

Date: 24 April 2020

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Spravato

International non-proprietary name: esketamine as esketamine hydrochloride

Pharmaceutical form: Nasal spray, solution

Dosage strength: 28 mg

Route(s) of administration: nasal

Marketing Authorisation Holder: Janssen-Cilag AG

Marketing Authorisation No.: 67103

Decision and Decision date: approved on 25 February 2020

Note:

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

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 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

AD	Antidepressant
ADA	Anti-drug antibodies
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC _{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
CL _{int}	Intrinsic clearance
C _{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DB	Double blind
DBP	Diastolic Blood Pressure
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IN	Intranasal
INN	International Nonproprietary Name
LoQ	List of Questions
MADRS	Montgomery-Asberg Depression Rating Scale
Max	Maximum
MAH	Marketing Authorisation Holder
MDD	Major Depressive Disorder
MDSI	Major depressive disorder with imminent risk for suicide
Min	Minimum
N/A	Not applicable
NMDAR	N-methyl-D-aspartate receptor
NO(A)EL	No Observed (Adverse) Effect Level
OATP	Organic anion transport polypeptide
OL	Open-label
PD	Pharmacodynamics
P-gp	P-glycoprotein
PSP	Pediatric Study Plan (US-FDA)
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
Pop PK	Population PK
RMP	Risk Management Plan
SAE	Serious adverse event
SBP	Systolic Blood Pressure
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TRD	Treatment-Resistant Depression

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status

The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)

The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

Spravato is indicated for treatment-resistant depression (Major Depressive Disorder in adults who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode).

2.2.2 Approved Indication

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 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).

2.2.3 Requested Dosage

Spravato must be co-administered with an oral antidepressant (AD). A treatment session consists of nasal administration of Spravato and post-administration observation under the supervision of a healthcare professional.

Usual dosage

Adults

The dosage recommendations for Spravato are shown in Table 1. Dose adjustments should be made based on efficacy and tolerability of the previous dose.

Table 1: Recommended Dosing for Spravato

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

* For patients ≥ 65 years Day 1 starting dose is 28 mg

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

After depressive symptoms improve, treatment is recommended for at least 6 months.

2.2.4 Approved Dosage

See information for healthcare professionals in the appendix

2.3 Regulatory History (Milestones)

Application	3 January 2019
Formal control completed	7 January 2019
List of Questions (LoQ)	11 March 2019
Answers to LoQ	1 July 2019
Predecision	20 August 2019
Answers to Predecision	21 November 2019
2 nd Predecision	10 December 2019
Answers to 2 nd Predecision	9 February 2020
Final Decision	25 February 2020
Decision	approval

2.4 Medical Context

Major depressive disorder (MDD) is one of the leading causes of disability worldwide, affecting about 300 million individuals globally including 40.2 million in Europe (WHO 2017). Treatment-resistant depression (TRD) manifests itself in about 30% of patients with MDD and up to 60% if TRD is defined as absence of remission (Geuden, The Journal of Clinical Psychiatry 62 Suppl 16, Suppl 16:26-31). MDD and TRD are coupled with functional impairment, poor quality of life, suicidal ideation and suicide attempts; the suicide risk is 30-fold above the risk in the general population; life expectancy in MDD is reduced by 10 years (Walker et al, JAMA 2015).

Definitions of TRD vary across regions, but agree on the following: "Depression may be considered resistant to treatment when at least two trials with antidepressants (ADs) from different pharmacologic classes (adequate in dose, duration, and compliance) fail to produce a significant clinical improvement" (APA Guidelines).

Up to 15 to 25% of cases of MDD result in chronification and involve the risk of developing additional mental health disorders such as anxiety or substance abuse; psychosomatic disorders, e.g. chronic fatigue syndrome or fibromyalgia, are other risks of long-term MDD/TRD. Suppression of brain neurogenesis, neuronal atrophy, cell death and hippocampal dysfunction were reported in several studies.

The WHO expects depression to become the leading economic burden of disease by 2030, with almost 50% of costs caused by TRD. The estimated yearly cost of depression in Switzerland is 8.3 billion euros (2013), with costs being directly related to disease severity; key cost drivers in TRD are workdays lost and disability insurance.

No pharmacological treatment options for TRD are approved in Switzerland or Europe so far. Some of the non-pharmacological treatment options for this condition like electroconvulsive therapy (ECT), magnetic resonance stimulation, deep vagal stimulation require hospitalisation in specific centres, are only applicable to selected patient populations, and the available evidence from randomised controlled trials (RCTs) is weak for most of these interventions.

Polypsychopharmacy, i.e. combining up to 2 to 3 ADs, neuroleptics, antiepileptics and benzodiazepines with long-term hospitalisation are often chosen as the "last resort" in TRD. These approaches involve the risk of complex, long-term mental and somatic adverse drug reactions, including metabolic, cardiovascular, neurological and gastrointestinal disorders, impaired cognition and occupational functioning, and emotional and social isolation; they rarely lead to substantial and long-lasting relief, however they may support patients in accepting the disorder, initiating psychotherapy and enduring their situation.

3 Quality Aspects

3.1 Drug Substance

INN: Esketamine hydrochloride
 Chemical name: (S)-2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride
 Molecular formula: C₁₃H₁₆ClNO.HCl
 Molecular mass: 274.2
 Molecular structure:



Physicochemical properties:

Esketamine hydrochloride is a white or almost white crystalline powder. It contains one stereogenic centre and is manufactured as a single stereoisomer. Only one crystalline form of esketamine hydrochloride is known (Form I). The compound is soluble in aqueous media.

Structure elucidation:

The structure of esketamine hydrochloride has been fully elucidated using several spectroscopic techniques such as mass spectroscopy, infrared spectroscopy and nuclear magnetic resonance spectroscopy. In addition, the crystal structure and the absolute configuration have been determined by single crystal X-ray diffraction.

Synthesis:

The drug substance is manufactured by a multi-step chemical synthesis with a final crystallisation. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification:

In order to ensure a consistent quality of esketamine hydrochloride, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines.

Stability:

The bulk drug substance is packaged in LDPE bags. A stability study was carried out according to the current guideline recommendations. Based on the results of this study, a satisfactory retest period was established.

3.2 Drug Product

Description and composition:

The drug product nasal spray is an aqueous solution of esketamine hydrochloride in water, at a concentration of 161.4mg/mL, corresponding to 140mg/mL of esketamine free base. The excipients are citric acid monohydrate, disodium edetate, sodium hydroxide and water for injection.

Pharmaceutical development:

The drug product was developed as a nasal spray. Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including a risk assessment for the attributes of the drug substance, excipients and the manufacturing process for potential impact on the critical quality attributes (CQAs) of the intended commercial drug product.

Manufacture:

The manufacturing process is described narratively and in sufficient detail, taking into account the pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.

Specification:

The drug product specification covers relevant physicochemical and spray performance characteristics. Identification, assay, purity, particulate matter, osmolality, fill volume, spray content uniformity, and droplet size distribution attributes are tested. They allow for proper control of the finished drug product. The control methods are validated according to ICH guidelines. Batch data show consistent quality of the drug product.

Container-Closure System:

The drug product solution is filled and stoppered into glass vials. The glass vials are assembled into the nasal spray device.

Stability:

Appropriate stability data have been generated following the relevant ICH guidelines. The data show good stability of the finished product and allow for an evidence-based assignment of the shelf life.

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

4 Nonclinical Aspects

The applicant submitted a comprehensive package of nonclinical studies with esketamine that was supplemented by nonclinical safety studies with ketamine and published literature data on (es)ketamine.

Pivotal safety pharmacology and toxicology studies with esketamine were conducted in compliance with GLP. The supplemental safety studies with ketamine were also conducted under GLP conditions. Bioanalytical validation studies were not available for all of these studies. This was considered not relevant for the evaluation since there was sufficient exposure of animals based on clinical signs.

Pharmacology

Published literature on ketamine suggests that inhibition of the N-methyl-D-aspartate receptor (NMDAR) plays a key role in the antidepressant mode of action. Based on the results of binding studies and functional assays, both esketamine and the enantiomer (R-)ketamine (arketamine) inhibit the NMDAR in a non-competitive manner, but esketamine has a slightly higher potency than arketamine. The esketamine-derived metabolite noresketamine (M10) also inhibited the NMDAR *in vitro*, with a similar potency than arketamine. Other main metabolites of esketamine (M4, M9, and M19) showed no antagonist activity towards the NMDAR *in vitro*.

