal crusting; nasal dryness; nasal pruritus.
Throat irritation includes: throat irritation; oropharyngeal pain.
Hyperhidrosis includes: hyperhidrosis; cold sweat.
Pollakiuria includes: pollakiuria; micturition disorder; micturition urgency.
Increased blood pressure includes: increased blood pressure; increased systolic blood pressure; increased diastolic blood pressure; hypertension; hypertensive heart disease; hypertensive crisis.

Description of selected undesirable effects

Dissociation/perceptual changes

Dissociation was one of the most common psychological effects of esketamine, including distortion of time and space and illusions, derealization and depersonalization. These undesirable effects were reported as transient and self-limited and occurred on the day of dosing. Dissociation was evaluated by adverse event reports and the CADSS questionnaire (Clinician-Administered Dissociative States Scale). A CADSS total score of more than 4 indicates presence of dissociative symptoms, and such an increase to a score of 4 or more occurred in a higher number of patients on esketamine compared to placebo during the short-term trials. The incidence of dissociation (CADSS total score >4) in adults <65 years of age treated with Spravato ranged from 61% to 69% in comparison to 8% in the control group. The incidence of dissociation (CADSS total score >4) in patients ≥65 years of age treated with Spravato was 75% in comparison to 14% in the control group. Dissociation symptoms resolved by 2 hours post dose. The incidence of severe dissociation was less than 4%.

Sedation/Somnolence

Undesirable effects of sedation and somnolence were primarily mild or moderate in severity, occurred on the day of dosing and resolved spontaneously the same day. Sedation was evaluated by adverse event reports and using the MOAA/s scale (Modified Observer’s Alertness/Sedation) (MOAA/s). In the

MOAA/s scale, 5 means “responds readily to name spoken in normal tone” and 0 means “no response after painful trapezius squeeze”. Any decrease in MOAA/s score from pre-dose is considered to indicate presence of sedation, and such a decrease occurred in a higher number of patients on esketamine than placebo during the short-term trials. The incidence of sedation (MOAA/s total score <5) in adults <65 years of age treated with Spravato ranged from 50% to 61% and patients ≥65 years of age treated with Spravato was 49%. A loss of consciousness (MOAA/s total score = 0) was seen in 0.3% of patients. Sedative effects typically resolved by 1.5 hours post-dose. Rates of somnolence were relatively stable over time during long-term treatment. In the cases of sedation, no symptoms of respiratory distress were observed, and hemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges.

Impaired cognition

In the short-term studies, treatment with Spravato plus oral AD did not influence any aspect of cognition studied in adult patients with TRD and was not associated with any systematic changes in cognition in the elderly patients. Consistently, in long-term studies, performance on each of the cognitive tests relative to baseline showed slight improvement or remained stable in each treatment phase. The long-term cognitive effects of Spravato have not been evaluated beyond one year.

Slowing of reaction time

In the subgroup of older patients (≥65 years of age) in the long-term open-label safety study, a slowing of reaction time was observed starting in Week 20 and until the end of the study, however, the performance in other cognitive tests remained stable.

Changes in blood pressure

Spravato causes an increase in systolic and/or diastolic blood pressure at all recommended dosages. The blood pressure increase is highest approximately 40 minutes after administration of Spravato and lasts approximately four hours. During the first four weeks of treatment, 8% to 17% of patients treated with Spravato and 1% to 3% of patients treated with placebo experienced an increase in systolic blood pressure of greater than 40 mmHg and/or an increase in diastolic blood pressure of 25 mmHg during the first 1.5 hours after administration of Spravato. A significant increase in blood pressure can occur after every administration, even when only minor effects on blood pressure were exhibited during previous administrations of Spravato (see *Warnings and precautions*). The frequency of markedly abnormal blood pressure elevations from clinical trials in the treatment of TRD are shown in Table 2.

Table 2: Increases in blood pressure in double-blind, randomized, controlled, short-term trials of Spravato + oral AD compared to placebo nasal spray + oral AD in the treatment of TRD

	Patients <65 years		Patients ≥65 years	
	Spravato + oral AD N=346	Placebo + oral AD N=222	Spravato + oral AD N=72	Placebo + oral AD N=65
Systolic blood pressure				
≥180 mmHg	9 (3%)	---	2 (3%)	1 (2%)
≥40 mmHg increase	29 (8%)	1 (0.5%)	12 (17%)	1 (2%)
Diastolic blood pressure				
≥110 mmHg	13 (4%)	1 (0.5%)	---	---
≥25 mmHg increase	46 (13%)	6 (3%)	10 (14%)	2 (3%)

If blood pressure remains high, medical measures should be taken immediately. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

Nasal tolerability and sense of smell

Across studies, the vast majority of esketamine-treated patients had no findings on nasal examination. For the patients who had nasal findings (including nasal discharge, nasal crust, or nasal erythema) all events were of mild severity with the exception of a few moderate findings. The most frequently reported post-dose nasal symptoms of moderate or severe intensity (reported in at least 5% of patients) in the Phase 3 studies were post-nasal drip, taste disturbance and stuffy nose. Other nasal symptoms of moderate or severe intensity included: runny nose, cough, dryness inside nose and sneezing. In addition, sense of smell was assessed over time; no difference was observed between patients treated with Spravato plus oral AD and those treated with oral AD plus placebo nasal spray during the double-blind maintenance phase of TRD3003.

Body weight

Spravato had no clinically meaningful effect on body weight over short- or long-term administration.

Laboratory values

Spravato has not been associated with any clinically important changes to laboratory parameters in serum chemistry, hematology, or urinalysis.

Reporting suspected Undesirable effects after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected Undesirable effects online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose were reported in clinical studies with Spravato. The potential for overdose of Spravato by the patient is minimized due to the product's design and the administration taking place under the supervision of a physician (see *Dosage/Administration*).

Signs and symptoms

There is limited clinical trial experience with esketamine nasal spray doses higher than the maximum recommended dose of 84 mg. The maximum single esketamine nasal spray dose tested in healthy volunteers was 112 mg which showed no evidence of toxicity and/or adverse clinical outcomes. However, compared to the recommended dose range, the 112-mg esketamine nasal spray dose was associated with higher rates of undesirable effects including dizziness, hyperhidrosis, somnolence, hypoesthesia, feeling abnormal, nausea and vomiting.

Treatment

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. Management of Spravato overdose should consist of treating clinical symptoms and relevant monitoring. Close supervision and monitoring should continue until the patient recovers.

Properties/Effects

ATC code

N06AX27

Mechanism of action

Esketamine, the S-enantiomer of racemic ketamine, is an antidepressant with a novel mechanism of action. It is a non-selective, non-competitive antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor, an ionotropic glutamate receptor.

Putative etiological contributors of depression, including stress and other conditions, are known to cause structural and functional impairment of synapses in brain regions involved with the regulation of mood and emotional behavior. Evidence within the literature suggests that through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signaling that restore synaptic function in these brain regions.