The applicant did not submit *in vivo* nonclinical studies to support the proposed antidepressant activity of esketamine, but referred to published data for ketamine. Ketamine has shown antidepressant activity in clinical studies and also in various animal models of depression, including studies in mice and rats.

Based on the results of the secondary pharmacodynamics studies, there is low potential for binding of esketamine or its main metabolites to other receptors than NMDAR under the proposed (sub-anaesthetic) clinical treatment conditions. However, esketamine and its metabolites readily distribute to brain tissue and achieve high concentrations, particularly M4, which may be responsible for some of the central nervous system (CNS) side effects observed in the clinical studies.

Dedicated safety pharmacology studies with esketamine were conducted to evaluate effects on cardiovascular and respiratory function. Effects of esketamine on CNS function were studied in the chronic toxicity studies and in the pre- and postnatal development (PPND) study (see *Toxicology*). The IC₅₀ value for inhibition of the hERG channel was 214 µM, which is significantly (>330-fold) above the highest clinical C_{max, total} after intranasal instillation of 84 mg. *In vivo* in dogs, intravenous (IV) administration of 0.3-3 mg/kg esketamine led to dose-dependent, transient increases in heart rate and blood pressure and shortened QT and PQ interval. The respiration rate was slightly increased at 3 mg/kg. Increases in heart rate were also observed in repeated-dose toxicity studies in dogs with intranasal (IN) administration at clinically relevant exposure levels. Increased blood pressure and heart rate were common findings in the clinic.

Pharmacokinetics

Esketamine was rapidly absorbed following IN administration (T_{max} within 5-30 min) to rats and dogs. Across animal species (dog, rat, mouse, rabbit), (es)ketamine showed a high systemic clearance and a large volume of distribution, consistent with the pharmacokinetics (PK) in humans. Oral bioavailability of esketamine in dog was low (1.3%), as in humans.

In rats and mice, systemic exposure to esketamine and noresketamine was decreased following repeated administration compared to single administration. The AUC values of noresketamine were generally higher than those of esketamine. In dogs, no time-dependent effect on exposure was observed. The exposure to esketamine was greater than the exposure to noresketamine in this species. Neither in rats nor in dogs were any consistent sex-related differences in exposure observed. In mice, there was a tendency for higher systemic exposure in males than in females.

Ketamine is known to have a wide tissue distribution and to cross the placenta. In a study with esketamine on brain distribution in male rats following oral administration of 80 mg/kg, esketamine and its metabolites M4, M9, M10 (noresketamine), and M19 were detected in brain, with tissue/plasma ratios >1 for esketamine (1.8), M4 (1.2), and M19 (3.3-3.9). Highest tissue

concentrations were determined for M4. Brain levels decreased with decreasing plasma concentrations.

It is known that ketamine is not highly bound to plasma proteins in rats, dogs, and humans. The percentages unbound for esketamine determined in plasma from patients were between 49% and 65%, consistent with literature values for ketamine.

Consistent with published literature, metabolite M9 (5,6-dehydronoresketamine) showed binding to fresh mouse and human whole blood *in vitro*. However, the clinical relevance of this finding is considered to be low since blood to plasma ratios for total radioactivity in the human mass balance study with ¹⁴C-esketamine were <1, i.e. there was no extensive binding of esketamine and metabolites (except M9) to components of whole blood.

Based on the results of *in vitro* studies in liver microsomes and S9 fractions and on the determination of selected esketamine-derived metabolites in plasma samples from *in vivo* studies, the metabolic pathways of esketamine in rats, dogs, and mice are comparable to those in humans. Noresketamine is the only human metabolite with plasma exposure >10% of AUC; exposure to this metabolite was above the clinical exposure in toxicity studies with rats and mice, i.e. its safety profile was sufficiently characterised.

Based on literature data for ketamine, the major excretion route is via urine in rats, dogs, and humans. Only low levels of ³H-esketamine were found in rat urine following IV administration, indicating that elimination of esketamine is mainly via metabolism.

Toxicology

Rats and dogs were selected for nonclinical safety evaluation with esketamine based on similarities of metabolic pathways to those in humans and published safety data on (es)ketamine in these species. Mice were used as a second species for carcinogenicity assessment. The clinical administration route (IN) was generally used in the toxicity studies, except for the studies in mice and juvenile rats, where subcutaneous (SC) administration was used to maximise exposure. The IN administration was up to the maximum feasible dose. There was daily treatment of animals in the pivotal toxicity studies, which is above the proposed clinical dosing regimen. Species selection, administration routes, and duration of toxicity studies were considered adequate.

Repeated-dose toxicity studies with esketamine were conducted up to 6 months in rats (doses 0.9, 3, and 9 mg/day) and up to 9 months in dogs (doses 24, 48, and 72 mg/day). In both species, treatment dose-dependently induced transient clinical signs related to exaggerated pharmacology. The most common findings were salivation, decreased or increased activity, ataxia, and uncoordinated movements. Transient CNS-related side effects were also common findings in the clinical trials. There was a decreased occurrence of clinical signs with repeated dosing in rats and dogs, indicating development of tolerance. Testing of neurobehavioural function in dogs and of learning and memory in rats in the chronic toxicity studies did not reveal any adverse effects of long-term esketamine treatment on cognitive function. The studies did not identify a systemic target organ or any relevant changes in clinical pathology parameters. In both species, there were some microscopic findings indicative of mild local effects in the nasal cavity in either the 3-month and/or the 6-/9-month toxicity studies. Some local effects in the nasal cavity were also occasionally reported in clinical studies. The highest doses in the repeated-dose studies (9 mg/day in rats and 72 mg/day in dogs) were associated with systemic esketamine exposure slightly above or within clinical exposure, so there is no safety margin. However, there were also no findings of special concern, i.e. observations that were not comparable with findings in the clinical studies.

Esketamine was not mutagenic with or without metabolic activation in the bacterial reverse mutation test, but tested positive for genotoxicity in an *in vitro* non-GLP micronucleus assay in the presence of metabolic activation. However, esketamine did not reveal clastogenic potential in two *in vivo* studies in rats (comet assay in liver cells and bone marrow micronucleus test). The esketamine and noresketamine plasma exposures in the animals were above clinical exposure, and the exposure in the liver tissue was adequate. In an *in vitro* study with simulated gastric fluid, there was no formation of N-nitroso-esketamine in the presence of nitrite and acidic conditions, indicating a low risk for the formation of this genotoxic substance after swallowing of esketamine.

In carcinogenicity studies in rats (IN administration) and transgenic (Tg.rasH2) mice (SC administration), no esketamine-related pre-neoplastic or neoplastic lesions were observed. Exposure of the animals was below (rat) or 4- to 7-fold above (mouse) the clinical exposure in terms of AUC. In a fertility and early embryonic development study in rats with IN administration of esketamine up to 9 mg/day, no adverse effects on fertility or reproductive capacity were observed. Increased incidence of irregular oestrus cycles at 9 mg/day and increased pre-coital length at ≥ 3 mg/day were possibly related to suppression of sex hormones/ovulation, which are known effects of ketamine in animal species. However, all females in the study mated and got pregnant.

The applicant did not submit studies on embryo-foetal development (EFD) with esketamine. Instead, two EFD studies conducted with the racemate ketamine administered via IN route to rats and rabbits were submitted to supplement the study package on reproduction toxicity. In the rat EFD study with ketamine, no effects on embryo-foetal viability or development were observed up to doses that were associated with maternal toxicity and an exposure about 12-fold the clinical exposure in terms of AUC. In the rabbit EFD study with ketamine, there were decreased foetal weights and skeletal malformations, such as short tail and cervical vertebral anomaly, at dose levels associated with maternal toxicity (≥ 30 mg/kg/day). At the NOEL for developmental toxicity (10 mg/kg/day), ketamine plasma exposure was significantly below the clinical exposure. Ketamine crosses the placenta and there are published data showing neurotoxic effects of ketamine in foetuses and pups from different animal species, including monkeys. Esketamine should therefore not be used during pregnancy, and women of childbearing potential should be advised to use contraception during treatment.

In the PPND study with esketamine in rats with IN doses up to 9 mg/day, no adverse effects on development or reproductive performance of F1 offspring were observed. However, since esketamine is known to be excreted in milk, it should not be used during lactation.

In several neurotoxicity studies with esketamine in rats, including a study in juvenile animals requested in the PIP, no neurohistopathological changes were observed. The positive control MK-801, another NMDAR antagonist, induced histological alterations (neuronal vacuolation and/or necrosis) in the brain. Esketamine exposure of the animals in these studies was up 59-fold the clinical C_{max} and up to 86-fold the clinical AUC.

The description and evaluation of the nonclinical data in the RMP are acceptable. Cardiovascular effects (increased blood pressure) and drug abuse potential are identified risks.

Impurities in drug substance and drug product are adequately controlled. There are no new excipients in the drug product.

Based on the ERA, esketamine and its metabolites will not represent a risk to the environment following the prescribed use of the drug product.

Nonclinical Conclusions

The pharmacology, pharmacokinetics, and toxicological profile of esketamine were sufficiently characterised by literature data and supplemental nonclinical studies. The nonclinical safety programme was considered adequate for the proposed chronic use of esketamine. Most of the effects observed in animal species were related to the pharmacological activity of esketamine and were comparable to findings in the clinical studies. Safety-relevant nonclinical data are included in the information for healthcare professionals. From the preclinical standpoint, the application is approvable.

5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

ADME

Absorption

After nasal administration, esketamine was rapidly absorbed (t_{max} 0.37 to 0.83 h). The absolute bioavailability of esketamine after intranasal administration was 48.5%. After oral administration as solution, it was only 14%.

Dose Proportionality

After nasal administration of single doses between 28 mg to 84 mg, there was a less than dose proportional increase of esketamine exposure between 28 mg and 56 mg and a dose proportional increase between 56 mg and 84 mg.

Pharmacokinetics after multiple Dosing

After nasal twice weekly administration of 84 mg esketamine for 2 weeks, no accumulation of esketamine or noresketamine was observed.

Distribution

The free fraction of both esketamine and noresketamine in plasma was about 60% and not affected by mild to moderate hepatic or mild to severe renal impairment.

After intravenous administration, the volume of distribution at steady state (V_{dss}) of esketamine was 709 L.

Metabolism

In vitro Data

Esketamine was mainly metabolised by CYP2B6 (about 60% of CL_{int}) and CYP3A4 (about 35 to 40% of CL_{int}). Noresketamine was further metabolised by CYP2A6, 2B6 and 3A4.

Clinical Data

N-demethylation of esketamine to noresketamine was the primary metabolic pathway after oral and IV dosing of esketamine.

Noresketamine was subsequently metabolised to numerous downstream metabolites via hydroxylation at the cyclohexanone ring, hydroxylamine formation, keto reduction, dehydrogenation and N-glucuronidation.

After administration of a ^{14}C -labelled esketamine dose, the main metabolite in plasma was noresketamine, accounting for 14.3% (oral administration) and 12.2% (intravenous administration) of the total radioactivity in plasma. The parent compound esketamine accounted for 0.61% and 5.75% of the total radioactivity in plasma after oral and intravenous administration, respectively. Based on AUC_{0-96h} , 75.3% and 68.8% of the total radioactivity in plasma was assigned to esketamine and its metabolites after oral and intravenous administration, respectively.

The findings after nasal administration were similar.

After intranasal administration of “cold” drug, the noresketamine/esketamine ratio for AUC_{inf} in healthy subjects was between 1.67 and 4.75.

Like esketamine, noresketamine is an N-methyl-D-aspartate receptor antagonist. However, noresketamine is expected to contribute minimally to the antidepressant activity of nasal esketamine based on preclinical experiments that demonstrated the metabolite has 3.3- to 5.7-fold lower affinity

for the N-methyl-D-aspartate receptor and 5- to 6-fold lower brain distribution, relative to the parent drug.

Very low levels of unchanged drug (0.3% and 0.8% of the dose after oral and intravenous administration, respectively) were observed in urine. In urine, 80.5% and 67.4% of the administered dose was assigned to metabolites or esketamine after oral and intravenous administration, respectively, of a ¹⁴C-tracer dose.

Because of the low amount of radioactivity excreted in faeces after oral or intravenous administration, no metabolite profiling was done in this matrix.

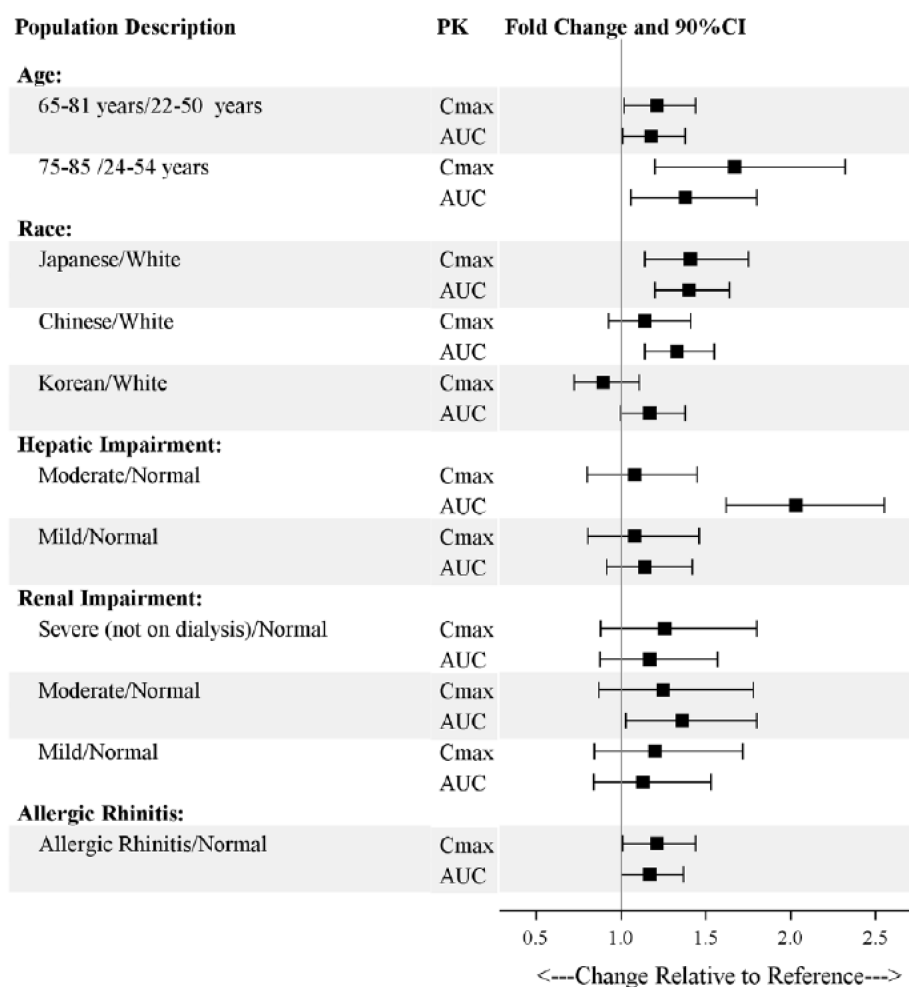
Elimination

After nasal administration, the half-life of both esketamine and noresketamine was about 8 h. After intravenous administration, esketamine CL was 88.8 L/h.

After oral administration of a ¹⁴C-labelled esketamine dose, 86.3% and 1.7% of the radioactivity was excreted in urine and faeces, respectively. After intravenous administration of a ¹⁴C-labelled esketamine dose, 78.4% and 1.81% of the radioactivity was excreted in urine and faeces, respectively.

Special Populations

An overview of the changes in total esketamine exposure in special populations evaluated in dedicated studies is depicted below:



Dosing recommendations:

No dose adjustments are required for patients with mild or moderate **hepatic impairment**. Longer post-dose monitoring may be required in patients with moderate hepatic impairment. No data are available on patients with severe hepatic impairment. The treatment with esketamine is not recommended in these patients.

No dose adjustments are required for patients with mild to severe **renal impairment**. No data on dialysis patients are available.

Starting dose 28 mg on Day 1 in **elderly patients** (≥ 65 years), increase dose in steps of 28 mg to 56 mg or 84 mg depending on tolerability and efficacy

The dosing recommendations for patients with hepatic or renal impairment were primarily based on pharmacokinetic data, while the recommendations for elderly patients were based on clinical data.

The **CYP2B6 phenotype** had no apparent impact on esketamine or noresketamine exposure.

The impact of health status (healthy subject or TRD patient), **gender, age, body weight, race, hepatic function and renal function** on the pharmacokinetics of esketamine and noresketamine was also investigated in a pop PK analysis, which included eight Phase 1 studies, two Phase 2 studies and three Phase 3 studies. The semi-mechanistic model described the esketamine and noresketamine plasma concentrations after intravenous, oral or intranasal administration quite well. The results of the pop PK analysis and the respective Phase 1 studies were consistent, i.e. none of the investigated covariates had a large impact on esketamine or noresketamine exposure. There were also no pharmacokinetic differences between **healthy subjects and TRD patients**.