Unlike other antidepressant therapies, esketamine's primary antidepressant action does not directly involve monoamine, GABA, or opioid receptors.

Pharmacodynamics

See *Mechanism of action*

Clinical efficacy

The efficacy and safety of Spravato nasal spray was investigated in five Phase 3 clinical studies in adult patients (18 to 86 years) with TRD who met DSM-5 criteria for MDD and were non-responders to at least two oral antidepressants treatments, of adequate dosage and duration, in the current major depressive episode. 1,833 adult patients were enrolled, of which 1,601 patients were exposed to Spravato.

Treatment-resistant depression (TRD) – Short-term studies

Spravato was evaluated in three Phase 3 short-term (4-week) randomised, double-blind, active-controlled studies in patients with TRD. Studies TRANSFORM-1 (TRD3001) and TRANSFORM-2 (TRD3002) were conducted in adults (18 to <65 years) and Study TRANSFORM-3 (TRD3005) was conducted in adults ≥65 years of age. Patients in TRD3001 and TRD3002 initiated treatment with Spravato 56 mg plus a newly initiated daily oral AD or a newly initiated daily oral AD plus placebo nasal spray on day 1. Spravato dosages were then maintained on 56 mg or titrated to 84 mg or matching placebo nasal spray administered twice-weekly during a 4-week double-blind induction phase. Spravato doses of 56 mg or 84 mg were fixed in Study TRD3001 and flexible in Study TRD3002. In Study TRD3005, patients ≥65 years initiated treatment with Spravato 28 mg plus a newly initiated daily oral AD or a newly initiated daily oral AD plus placebo nasal spray (day 1). Spravato dosages were titrated to 56 mg or 84 mg or matching placebo nasal spray administered twice-weekly during a 4-week double-blind induction phase. In the flexible dose studies, TRD3002 and TRD3005, up titration of Spravato dose was based on clinical judgement and dose could be down titrated based on tolerability. A newly initiated open-label oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) was initiated on day 1 in all studies. The selection of the newly initiated oral AD was determined by the investigator based on the patient's prior treatment history. In all short-term studies, the primary efficacy endpoint was change in MADRS total score from baseline to day 28.
Baseline demographic and disease characteristics for patient in TRD3002, TRD3001, and TRD3005 are presented in Table 3.

Table 3: Baseline demographic characteristics for TRD3002, TRD3001, and TRD3005 (full analysis sets)

	Study TRD3002 (N=223)	Study TRD3001 (N=342)	Study TRD3005 (N=137)
Age, years			
Median (Range)	47.0 (19; 64)	47.0 (18; 64)	69.0 (65; 86)
Sex, n (%)			
Male	85 (38.1%)	101 (29.5%)	52 (38.0%)
Female	138 (61.9%)	241 (70.5%)	85 (62.0%)
Race, n (%)			
White	208 (93.3%)	262 (76.6%)	130 (94.9%)
Black or African American	11 (4.9%)	19 (5.6%)	--
Prior oral ADs with nonresponse (i.e., failed ADs)			
Number of specific ADs, n (%)			
2	136 (61.0%)	167 (48.8%)	68 (49.6%)
3 or more	82 (36.8%)	167 (48.8%)	58 (42.3%)
Newly initiated oral AD medication initiated at randomisation, n (%)			
SNRI	152 (68.2%)	196 (57.3%)	61 (44.5%)
SSRI	71 (31.8%)	146 (42.7%)	76 (55.5%)
Withdrawn from study (for any reason), n/N (%)	30/227 (13.2%)	31/346 (9.0%)	16/138 (11.6%)

In the flexible dose study TRD3002, at day 28, 67% of the patients randomised to Spravato were on 84 mg. In study TRD3002, Spravato plus a newly initiated oral AD demonstrated statistical superiority compared to a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 4), and symptom reduction was observed as early as 24 hours post-dose.

In study TRD3001, the treatment effect (defined as change in MADRS total score from baseline at the end of the 4-week induction phase) for Spravato 84 mg plus a newly initiated oral AD did not show statistical significance relative to the oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 4).

In study TRD3005, at day 28, 64% of the patients randomised to Spravato were on 84 mg, 25% on 56 mg, and 10% on 28 mg. In study TRD3005, the treatment effect (defined as change in MADRS total score from baseline at the end of the 4-week induction phase) for Spravato plus a newly initiated oral AD did not show statistical significance relative to the oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 4). Subgroup analyses suggest limited efficacy in the population over 75 years old.

Table 4: Primary Efficacy Results for Change in MADRS Total Score for 4 Week Clinical Trials (ANCOVA LOCF)

Study No.	Treatment Group[§]	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline to end of Week 4 (SE)	LS Mean Difference (95% CI)[†]	2-sided p-value
TRD3001	Spravato 56 mg + oral AD	115	37.4 (4.8)	-18.7 (1.3)	-4.1 (-7.5, -0.6)[#]	N/Aº
	Spravato 84 mg + oral AD	114	37.8 (5.6)	-17.3 (1.3)	-2.0 (-5.5, 1.4)[#]	0.250
	Oral AD + placebo nasal spray	113	37.5 (6.2)	-14.8 (1.3)		
TRD3002	Spravato (56 mg or 84 mg) + oral AD	114	37.0 (5.7)	-18.0 (1.3)	-3.5 (-6.7, -0.3)[‡]	0.034[‡]
	Oral AD + placebo nasal spray	109	37.3 (5.7)	-14.5 (1.3)		
TRD3005 (≥65 years)	Spravato (28 mg, 56 mg or 84 mg) + oral AD	72	35.5 (5.9)	-10.9 (1.7)	-3.6 (-7.2, -0.03)[#]	0.052
	Oral AD + placebo nasal spray	65	34.8 (6.4)	-6.9 (1.7)		

SD = standard deviation; SE = standard error; LS Mean = least-squares mean; CI = confidence interval; AD = antidepressant

§ Nasally administered esketamine or placebo; oral AD = standard of care (newly initiated AD)

† Difference (Spravato + oral AD minus Oral AD + placebo nasal spray) in least-squares mean change from baseline

‡ Treatment groups that were statistically significantly superior to Oral AD + placebo nasal spray

Median unbiased estimate (i.e., weighted combination of the LS means of the difference from Oral AD + placebo nasal spray), and 95% flexible confidence interval

º As the 84 mg was not statistically significant, the p-value for the comparison of Spravato 56 mg + oral AD vs Oral AD + placebo is not presented due to the testing hierarchy.

Time course of treatment response

In Study TRD3002, an antidepressant effect of Spravato with reduction in depressive symptoms was observed as early as 24 hours after administration of the first dose. An increased improvement was observed in subsequent weeks with achievements of the full antidepressant effect of Spravato seen by Day 28. The mean change in MADRS total score for flexibly dosed Spravato (56 mg or 84 mg) plus oral AD was consistently greater than for oral AD plus nasally-administered placebo at all timepoints (weeks 1, 2, 3, and 4). At Day 28, 67% of the patients randomized to Spravato received a dose of 84 mg. A consistent treatment effect was observed in Studies TRD3001 and TRD3005.