Interactions

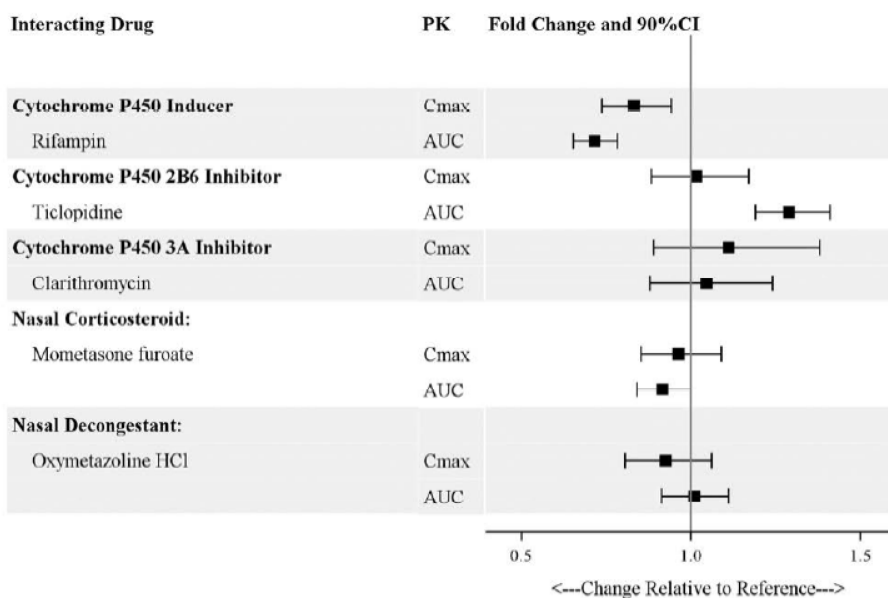
Impact of other Drugs on Esketamine

As mentioned above, esketamine was mainly metabolised by CYP2B6 and CYP3A4. Noresketamine was further metabolised by CYP2A6, 2B6 and 3A4.

Consequently, the impact of a strong CYP inducer (rifampicin), a strong CYP3A4 inhibitor (clarithromycin) and a CYP2B6 inhibitor (ticlopidine) on the pharmacokinetics of esketamine was investigated in clinical interaction studies.

Furthermore, the potential impact of other common nasally administered compounds (corticosteroid and decongestant) on the absorption of nasally administered esketamine was investigated.

A summary of the changes in esketamine exposure after administration of perpetrators is depicted below:



None of the co-administered compounds had a major impact on esketamine exposure.

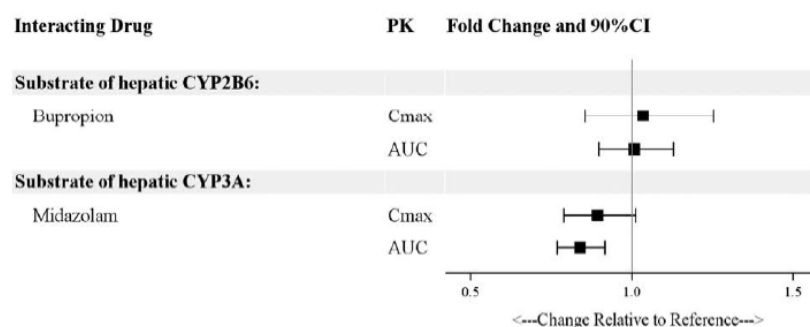
Neither esketamine nor noresketamine were substrates for P-gp, BCRP, OATP1B1 or OATP1B3 *in vitro*. Noresketamine was not a substrate for OCT2, OAT1, OAT3 or OCT1 *in vitro*. Therefore, no *in vivo* interactions between esketamine and inhibitors of these transporters are to be expected.

Impact of Esketamine on other Drugs

The *in vitro* studies to assess the interaction potential of esketamine and its major metabolites as perpetrators were conducted according to current regulatory guidelines with regard to the CYP/transporters and esketamine/metabolite concentrations investigated. In addition, the potential inhibition of UGT1A1 and 2B7 by esketamine and/or its major metabolites was investigated.

These *in vitro* data indicated a potential to interact *in vivo* with CYP2B6 and 3A4 (inhibition and/or induction) and OCT2 (inhibition) for esketamine and/or its metabolites.

Based on the results of the *in vitro* studies, clinical interaction studies were conducted with bupropion (CYP2B6 substrate) and midazolam (CYP3A4 substrate). The results are summarised below:



Esketamine had no clinically relevant impact on the exposure of both CYP substrates. The potential impact of esketamine on OCT2 substrates was not further investigated, but it is appropriately addressed in the product information.

No specific dosing recommendations regarding pharmacokinetic drug-drug interactions are required for esketamine.

Pharmacodynamics

Secondary Pharmacology (Safety)

Esketamine did not cause a QTc prolongation at therapeutic and suprathreshold exposure (2.9-fold higher C_{max}) in a dedicated tQT study.

As esketamine causes a concentration-dependent increase in heart rate, the QT correction used in the initial evaluation was not sufficient, resulting in QTc shortening in the original analysis. The missing effect of esketamine on QTc was confirmed by the application of an appropriate ANOVA model.

Esketamine leads to a significant deterioration of cognitive function, measured with a subset of the Cogstate® computerised test battery at 40 minutes post dose compared to placebo. At time points ≥ 2 h post dose, no statistically significant differences between esketamine and placebo were detected. However, esketamine increased sleepiness for up to 4 h post dose.

The ability to drive a car was investigated at different post-esketamine dose intervals in two clinical pharmacodynamic placebo- and active-controlled studies employing on-road driving tests with the standard deviation from lateral position (SLDP) as the primary endpoint

The first study was done in healthy subjects, with the driving test performed 8 h after administration of a single 84 mg dose of esketamine and mirtazapine as active control. In contrast to mirtazapine, esketamine was not inferior to placebo. However, two subjects discontinued the driving tests due to adverse events (somnolence, dizziness etc.).

The second study was done in patients with major depressive disorders. It included a single-dose part with the driving test performed on the next day post dose (at 18 ± 2 h after intranasal administration on Day 1) and a multiple-dose part with the driving test performed 6 h post dose on Days 11, 18 and 25. In both parts of the study, the results for esketamine were not statistically significantly different from placebo. In the single-dose part, ethanol was used as active control and produced the expected effect on driving performance.

The recommendations in the product information regarding the operation of machines or driving during esketamine treatment are based on the study in patients described above.

The abuse potential of nasal esketamine was investigated in recreational drug users. The primary endpoint was “drug liking at the moment” assessed by a visual analogue scale. There was a statistically significant difference between nasal esketamine and placebo, i.e. esketamine achieved a higher score.

Pharmacodynamic Interactions

Though pharmacodynamics interactions are likely to occur, no formal pharmacodynamics interaction studies were conducted. The risk of pharmacodynamic interactions with CNS depressants, psychostimulants and MAO inhibitors is appropriately addressed in the product information.

5.2 Dose Finding and Dose Recommendation

Dose finding

Three phase 2 studies were submitted to assess the optimum dose. The initial phase 2 study TRD2001 assessed the efficacy and safety of two doses of IV esketamine in TRD compared to placebo; it was a proof of concept study and provided the PK model for the development of a nasal spray formulation. Results showed quick response with significant effects after two days. The phase 2 study TRD2002 with IV ketamine assessed two different dosing frequencies. Results of this study suggest that biweekly administration of ketamine was similarly effective compared to administration three times a week. The third dose-finding study TRD2003 was done to support the decision on intranasal esketamine dosages to be included in phase 3 studies. Twice a week doses of 28, 56 or 84 mg esketamine were given compared to placebo. The results show that higher doses had better effects on the reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) score, suggesting a dose-response relationship for esketamine.

Dose Recommendation

The superior results for the 84 mg dose in the phase 2 study TRD2003 were not confirmed in the fixed-dose phase 3 trial TRD 3001 (see below). Therefore, the 56 mg dose is recommended. For some patients the 84 mg dose could still be a better option.