Therapeutic response and remission rates

Therapeutic response was defined as ≥50% reduction in the MADRS total score from baseline of the induction phase. Based on the reduction in MADRS total score from baseline, the proportion of patients in Studies TRD3001, TRD3002 and TRD3005 who demonstrated response to Spravato plus oral AD treatment was greater than for oral AD plus placebo nasal spray throughout the 4-week double-blind induction phase (Table 5).

Remission was defined as a MADRS total score ≤12. In all three studies, a greater proportion of patients treated with Spravato plus oral AD were in remission at the end of the 4-week double-blind induction phase than for oral AD plus placebo nasal spray (Table 5).

Table 5: Response and Remission Rates in 4 Week Clinical Trials Based on LOCF Data

Study No.	Treatment Group[§]	Number of Patients (%)					
		Response Rate[†]					Re-mission Rate[‡]
		24 hours	Week 1	Week 2	Week 3	Week 4	Week 4
TRD3001	Spravato 56 mg + oral AD	20 (19,0%)	21 (18,3%)	30 (26,1%)	52 (45,2%)	61 (53,0%)	40 (34,8%)
	Spravato 84 mg + oral AD	17 (16,3%)[#]	16 (14,3%)	26 (23,2%)	35 (31,0%)	54 (47,8%)	40 (35,4%)
	Oral AD + Placebo nasal spray	8 (7,9%)	5 (4,4%)	15 (13,3%)	27 (23,9%)	42 (37,2%)	33 (29,2%)
TRD3002	Spravato 56 mg or 84 mg + oral AD	18 (16,5%)	15 (13,4%)	29 (25,9%)	54 (48,2%)	71 (63,4%)	54 (48,2%)
	Oral AD + placebo nasal spray	11 (10,8%)	13 (11,9%)	23 (21,1%)	36 (33,0%)	54 (49,5%)	33 (30,3%)
TRD3005 (≥65 years)	Spravato 28 mg, 56 mg or 84 mg + oral AD	NA	4 (6,1%)	4 (5,6%)	9 (12,7%)	17 (23,9%)	11 (15,5%)
	Oral AD + placebo nasal spray	NA	3 (4,8%)	8 (12,5%)	10 (15,6%)	8 (12,5%)	4 (6,3%)

AD=antidepressant; NA=not available

§ Nasally administered Spravato or placebo; oral AD=standard of care (newly initiated AD)

† Response was defined as ≥50% reduction in the MADRS total score from baseline

‡ Remission was defined as MADRS total score ≤12

First dose was Spravato 56 mg + oral AD

Long-term data

Treatment-resistant depression (TRD) – Long-term studies

Relapse-prevention study

Study SUSTAIN-1 (TRD3003) was a long-term randomized, double-blind, parallel-group, active-controlled, multicenter, relapse prevention study. Overall a total of 705 patients were enrolled;

437 directly enrolled; 150 patients who transferred from Study TRD3001, and 118 patients transferred from Study TRD3002 were included. Patients directly enrolled were administered Spravato (56 mg or 84 mg twice weekly) plus oral AD in a 4-week open-label induction phase. Patients who were responders [(MADRS total score reduction ≥50% from baseline)], continued receiving treatment with Spravato plus oral AD in a 12-week optimization phase. At the end of the open label induction phase, 52% of patients were in remission (MADRS total score ≤12) and 66% of patients were responders (≥50% improvement in MADRS total score). A total of 455 esketamine-treated patients entered the subsequent optimization phase, patients in stable remission or stable response were randomized to continue with Spravato or stop Spravato and switch to placebo nasal spray. After an initial 16 weeks of treatment with Spravato plus oral AD, 176 (39%) patients were in stable remission and 121 (27%) patients were in stable response (but not in stable remission). Stable remission was defined as MADRS total score ≤12 in at least 3 of the last 4 weeks of the optimization phase and stable response was defined as ≥50% reduction in the MADRS total score from baseline for the last 2 weeks of the optimization phase, but not in stable remission.
The baseline demographic and disease characteristics of the patients randomized to the double-blind maintenance phase were comparable in both groups, median patient age was 48 years (range 19 to 64 years), 66% were female; 90% Caucasian.

Stable Remission
Patients in stable remission who continued treatment with Spravato plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients in the control group (oral AD plus placebo nasal spray). Relapse was defined as a MADRS total score ≥22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse. The median time to relapse for the control group (oral AD plus placebo nasal spray) was 273 days, whereas the median was not estimable for Spravato plus oral AD as this group did not attain a 50% relapse rate at any point during the study.
For patients in stable remission, the estimated hazard ratio (95% confidence interval) of Spravato plus oral AD relative to control group (oral AD plus placebo nasal spray) based on weighted estimates was 0.49 (95% confidence interval: 0.29, 0.84), p=0.003 indicating that, patients who were in stable remission and continued treatment with Spravato plus oral AD group were on average 51% less likely to relapse than patients who switched to control group (oral AD plus placebo nasal spray).