5.3 Efficacy

Four randomised controlled studies relevant for efficacy evaluation were submitted: the two pivotal short-term randomised controlled trials TRD3001 and TRD3002 in adult patients with TRD, the short-term study in the elderly TRD3005 and the controlled long-term study with randomised withdrawal design TRD3003. In the pivotal studies, esketamine was always given twice a week on top of a daily administered oral antidepressant. The same schedule was adopted in the placebo groups, with a daily oral antidepressant combined with intranasal placebo twice a week. Over all phase 3 trials, most patients (around 80%) were white, with low percentages of black patients or patients of other races. Around two-thirds of subjects (60 to 70% in the four pivotal controlled studies) were women, which is consistent with the gender distribution for the MDD population reported from epidemiological data.

Design of pivotal short-term studies

The two pivotal short-term studies TRD3001 and TRD3002 included patients from 18 to 64 years of age with treatment-resistant depression, which was defined as nonresponse to at least two different oral antidepressants, prescribed in adequate dosages for an adequate duration (6 weeks).

Nonresponse to one antidepressant had to be demonstrated prospectively prior to randomisation, and the second nonresponse could have been confirmed during the screening phase right before study start.

For all patients, a MADRS score >28 on weeks 2 and 4 during screening had to be documented, which ensured the enrolment of TRD subjects with moderate-severe symptoms. Exclusion criteria and the list of disallowed medications (incl. warfarin, the oral anticoagulants rivaroxaban, dabigatran etc., anticonvulsants, antipsychotics, and CYP3A4 inducers) were extensive and led to a highly selected patient population. Relevant somatic exclusion criteria were e.g. coronary artery disease with myocardial infarction, unstable angina or revascularisation during the past 12 months, clinically relevant ECG changes, history of uncontrolled hypertension defined as systolic blood pressure / diastolic blood pressure (SBP/DBP) > 140/90 mmHg (SBP/DBP >150/90 in the elderly study TRD3005).

The pivotal short term studies had three phases: a 4-week screening/prospective observational phase, during which response to the current oral antidepressant was assessed, a 4-week randomised controlled treatment phase, and a 24-week follow-up phase, which aimed to investigate esketamine safety, tolerability and potential withdrawal symptoms. At the start of the randomised controlled treatment phase, the current antidepressant was discontinued and replaced by escitalopram, sertraline, duloxetine or venlafaxine, in combination with intranasal esketamine or placebo. Esketamine or placebo were administered twice weekly and the concomitant antidepressants every day. In study TRD3001, fixed doses of 56 mg and 84 mg esketamine were investigated, whereas in

TRD3002 flexible doses of 56 mg or 84 mg esketamine were chosen based on symptom severity and the investigator's decision.

The primary efficacy outcome was the change vs. baseline vs. comparator group in the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS), which is a validated and accepted rating score in depression. Ratings were performed by independent remote raters. Key secondary efficacy outcomes included onset of clinical response by Day 2 (MADRS), Patient Health Questionnaire – 9-Item, Sheehan Disability Scale (SDS), Clinical Global Impression of Severity (CGI-S), remission (MADRS score <12), response (MADRS score reduction >50%).

In study TRD3001, 702 patients were screened, 345 were enrolled, with around 115 patients in each treatment group. Mean age of enrolled subjects was 46.3 years. The majority were female (70.5%) and white (76.6%). Mean MADRS score was 31.4. In TRD3002, 435 patients were screened and 227 enrolled, with around 110 patients in each treatment group. Treatment groups in both studies were similar with respect to baseline characteristics. Mean age was 45.7 years and most of the subjects were female (61.9%) and white (93.3%). The mean baseline MADRS total score corresponded to severe depression with 37.1. The elderly study TRD3005 had a similar design to TRD3001 and TRD3002, but included patients with TRD aged 65 years and older and had flexible dosing with 28, 56 and 84 mg esketamine plus oral antidepressant.

Efficacy results

Study TRD3001 did not meet its primary endpoint, since the esketamine 84 mg (plus oral antidepressant) separated from placebo (plus oral antidepressant) by only 2.0 points on MADRS, which was not statistically significant, and the predefined testing sequence stopped. The esketamine 56 mg dose performed better numerically, with -4.1 points on MADRS vs. placebo vs. baseline, but this was not a formal efficacy evaluation. In study TRD3002, flexible doses of 56 mg and 84 mg esketamine reached a statistically significant difference of 4.0 points on MADRS vs. the placebo group vs. baseline at 4 weeks of treatment.

Secondary endpoint analyses for remission and response led to the following results: In study TRD3001, 53% of patients in the 84 mg group had a response at 4 weeks, compared to 54% in the 56 mg group and 39% in the placebo group. Remission rates were 36%, 39% and 31% for esketamine 84 mg, 56 and placebo. In TRD3002, 69% of the esketamine-treated patients had a response compared to 52% in the placebo group. In the esketamine group, 52% had a remission compared to 31% in the placebo group. For most other secondary endpoints, at least numerical advantages for the esketamine groups were documented. In the elderly study TRD3005, the primary endpoint analysis at 4 weeks of treatment showed a numerical difference of 3.6 points in favour of the esketamine group vs. placebo, but statistical significance was not reached.

In addition to the short-term studies, the long-term study TRD3003 investigated esketamine vs. placebo in patients with stable remission or stable response who had finished the short-term studies, or who had entered the study directly. The randomised withdrawal design had four phases with a 4-week screening phase, 4-week open-label esketamine treatment phase, 12-week optimisation phase, and a variable double-blind randomised withdrawal maintenance phase. 297 patients were assigned to the maintenance phase. The primary endpoint was met, with a statistically significant difference in time to relapse in favour of the esketamine group, and a hazard ratio of 0.49, which meant that it was 51% less likely for the esketamine group patients to experience relapse. After three months of the randomised controlled study phase, there were fewer than 100 patients combined in both arms, which weakens the strength of evidence for the long-term treatment.

Conclusion on efficacy

Although not all primary endpoints had been reached with statistically significant results, the effects shown for intranasal esketamine in the TRD population can be regarded as clinically relevant. The treatment differences that were documented for intranasal esketamine (plus oral antidepressant) versus placebo (plus oral antidepressant) in the pivotal controlled randomised studies in the primary endpoint analyses (MADRS) were at least as large as the effects of marketed antidepressants that were used in patients with inadequate response to previous antidepressant therapy.

More details about efficacy results are displayed in the approved Information for Healthcare Professionals.

5.4 Safety

Exposure

Overall, safety data for intranasal esketamine are available for 2,283 subjects, who received at least one dose of esketamine nasal spray in completed phase 1, phase 2 and phase 3 clinical studies, including patients with treatment-resistant depression (TRD population) and patients with major depression and imminent risk for suicide (MDSI population). The primary assessment of clinical safety for this application is based on the TRD population of 6 completed phase 2 and 3 studies, which enrolled 1,708 subjects. Of the esketamine-treated subjects who completed phase 3 studies in TRD (n=1,601), 479 (29.9%) had at least 6 months, and 178 (11.1%) at least 12 months of treatment exposure. Of the subjects treated with esketamine in phase 3 studies, 194 were 65 years of age and older. Of these 60 (35.5%) had at least 6 months of treatment exposure and 23 (13.6%) were treated for at least 12 months. Across the phase 2 & 3 TRD studies, combined cumulative exposure to esketamine was 611 patient-years.

Adverse events (AEs)

In general it should be noted that, concomitantly to intranasal treatment initiation with esketamine and intranasal placebo, an oral antidepressant was newly initiated in both groups.

The study protocols recommended taking the oral antidepressant at least three hours after the intranasal study drug, in order to minimise the risk of confounding AEs related to intranasal or oral medication. Based on the experience from phases 1 and 2, it was expected that most AEs associated with esketamine would be transient, occur shortly after dosing and resolve within two hours.

Most frequent treatment emergent adverse events (TEAEs), reported in at least 10% of subjects, treated with esketamine were: nausea, dissociation, dizziness, vertigo, headache, dysgeusia, sedation, hypoaesthesia, paraesthesia, and oral hypoaesthesia. There is no conclusive evidence of a dose-related effect with regard to the incidence of TEAEs, with the exception of dissociation. The distribution of AEs was similar between age groups (except acute hypertension). Pooled data for 1,709 patients, treated with esketamine in double-blind and open-label phase 3 studies and 486 treated with placebo showed the following incidence of most common AEs:

TEAE in completed phase 3 studies (OL and DB)	All esketamine + oral AD (n=1709)	Placebo + oral AD (n=486)
Dissociation	690 (40.4%)	30 (6.2%)
Dizziness	628 (36.7%)	33 (6.8%)
Sedation	434 (25.4%)	35 (7.2%)
Nausea	458 (26.8%)	28 (5.8%)
Headache	410 (24.0%)	60 (12.3%)
Vertigo	303 (17.7%)	16 (3.3%)
Dysgeusia	293 (17.1%)	54 (11.1%)
Blood pressure increase	220 (12.9%)	19 (3.9%)
Hypoaesthesia	285 (16.7%)	7 (1.4%)
Vomiting	177 (10.4%)	6 (1.2%)
Lethargy	148 (8.7%)	21 (4.3%)

Death

As per the cut-off date, 4 March 2018, four deaths were reported in the six completed phase 2 and 3 studies, plus one death in an ongoing long-term maintenance study. Three deaths were caused by suicide, two of which occurred on day 12 and day 20 after the last esketamine dose, and the third four days after the last dose. One death was caused following a motorcycle accident, 28 hours after the patient's last dose of esketamine. Another death occurred in a 60-year old male with a history of hypertension and obesity, who died suddenly from acute cardiac and respiratory failure, five days

after the last esketamine dose and on day 113 of treatment with esketamine. In each of the five cases, the investigators considered death to be unrelated to the esketamine. No deaths were recorded in patients treated with placebo. The death rate in the assessed phase 2 and 3 esketamine studies was 0.2% (4/1.708). Even though the extent to which different studies are comparable can be called into question, this rate corresponds to published reports in MDD populations.

Serious adverse events (SAEs)

In the pooled analysis of the short-term double-blind studies TRD3001 and TRD3002, occurrence of serious AEs in subjects treated with esketamine, was <1% and similar to the placebo group: 0.9% (vs. 0.5% for oral antidepressant + placebo). A higher SAE rate, albeit similar to that for placebo, occurred in the short-term study in elderly patients (TRD3005): 4.2% (vs 3.1% for oral antidepressant + placebo). SAEs, reported in pooled short-term studies TRD3001 and TRD3002, occurred in three patients treated with esketamine (depression, headache, road traffic accident with subsequent death). In TRD3005 (study in the elderly) in three cases with esketamine (anxiety disorder, blood pressure increase, hip fracture) and two with placebo (feeling of despair and gait disturbance, dizziness). SAEs occurred in 17 subjects treated with esketamine in the long-term relapse prevention study and included depression, MDD, anxiety, disorientation, suicidal ideation, and panic attack.

Adverse events of special interest

Dissociation

Dissociation was the most common individual TEAE in esketamine-treated subjects in phase 2 and 3 studies. The psychological effects of dissociative and perceptual changes included distortion of time and space and illusions, derealisation and depersonalisation. Dissociative symptoms started shortly after dosing, peaked by 40 minutes postdose and typically resolved after 1.5 to 2 hours. Dissociative or perceptual changes resolved on the same day without treatment.

Dissociative symptoms were assessed using the Clinician Administered Dissociative States Scale score (CADSS). The score ranges from 0 to 92, and a higher score means a more severe condition. Scores between 0 and 4 are considered to be in the normal range. The incidence of severe dissociation was reported as less than 4% across studies, and dissociation was not considered serious for the subjects and as such reported as a mild or moderate TEAE. Although the highest CADSS scores were observed at the start of treatment, the dissociative effects decreased only partially with repeat administration; no continued decrease in CADSS was observed in long-term studies.

In study TRD3001 the average increase in CADSS was greater with 84 mg than 56 mg, indicating a dose effect. Increases in CADSS total scores were observed in a high proportion of subjects in the esketamine plus oral AD group in the short-term double-blind studies TRD3001, TRD3002, and TRD3005, ranging from 89.5% to 93.1% of subjects. Dissociative symptoms were also reported in placebo groups (28% to 40%). In the relapse-prevention study TRD3003, a CADSS score increase was observed in 85.1% of esketamine-treated subjects in the induction phase, 70.5% during the optimisation phase, and 77.5% during the maintenance phase (vs. 18.9% in the placebo group). In the open-label, long-term safety study TRD3004, an increase in CADSS total score was observed in 92.0% of esketamine-treated patients during the induction phase and 86.1% during the maintenance phase.

Blood pressure

Transient increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were observed in phase 2 and 3 studies shortly after esketamine dosing, with the maximum increase at 40 minutes (corresponding to the time of peak esketamine plasma levels). Mean values (but not in all patients) returned to values close to pre-treatment within 1.5 to 2 hours after administration. Across phase 3 studies/study phases, elevations of SBP to ≥ 180 mm Hg or DBP to ≥ 110 mm Hg (acute hypertension) were reported at rates of <5% (4.9%) with esketamine treatment for the pooled studies TRD3001/3002 (vs. 0.9% for total oral AD + placebo group) and all study phases of TRD3003 and TRD3004. In study TRD3005 in elderly patients >65 years, the percentage of acute hypertension was

11.1% compared to 6.2% for oral AD + placebo, and compared to 4.9% in younger adults (TRD3001, TRD3002).

Sedation

Across phase 2 and 3 studies, sedation was one of the most common effects and AEs associated with esketamine treatment. Sedation was measured objectively using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale and also evaluated based on TEAE reporting. Based on the MOAA/S, sedative effects were mild in most cases, with onset shortly after start of dosing and resolved by 1.5 hours postdose in most patients.

For abuse potential, driving performance and cognitive functioning, see Clinical Pharmacology.

Suicidality

Suicidal patients were excluded from the study programme. Suicidal ideation was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). A decrease from baseline to the endpoint in esketamine treatment groups was shown.

Most subjects reported no suicidal ideation or behaviour during any of the completed TRD studies. For subjects with no suicidal ideation or behaviour at baseline, the rates of reported suicidal ideation (based on C-SSRS) at least once during the treatment phase were similar for the esketamine and placebo groups in short-term DB studies.

Across all phase 3 studies, 10 cases of suicidal behaviour were reported, based on the C-SSRS (score of 6-10); all of these patients had a lifetime history of suicidal ideation or suicidal behaviour. Three cases of suicide were not related to the study drug, according to the investigator's judgement.

Conclusion on safety

The administration of esketamine is associated with important safety concerns, including psychiatric and somatic TEAEs. The incidence of TEAEs was high across phase 3 studies, e.g. according to pooled safety data (phase 3 and 2), dissociation occurred in up to 40% of patients, nausea in 27%, vomiting in 10%, dizziness in 37%, sedation in 25%, and blood pressure increase in 13%. The administration of esketamine requires a concise definition of measures to be taken prior, during and after dosing. Due to a high incidence of gastrointestinal AEs (vomiting, nausea), patients should not eat two hours, or drink 30 minutes, prior to administration of esketamine. A possible risk of aspiration (sedation + vomiting) should be considered. Furthermore, increases in blood pressure occurred on all dosing days in all subjects within 40 minutes after esketamine administration, and mean values returned to baseline values within 1.5 to 2 hours in up to 90% of patients, but not in all patients. Phase 3 studies excluded patients with SBP >140mmHg and DBP >90mmHg. Therefore, patients must be treated and remain under surveillance in a supervised setting that requires the presence of a trained physician for at least two hours post-dosing; this requirement includes the ability to monitor patients and readiness for resuscitation measures.

5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Given the burden of treatment-resistant depression on patients and health care systems, the effects of esketamine shown in the submitted study programme appear to offer a new option for rapid relief of depressive symptoms in patients who do not respond to available treatment options.

Favourable effects

The absolute bioavailability of esketamine after intranasal administration was considerably higher compared to oral administration. Between 56 mg and 84 mg, the esketamine exposure increased proportionally to the administered dose. No accumulation occurred after twice weekly administration. Apart from elderly patients (for clinical reasons), no dose adjustments are required for demographic factors. The interaction potential of intranasal esketamine as victim or perpetrator appears to be low. The tQT study was negative

Intranasal esketamine, administered in addition to an oral antidepressant, improved depressive symptoms in patients suffering from treatment-resistant depression, defined as MDD with non-response to at least two antidepressants in the current episode. Esketamine in combination with an oral antidepressant showed statistically significant effects within the first week; maximum efficacy was reached after a 4-week treatment period in phase 2 and 3 studies. Oral antidepressants may take up to several weeks before the full antidepressant efficacy is reached. Even though esketamine (combined with an oral antidepressant) did not meet the primary efficacy endpoint in two (TRD3001, TRD3005) out of four pivotal phase 3 studies, numerically favourable results over intranasal placebo plus oral antidepressant were reached in all studies. These differences, with an averaged decrease of 3 to 4 points on the MADRS scale, have been considered clinically relevant for other antidepressants in previous clinical registration studies, when administered as monotherapy (i.e. not on top of another AD) and compared to placebo (i.e. not an active comparator, as in esketamine phase 3 studies). Esketamine has shown to significantly reduce relapse rates in patients who achieved stable response or remission after 16 weeks of treatment (TRD3003). In phase 3, secondary endpoints indicate that esketamine's antidepressant effect was associated with an improvement in overall mental and physical health and performance status, incl. investigator and patient rating scales (SDS, PHQ-9, CGI-S).