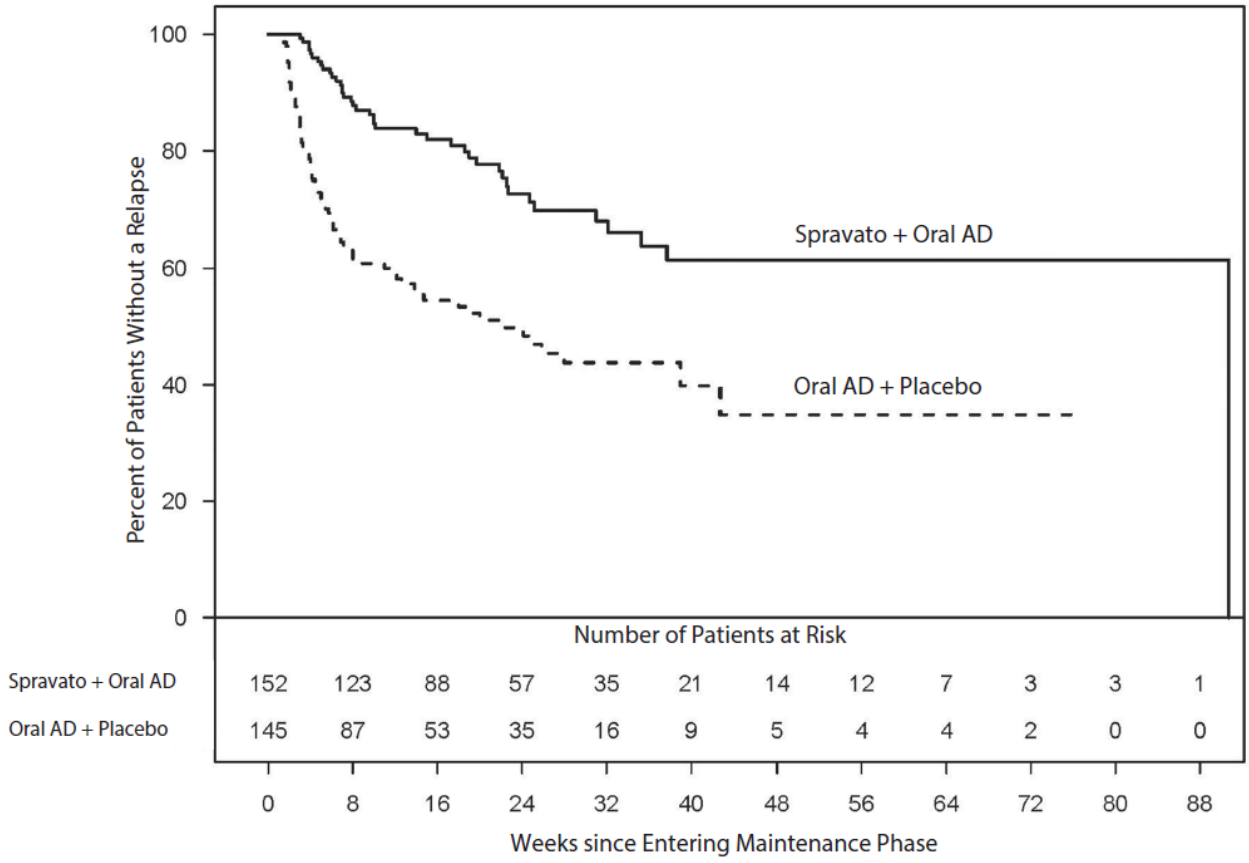
Stable Response
The efficacy results were also consistent for patients in stable response who continued treatment with Spravato plus an oral AD; patients experienced a statistically significantly longer time to relapse of depressive symptoms than did patients in the control group (oral AD plus placebo nasal spray). The

median time to relapse was 88 days in the control group and 635 days in the group treated with Spravato.

For patients in stable response, the estimated hazard ratio (95% confidence interval) of Spravato plus an oral AD relative to control group (oral AD plus placebo nasal spray) based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55), indicating that, patients who were stable responders and continued treatment with Spravato plus oral AD were on average 70% less likely to have a relapse than patients who switched to the control group (oral AD plus placebo nasal spray).

The cumulative proportion of patients who remained relapse free for stable remitters and stable responders combined from TRD3003 are shown in Figure 1.

Figure 1: Time to relapse in patients in stable response and stable remission in study TRD3003



Dosing Frequency

The dosing frequency for patients in stable remission or stable response during the maintenance phase was 23% and 55%, respectively for weekly dosing, and every other week dosing frequency was 69% and 34%, respectively. Some patients also had both weekly or every other week dosing frequency, 8% and 11%, respectively. Of the patients randomized to Spravato, 60% received 84 mg and 40% received 56 mg dose.

Dose-response study in TRD

A Phase 2, doubly-randomized, double-blind, placebo-controlled, dose-ranging study, enrolled 108 adult patients with TRD. In addition to continued oral AD therapy, patients were treated with esketamine 14 mg, 28 mg, 56 mg or 84 mg or placebo administered nasally twice a week for 2 weeks. Treatment with the 28-mg, 56-mg and 84-mg doses of Spravato significantly improved depressive symptoms in patients with TRD, as demonstrated by the change in MADRS total score after 1 week. While Spravato doses of 28 mg, 56 mg and 84 mg were efficacious in the treatment of TRD, the duration of the efficacy of the 28-mg dose was shorter.

Acute short-term treatment of a psychiatric emergency in the context of major depression

Spravato was evaluated in two identical Phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo-controlled studies, Aspire I (SUI3001; NCT03039192) and Aspire II (SUI3002; NCT03097133) in adult patients with moderate to severe MDD (MADRS total score >28) who had active suicidal ideation with intent. 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 hospitalization and a newly initiated or optimized oral AD therapy (AD monotherapy or AD plus augmentation) as determined by the investigator. 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 AD 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 6).

Table 6: Primary Efficacy Results for Change from Baseline in MADRS Total Score at 24 Hours After First Dose (Studies SUI3001 and SUI3002) (ANCOVA)*

Study No.	Treatment Group§	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline to 24 hr Post First Dose (SE)	LS Mean Difference (95% CI)† p-value
SUI3001	Spravato 84 mg + SOC	111	41.3 (5.87)	-15.9 (1.04)	-3.8 (-6.56; -1.09)‡ P=0.006
	Placebo nasal spray + SOC	112	41.0 (6.29)	-12.0 (1.02)	-
SUI3002	Spravato 84 mg + SOC	113	39.4 (5.21)	-16.0 (1.02)	-3.9 (-6.60; -1.11)‡ P=0.006
	Placebo nasal spray + SOC	113	39.9 (5.76)	-12.2 (1.05)	-
Pooled Studies (SUI3001 and SUI3002)	Spravato 84 mg + SOC	224	40.3 (5.61)	-16.0 (0.72)	-3.8 (-5.75; -1.89)‡
	Placebo nasal spray + SOC	225	40.4 (6.04)	-12.1 (0.72)	-

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

* ANCOVA LOCF: For SUI3001, 1 subject (in the placebo + SOC group) did not have the Day 2 (24 hours post first dose) MADRS total score, and the MADRS total score was carried forward from 4 hours after the first dose. For SUI3002, of the 6 subjects who did not have the Day 2 (24 hours post first dose) MADRS total score, 5 of them were able to carry the MADRS total score from 4 hours after the first dose.

§ 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 -4.81 (-7.26; -2.36) for the subpopulation that reported a prior suicide attempt (N=282) and -2.32 (-5.54; 0.91) for the subpopulation that did not report a prior suicide attempt (N=166).

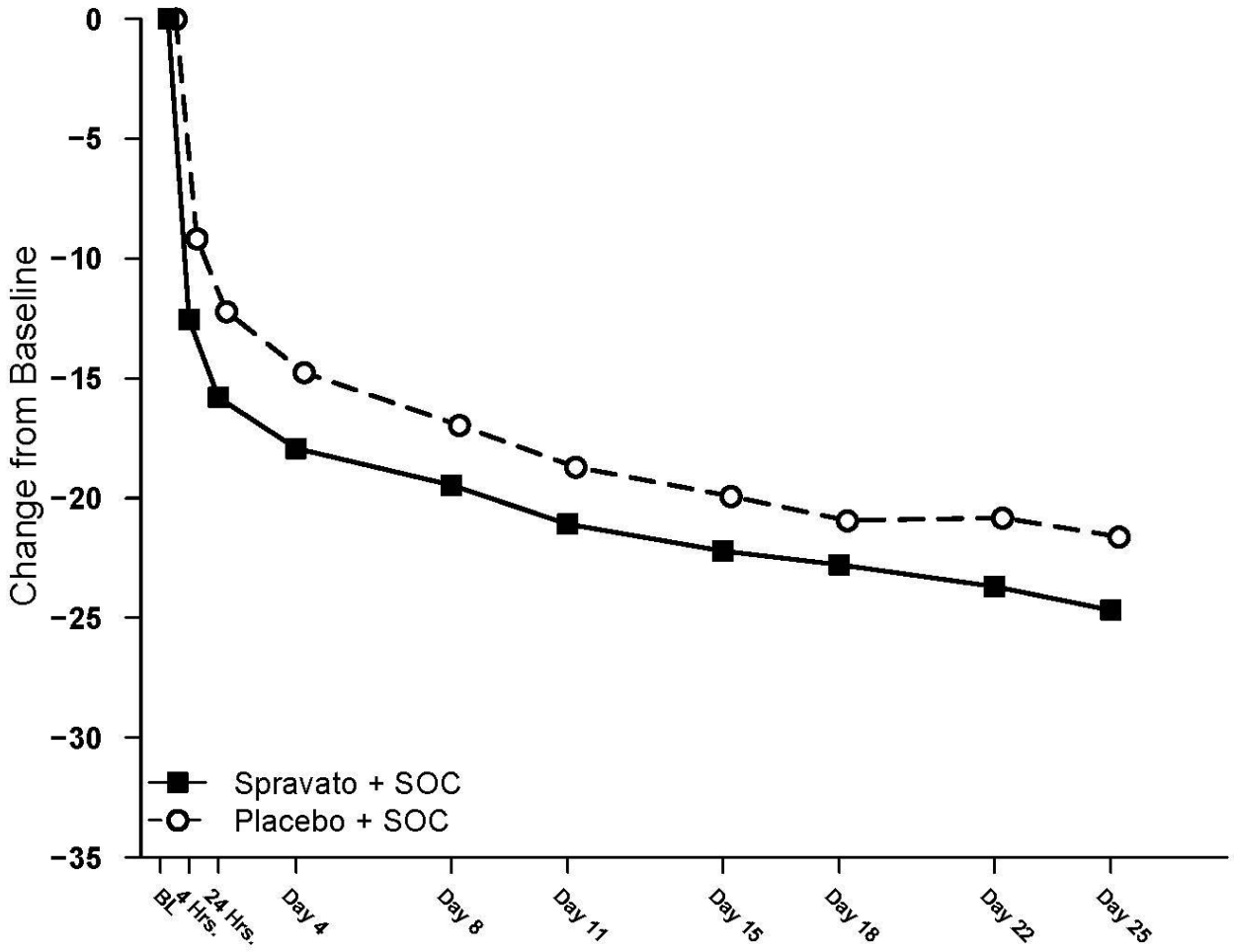
In the 18% of patients with moderately severe depressive episode (MADRS total score at baseline <35) Spravato plus standard treatment showed no superiority over placebo plus standard treatment at day 2 (24 hours after the first dose) in a post-hoc analysis of pooled data from SUI3001 and SUI3002.

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, 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 2 depicts time course of the primary efficacy measure of change in MADRS total score using pooled SUI3001 and SUI3002.

Figure 2: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in SUI3001 and SUI3002 (Pooled, Full Analysis Set) – MMRM*



* 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 double-blind treatment phase (Table 7).

Table 7: Patients Who Achieved Remission of MDD; Double-blind Treatment Phase; Full Efficacy Analysis Set

	SUI3001		SUI3002		Pooled Studies (SUI3001 and SUI3002)	
	Placebo + SOC	Spravato + SOC	Placebo + SOC	Spravato + SOC	Placebo + SOC	Spravato + SOC
	112	112	113	114	225	226
Day 1, 4 hours post first dose						
Patients with Remission of MDD	9 (8.0%)	12 (10.7%)	4 (3.5%)	12 (10.5%)	13 (5.8%)	24 (10.6%)
Day 2, 24 hours post first dose						
Patients with Remission of MDD	10 (8.9%)	21 (18.8%)	12 (10.6%)	25 (21.9%)	22 (9.8%)	46 (20.4%)
Day 25						
Patients with Remission of MDD	38 (33.9%)	46 (41.1%)	31 (27.4%)	49 (43.0%)	69 (30.7%)	95 (42.0%)

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

The secondary efficacy measure was the change in Clinical Global Impression of Suicidal Severity - Revised (CGI-SS-r) score at 24 hours after first dose (Day 2). The CGI-SS-r is a one-item, clinician-rated assessment used to rate the current severity of a patient's suicidal ideation and behavior. Scores on the CGI-SS-r range from 0 to 6, with higher scores indicating more severe suicidal ideation and behaviour. In Study SUI3001 and Study SUI3002, Spravato plus standard of care did not demonstrate superiority compared to placebo nasal spray plus standard of care in improving CGI-SS-r.
The long-term efficacy of Spravato to prevent suicide has not been established.

Further information

Effect on driving

Two studies were conducted to assess the effects of Spravato on driving skills, one study in adult subjects with MDD and one study in healthy subjects. On-road driving performance was assessed by the mean standard deviation of the lateral position (SDLP), a measure of driving impairment.
A single-blind, placebo-controlled study in 25 adult patients with MDD evaluated the effects of a single 84 mg dose of esketamine nasal spray on next day driving and the effect of repeated administration of 84 mg of intranasal Spravato on same-day driving performance. For the single dose treatment phase, an ethanol-containing beverage was used as a positive control. The SDLP after administration of single 84-mg dose of esketamine nasal spray was similar to placebo 18 hours post-dose. For the multiple

dose treatment phase, the SDLP after repeated administration of 84 mg intranasal Spravato was similar to placebo 6 hours post dose on Day 11, Day 18, and Day 25. The upper limit of the two-sided 95% confidence interval of the mean difference between a single-dose of esketamine and placebo was 0.58 cm, which is less than the pre-specified non-inferiority margin of 2.4 cm. The lower limit of the 95% confidence interval of the mean difference between ethanol and placebo was 1.03 cm ($p<0.001$), verifying assay sensitivity.

A randomized, double-blind, cross-over, placebo-controlled study in 23 healthy subjects evaluated the effects of a single 84 mg dose of esketamine nasal spray on driving. Mirtazapine was used as a positive control. Driving performance was assessed at 8 hours after esketamine or mirtazapine administration. The SDLP after esketamine nasal spray administration was similar to placebo. The upper limit of the two-sided 95% confidence interval of the mean difference between esketamine and placebo was 0.86 cm, which is less than the pre-specified non-inferiority margin of 2.4 cm. The lower limit of the 95% confidence interval of the mean difference between mirtazapine and placebo was 1.12 cm ($p=0.001$), verifying assay sensitivity. Of the 23 subjects evaluated, 21 subjects completed the test successfully. Two subjects discontinued the driving test after receiving esketamine because of a perceived inability to drive.