Unfavourable effects

Esketamine leads to a significant impairment of cognition, including the ability to drive a car. Esketamine had a clear abuse potential in the corresponding phase 1 study. As the primary submission included only the driving ability study in healthy subjects and the single-dose part of the patient study, there were some discussions about the time interval required between esketamine dose and driving/operating machines. This point was resolved after submission of the multiple-dose part of the patient study.

Another uncertainty associated with the unfavourable effects of esketamine was the lack of pharmacodynamic interaction studies. This point was resolved by the addition of a corresponding paragraph to the product information.

The safety and tolerability profile of esketamine is associated with a high incidence of adverse drug reactions (ADRs) and TEAEs. The pattern of adverse reactions – including dissociation, depersonalisation, nausea, dizziness, sedation and blood pressure increase – carries the risk of psychiatric and/or somatic decompensation, such as paranoia, psychosis or hypertensive crisis, and thus requires the presence of a trained physician, with the ability to monitor patients and readiness for resuscitation measures. Due to its potential for abuse and dependence, esketamine will need to be distributed through well-controlled distribution channels and its use thoroughly documented.

Benefit-risk assessment

The pharmacokinetic profile of intranasally administered esketamine appears quite favourable. The remaining, mainly pharmacodynamic, issues are appropriately addressed in the product information. Based on the available clinical data on efficacy and safety, the benefits of esketamine can outweigh the mentioned risks, if distributed via well-controlled channels, used safely in appropriate, selected settings, in eligible patients and by trained physicians, following concise instructions pre- and postdosing and during treatment.

5.6 Approved Indication and Dosage

See Information for Healthcare Professionals in the Appendix.

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.

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.

▼ 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 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 an oral antidepressant. 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 is 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 in patients with treatment-resistant depression (TRD) (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

The dosage recommendations for Spravato 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

Induction Phase	Maintenance Phase
<u>Weeks 1-4 (two treatment sessions/week):</u>	<u>Weeks 5-8:</u>
Starting Day 1 dose*: 56 mg	56 mg or 84 mg once weekly
Subsequent doses: 56 mg or 84 mg	<u>From Week 9:</u>
	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.

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)

In case one or two treatment sessions are missed, the next session should be scheduled when the next dosage session was scheduled to occur based on current treatment frequency. If more than 2 treatment sessions have been missed, per clinical judgment, adjustment of the dose or frequency of Spravato may be clinically appropriate.

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

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.

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

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 antidepressant (n=72) was compared with intranasally applied placebo in combination with an oral

antidepressant (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).

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). This risk persists until significant remission occurs. As this does not usually occur during the first treatment weeks, therefore, patients should be closely monitored over a longer period of time and until recovery respectively. It is general clinical experience that the risk of suicide may increase in the early stages of treatment.

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. A meta-analysis of placebo-controlled clinical trials conducted on the use of 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.

Close supervision of patients and in particular those at high risk should accompany treatment especially in early treatment and following dose 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.

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) increase 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

Spravato was evaluated for safety in 1709 patients diagnosed with TRD (treatment-resistant depression) (patients with MDD and were non-responders to at least two oral antidepressants (ADs) treatments, of adequate dosage and duration, in the current major depressive 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

Common Undesirable effects

The most commonly observed undesirable effects in patients with TRD (treatment-resistant depression) treated with Spravato plus oral antidepressant (incidence $\geq 10\%$ and greater than oral antidepressant plus placebo nasal spray) were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoesthesia, blood pressure increased, anxiety 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 (TRD3005), the proportion of patients that received Spravato plus oral antidepressant 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 antidepressant 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 antidepressant and oral antidepressant 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%).

Listing of undesirable effects

Within the designated system organ classes, undesirable effects are listed under headings of frequency, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).^a

Psychiatric disorders

Very common: dissociation (40%)^b, anxiety (13%)^b.

Common: euphoric mood.

Nervous system disorders

Very common: dysgeusia (17%)^b, dizziness (37%)^b, sedation (25%)^b, hypoesthesia (17%)^b, headache (24%)^b.

Common: mental impairment, tremor, lethargy, dysarthria^b.

Ear and labyrinth disorders

Very common: vertigo (18%)^b.

Cardiac disorders

Common: tachycardia^b.

Respiratory, thoracic and mediastinal disorders

Common: nasal discomfort^b.

Gastrointestinal disorders

Very common: nausea (27%), vomiting (10%).

Common: dry mouth.

Uncommon: salivary hypersecretion.

Skin and subcutaneous tissue disorders

Common: hyperhidrosis.

Renal and urinary disorders

Common: pollakiuria^b.

General disorders and administration site conditions

Common: feeling abnormal, feeling drunk.

Investigations

Very Common: blood pressure increased (13%)^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; 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.

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; listlessness.

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; extrasystole.

Nasal discomfort includes: nasal discomfort; nasal crusting; nasal dryness; nasal pruritus.

Pollakiuria includes: pollakiuria; micturition disorder.

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 antidepressant did not influence any aspect of cognition studied in adult patients with treatment-resistant depression 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 treatment-resistant depression 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 antidepressant and those treated with oral antidepressant 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 EIViS 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 (AMPA) 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 treatment-resistant depression (TRD) who met DSM-5 criteria for major depressive disorder and were non-responders to at least two oral antidepressant 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 – Short-term studies

Spravato was evaluated in three Phase 3 short-term (4-week) randomised, double-blind, active-controlled studies in patients with treatment resistant depression. 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 \geq 65 years of age. Patients in TRD3001 and TRD3002 initiated treatment with Spravato 56 mg plus a newly initiated daily oral antidepressant (AD)

Product information for human medicinal products

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 antidepressants with nonresponse (i.e., failed antidepressants)			
Number of specific antidepressants, 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 antidepressant 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.

Product information for human medicinal products

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/A [Ⓞ]
	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

[Ⓞ] 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 antidepressant was consistently greater than for oral antidepressant 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 $\geq 50\%$ 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 antidepressant treatment was greater than for oral antidepressant 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 antidepressant were in remission at the end of the 4-week double-blind induction phase than for oral antidepressant plus placebo nasal spray (Table 5).

Product information for human medicinal products

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

Study No.	Treatment Group [§]	Number of Patients (%)					Re- mission Rate [‡]
		24 hours	Week 1	Week 2	Week 3	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 antidepressant AD=standard of care (newly initiated antidepressant)

[†] 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 antidepressant

Long-term data

Treatment-resistant depression – 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 antidepressant in a 4-week open-label induction phase. Patients who were responders [(MADRS total score reduction $\geq 50\%$ from baseline)], continued receiving treatment with Spravato plus oral antidepressant 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 ($\geq 50\%$ 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 antidepressant, 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 $\geq 50\%$ 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 antidepressant experienced a statistically significantly longer time to relapse of depressive symptoms than did patients in the control group (oral antidepressant 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 antidepressant plus placebo nasal spray) was 273 days, whereas the median was not estimable for Spravato plus oral antidepressant 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 antidepressant relative to control group (oral antidepressant 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 antidepressant group were on average 51% less likely to relapse than patients who switched to control group (oral antidepressant plus placebo nasal spray).