Effect on QT/QTc interval and cardiac electrophysiology

Treatment with Spravato did not prolong the QTc interval. The effect of Spravato (84 mg nasal spray and 0.8 mg/kg esketamine intravenously infused over 40 minutes) on the QTc interval was evaluated in a randomized, double-blind, placebo-, and positive-controlled (moxifloxacin 400 mg), 4-period, crossover study in 60 healthy subjects. Maximum esketamine concentrations in plasma produced by the intravenous infusion were approximately 3-times higher than the maximum concentrations produced by the nasal dose of 84 mg. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval remained below 10 msec, at all evaluated time-points, based on Fridericia's correction method (QTcF) for both treatment groups.

Pharmacokinetics

Absorption

The mean absolute bioavailability of 84 mg esketamine administered as a nasal spray is approximately 48%.

Esketamine is rapidly absorbed by the nasal mucosa following nasal administration and can be measured in plasma within 7 minutes following a 28-mg dose. The time to reach maximum plasma concentration (t_{max}) is typically 20 to 40 minutes after the last nasal spray of a treatment session (see *Dosage/Administration*).

The esketamine C_{max} and AUC_{inf} following intranasal administration exhibited a less than dose-proportional increase between 28 mg and 56 mg. Between 56 mg and 84 mg, both parameters rose proportionally to the dose administered.
The pharmacokinetic profile of esketamine is similar after a single dose and repeat dose administration with no accumulation in plasma when esketamine is administered twice a week.

Distribution

The mean steady-state volume of distribution of esketamine administered by the intravenous route is 709 L.
The proportion of the total concentration of esketamine that is bound to proteins in human plasma is on average 43 to 45%. The degree to which esketamine is bound to plasma proteins is not dependent on hepatic or renal function.

Metabolism

Esketamine is extensively metabolized in the liver. The primary metabolic pathway of esketamine in human liver microsomes is N-demethylation to form noresketamine. The main CYP enzymes responsible for esketamine N-demethylation are CYP2B6 and CYP3A4. Other CYP enzymes, including CYP2C19 and CYP2C9, contribute to a much smaller extent. Noresketamine is subsequently metabolized via CYP-dependent pathways to other metabolites, some of which undergo glucuronidation. On average, the plasma C_{max} and AUC_{∞} of noresketamine are approximately 2-times and 3-times greater, respectively, than corresponding parameters for esketamine. However, the pharmacologic activity of intranasally administered esketamine is largely attributable to parent drug since esketamine has greater potency as a NMDA receptor antagonist and higher unbound concentrations in the brain of animals, relative to noresketamine.

Elimination

The mean clearance of esketamine administered by the intravenous route was approximately 89 L/hour. After C_{max} was reached following nasal administration, the decline in esketamine concentrations in plasma was rapid for the first few hours and then more gradual. The mean terminal half-life following administration as a nasal spray generally ranged from 7 to 12 hours.
Following intravenous administration of radiolabelled esketamine, approximately 78% and 2% of administered radioactivity was recovered in urine and feces, respectively. Following oral administration of radiolabelled esketamine, approximately 86% and 2% of administered radioactivity was recovered in urine and feces, respectively. The recovered radioactivity consisted primarily of esketamine metabolites. For the intravenous and oral routes of administration, <1% of the dose was excreted in the urine as unchanged drug.

Kinetics in specific patient groups

Hepatic impairment

The C_{max} and AUC_{∞} of esketamine produced by a 28-mg doses were similar between subjects with Child-Pugh class A (mild) hepatic impairment and healthy subjects. The C_{max} and AUC_{∞} of esketamine were 8% higher and 103% higher, respectively, in subjects with Child-Pugh class B (moderate) hepatic impairment, relative to healthy subjects.
There is no clinical experience with esketamine administered as a nasal spray in patients with Child-Pugh class C (severe) hepatic impairment.

Renal impairment

Relative to the subjects with normal renal function (creatinine clearance [CL_{CR}], 88 to 140 ml/min), the C_{max} of esketamine was on average 20 to 26% higher in subjects with mild (CL_{CR}, 58 to 77 ml/min), moderate (CL_{CR}, 30 to 47 ml/min), or severe (CL_{CR}, 5 to 28 ml/min, not on dialysis) renal impairment following administration of a 28-mg dose of esketamine nasal spray. The AUC_{∞} was 13 to 36% higher in the subjects with mild to severe renal impairment.
There is no clinical experience with esketamine administered as a nasal spray in patients on dialysis.

Elderly patients

The pharmacokinetics of esketamine administered as a nasal spray was compared between elderly but otherwise healthy subjects and younger healthy adults. The mean esketamine C_{max} and AUC_{∞} values produced by a 28-mg dose were 21% and 18% higher, respectively, in elderly subjects (age range 65 to 81 years) compared with younger adult subjects (age range 22 to 50 years). The mean esketamine C_{max} and AUC_{∞} values produced by an 84-mg dose were 67% and 38% higher, respectively, in elderly subjects (age range 75 to 85 years) compared with younger adult subjects (age range 24 to 54 years). The terminal half-life of esketamine was similar in the elderly and younger adult subjects.

Genetic polymorphisms

CYP2B6 polymorphism does not affect the pharmacokinetics of intranasally administered esketamine based on the extensive overlap in the range of plasma esketamine C_{max} and AUC_{last} values in subjects considered to be poor (allelic variant *6/*6), intermediate (allelic variants *1/*6, *5/*6), and extensive (allelic variants *1/*1, *5/*5, *1/*5) metabolizers of CYP2B6 substrates.

Race

The pharmacokinetics of esketamine nasal spray was compared between healthy Asian subjects and Caucasian subjects. Mean plasma esketamine C_{max} and AUC_{∞} values produced by a single, 56-mg dose of esketamine were approximately 14% and 33% higher, respectively, in Chinese subjects compared to Caucasians. Both parameters were approximately 40% higher in Japanese subjects, relative to Caucasian subjects. On average, esketamine C_{max} was 10% lower and AUC_{∞} was 17%

greater in Korean subjects, relative to Caucasian subjects. The mean terminal half-life of esketamine in the plasma of Asian subjects ranged from 7.1 to 8.9 hours and was 6.8 hours in Caucasian subjects.

Gender

A population pharmacokinetic analysis was conducted that included healthy subjects (138 males and 118 females) and patients with MDD (295 males and 496 females). The results indicated that the pharmacokinetics of esketamine administered as a nasal spray is not influenced by gender.

Body Weight

A population pharmacokinetic analysis was conducted that included 256 healthy subjects and 791 patients with MDD. The total body weight of the subjects ranged from 39 to 207 kg. The results indicated that the pharmacokinetics of esketamine administered as a nasal spray is not influenced by body weight.

Allergic rhinitis

The pharmacokinetics of a single, 56-mg dose of esketamine administered as a nasal spray was similar in subjects with allergic rhinitis who were exposed to grass pollen compared to healthy subjects.

Preclinical data

Safety pharmacology

In dogs, transient increases in heart rate and blood pressure were noted at esketamine exposures comparable to the human exposure at the Maximum Recommended Human Dose (MRHD) of 84 mg.

Repeat-dose toxicity

In repeat-dose toxicity studies up to 6 months in rats and 9 months in dogs no adverse findings were noted at esketamine exposures below or comparable to the human exposure at the MRHD of 84 mg.

Genotoxicity

Esketamine was not mutagenic with or without metabolic activation in the Ames test. Genotoxic effects with esketamine were seen in a screening *in vitro* micronucleus test in the presence of metabolic activation. However, intravenously administered esketamine was devoid of genotoxic properties in an *in vivo* bone marrow micronucleus test in rats and in an *in vivo* Comet assay in rat liver cells. In simulated gastric fluid there is no evidence that N-nitroso-esketamine is formed out of the fraction of the nasally-administered dose of esketamine that is orally absorbed.

Carcinogenicity

Once-daily nasal administration of esketamine did not increase the incidence of tumors in a 2-year carcinogenicity study in rats at doses up to 9 mg/day. At this dose, the exposure to esketamine was below the human exposure at the MRHD of 84 mg. Esketamine was not carcinogenic either upon

once-daily subcutaneous administration in a 6-month study in transgenic (Tg.rasH2) mice at doses up to 70/40 mg/kg/day. At that dose, the esketamine exposure was about 4 times as high based on AUC as after the MRHD of 84 mg.

Reproductive toxicity

In an embryo-fetal developmental toxicity study in rats with nasally-administered ketamine, the racemic mixture of arketamine and esketamine, up to 150 mg/kg/day the offspring was not adversely affected in the presence of maternal toxicity. The AUC-based safety margin estimated for esketamine at the 150 mg/kg/day dose of ketamine was approximately 12-fold compared after MRHD of 84 mg esketamine. In an embryo-fetal developmental toxicity study with nasally-administered ketamine in rabbits, skeletal malformations were noted at 30 and 100/50 mg/kg/day in the presence of maternal toxicity. A relationship to ketamine treatment cannot be excluded. The estimated exposure to esketamine at NOAEL of 10 mg/kg/day was below the maximum exposure to esketamine at 84 mg in humans.
Animal studies with ketamine showed evidence of developmental neurotoxicity. The potential for esketamine to have neurotoxic effects on developing fetuses cannot be excluded. Ketamine administered intravenously at high anesthetic dose levels to female rats in the second trimester of pregnancy caused neuronal cell abnormalities in the brains of their offspring which showed behavioral changes and impaired memory up to young adult age. When female monkeys were treated intravenously with ketamine at high anesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses. Ketamine-induced neuronal cell death was also observed with early postnatal intraperitoneal or subcutaneous treatment of rat and mice pups, a period of rapid brain growth. This period of brain development translates into the third trimester of human pregnancy.
In a pre- and postnatal developmental toxicity study with nasally-administered esketamine up to 9 mg/day in rats, no adverse effects occurred in the dams nor their offspring.

Fertility

In a fertility and early embryonic developmental toxicity study, esketamine nasally-administered to rats at 0.9, 3, or 9 mg/day caused maternal and paternal toxicity at 3 and 9 mg/day. Fertility and reproductive capacities were not adversely affected at any dose.

Other information

Shelf life

Do not use this medicine after the expiry date «EXP» stated on the pack.

Special precautions for storage

Do not store above 30°C.

Keep out of the reach of children.

Instructions for handling

Each Spravato pack is provided with a separate Instructions for Use that fully describes the administration instructions of the nasal spray.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67103 (Swissmedic)

Packs

The medicinal product is packaged in a primary container consisting of a type-I vial with a rubber stopper. The filled and stoppered vial is assembled into a manually activated single-use nasal spray. The device dispenses two sprays, delivering a total volume of 0.2 ml of medicinal product.
Spravato is available in pack sizes containing 1, 2, or 3 single-use nasal sprays. Within each pack, each device is individually packaged in a sealed blister pack. [A]

Marketing authorisation holder

Janssen-Cilag AG, Zug

Date of revision of the text

March 2021

INSTRUCTION FOR USE
SPRAVATO

(esketamine hydrochloride)

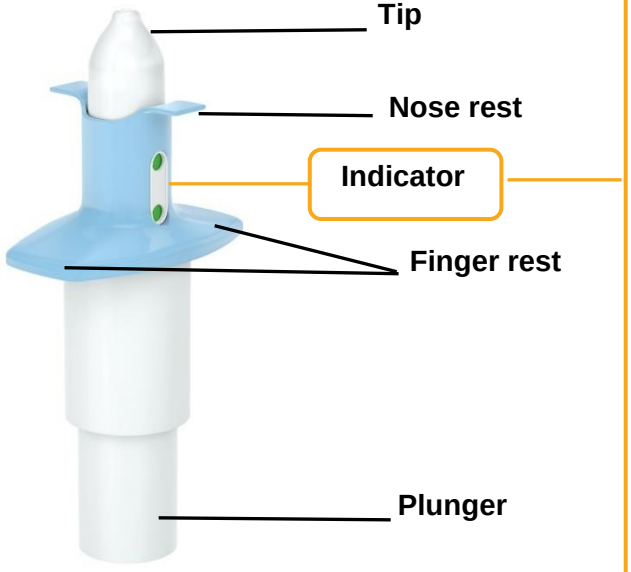
Nasal Spray

28 mg per device

Important

This device is intended for self-administration by the patient, **under direct supervision of a physician** (please see professional information). Read this Instructions for Use in full before training and supervising patient.

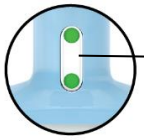
Nasal Spray



Indicator

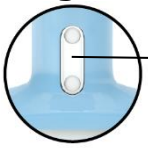
One device contains 2 sprays.
(1 spray for each nostril)

2 green dots (0 mg delivered)



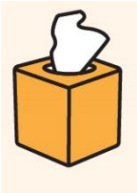
1 green dot

No green dots (28 mg delivered)



Step 1 Get ready

Before first use only:

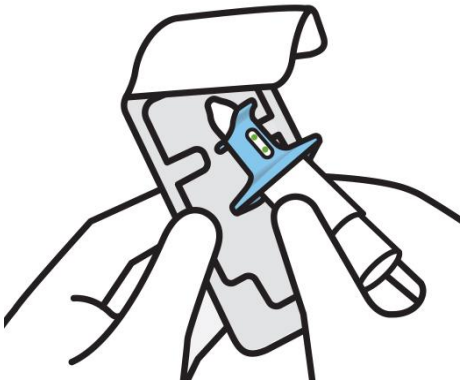


Instruct patient to blow nose **before first spray only**.

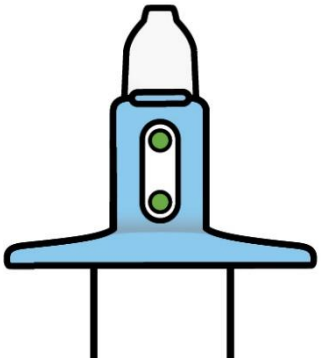
Confirm required number of nasal spray devices.

28 mg = 1 device
56 mg = 2 devices
84 mg = 3 devices

Step 2 Prepare device



Check expiration date «EXP».
If expired, get a new device.
Peel blister and remove device.



Do not prime device.
This will result in a loss of medication.

Check that indicator shows **2 green dots**. If not, dispose of device and get a new one.

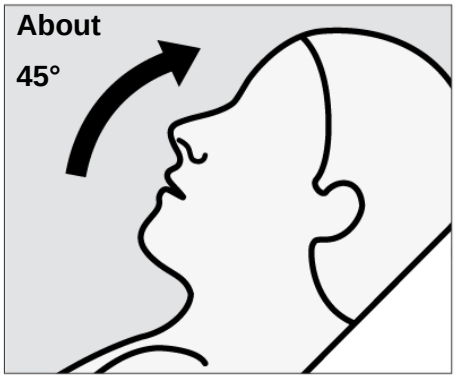
Hand device to patient.

Step 3 Prepare patient

Patient should:

Hold device as shown with the thumb gently supporting the plunger.

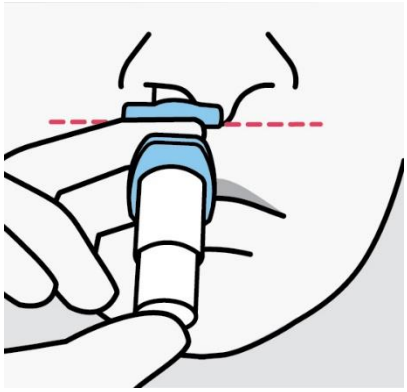
Do not press the plunger.



Patient should:

Recline head at about **45 degrees** during administration to keep medication inside the nose.

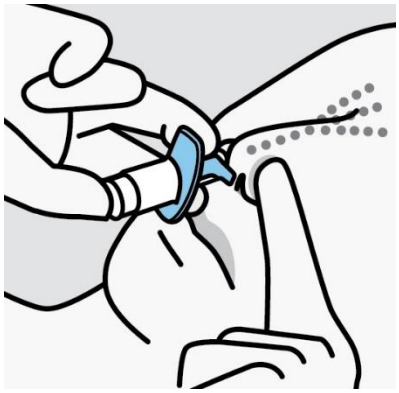
Step 4 Patient sprays once into each nostril



Patient should:

Insert tip straight into the **first nostril**.

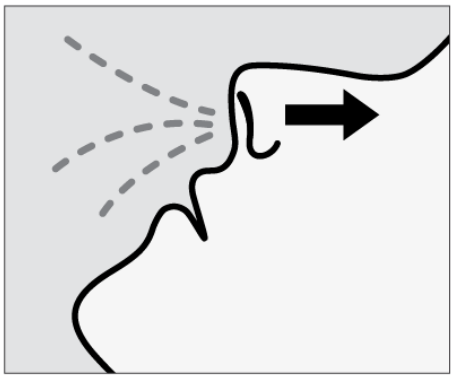
Nose rest should touch the **skin between the nostrils**.



Patient should:

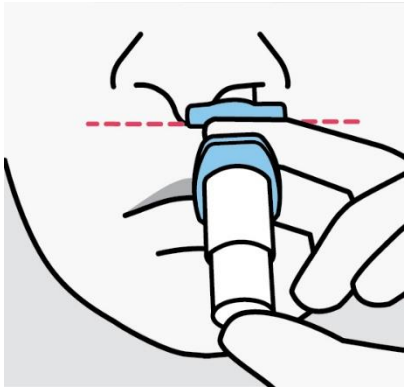
Close opposite nostril.

Breathe in through nose while pushing plunger all the way up until it stops.



Patient should:

Sniff gently after spraying to keep medication inside nose.

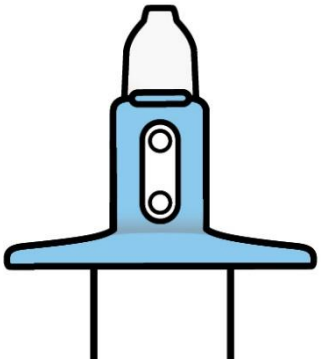


Patient should:

Switch hands to insert tip into the **other nostril**.

Repeat Step 4 to deliver second spray.

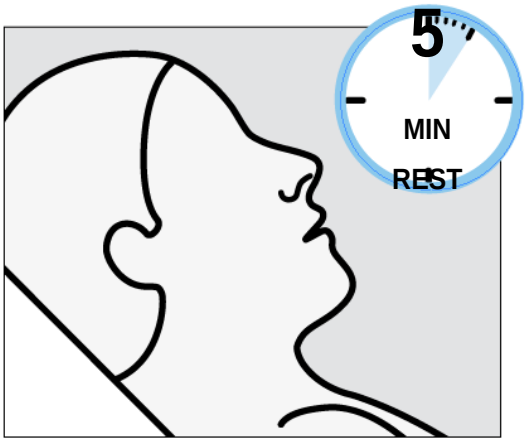
Step 5 Confirm delivery and rest



Take device from patient.

Check that indicator shows **no green dots**. If you see a green dot, get patient to spray again into the second nostril.

Check indicator again to confirm device is empty.



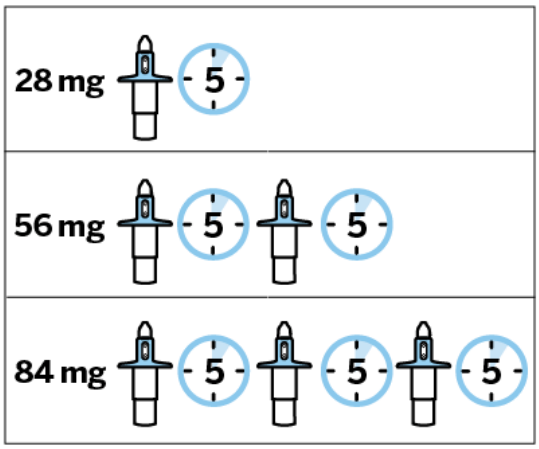
Patient should:

Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device**.

Do not blow nose.

If liquid drips out, dab nose with a tissue.

Next device (if required)



Repeat Steps 2-5 if more than one device is required.

IMPORTANT: Ensure that patient **waits for 5 minutes after each device** to allow medication to absorb.

Disposal

Dispose of used device(s) in accordance with local requirements.

Revision history

Application ID	Milestone	Created on	Change	Initials
TEXT	TEXT	DATE	TEXT	TEXT
TEXT	TEXT	DATE	TEXT	TEXT
TEXT	TEXT	DATE	TEXT	TEXT
TEXT	TEXT	DATE	TEXT	TEXT
TEXT	TEXT	DATE	TEXT	TEXT
TEXT	TEXT	DATE	TEXT	TEXT