Stable Response

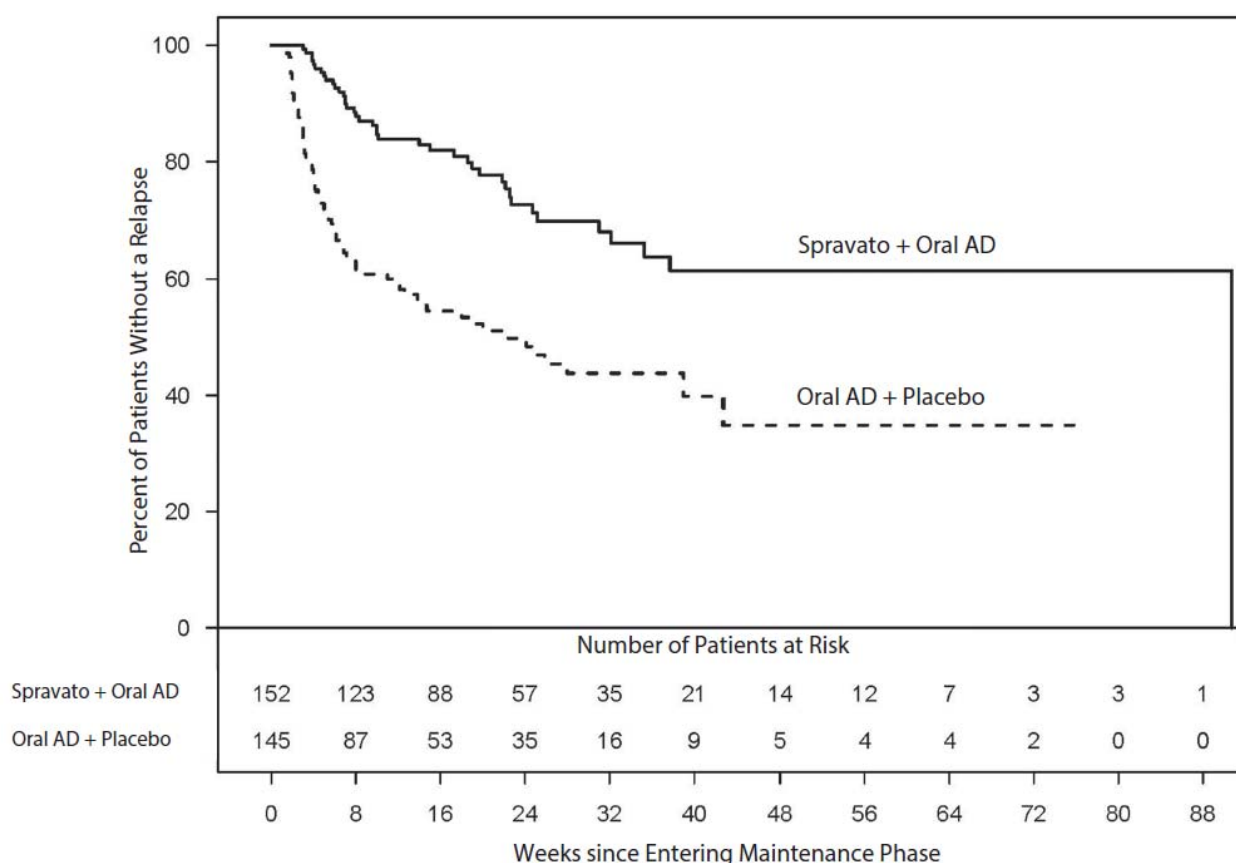
The efficacy results were also consistent for patients in stable response who continued treatment with Spravato plus an oral antidepressant; patients experienced a statistically significantly longer time to relapse of depressive symptoms than did patients in the control group (oral antidepressant plus 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 antidepressant relative to control group (oral antidepressant 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 antidepressant were on average 70% less likely to have a relapse than patients who switched to the control group (oral antidepressant 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 treatment-resistant depression

A Phase 2, doubly-randomized, double-blind, placebo-controlled, dose-ranging study, enrolled 108 adult patients with treatment-resistant depression. In addition to continued oral antidepressant 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 treatment-resistant depression, 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 treatment-resistant depression, the duration of the efficacy of the 28-mg dose was shorter.

Further information

Effect on driving

Two studies were conducted to assess the effects of Spravato on driving skills, one study in adult subjects with major depressive disorder 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 major depressive disorder 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 major depressive disorder (203 males and 361 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 564 patients with major depressive disorder. The total body weight of the subjects ranged from 39 to 170 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

February 2020

**Instructions for Use
Spravato**

(esketamine hydrochloride)

Nasal Spray

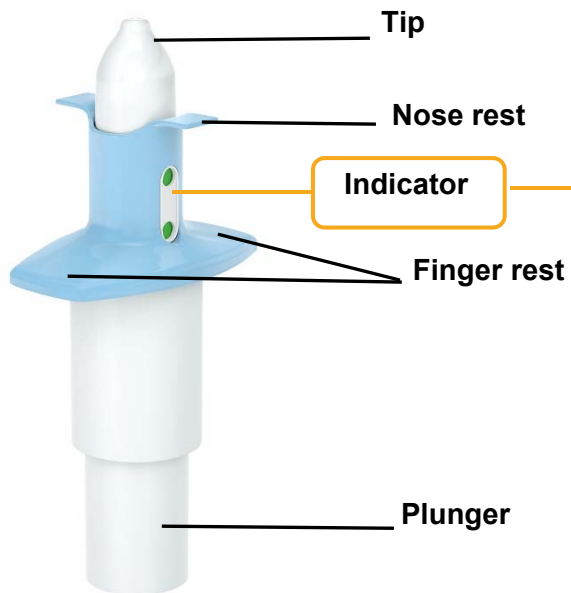


28 mg per device

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.

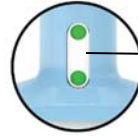
Nasal Spray



Indicator

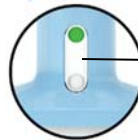
One device contains 2 sprays.
(1 spray for each nostril)

2 green dots (0 mg delivered)



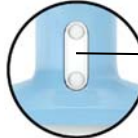
Device full

1 green dot



**One spray
delivered**

No green dots (28 mg delivered)



Device empty

Step 1 **Get ready**

Before first use only:



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



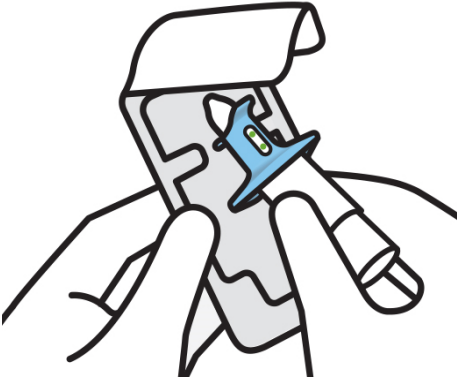
Confirm required
number of nasal spray devices.

28 mg = 1 device

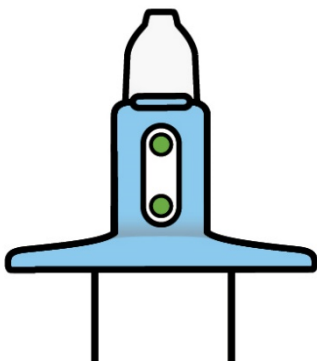
56 mg = 2 devices

84 mg = 3 devices

Step 2 Prepare device



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



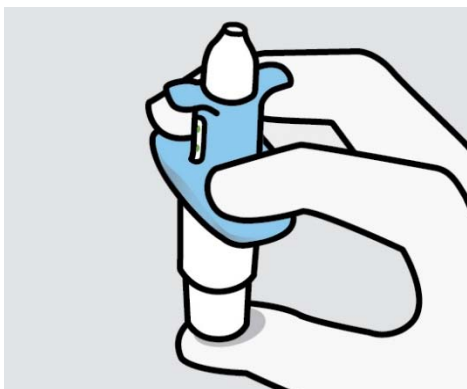
Do not prime device.

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.

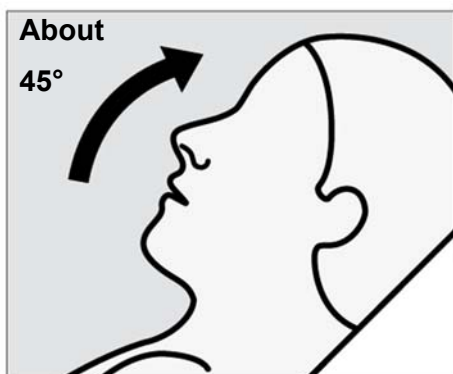
Step 3 Prepare patient



Patient should:

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

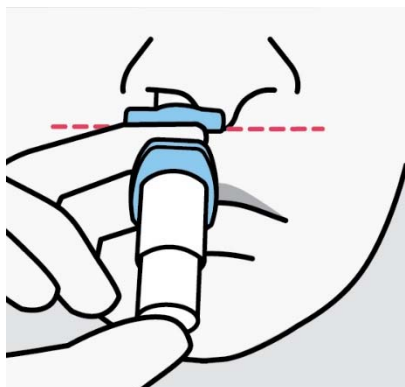
Do not press the plunger.



Patient should:

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

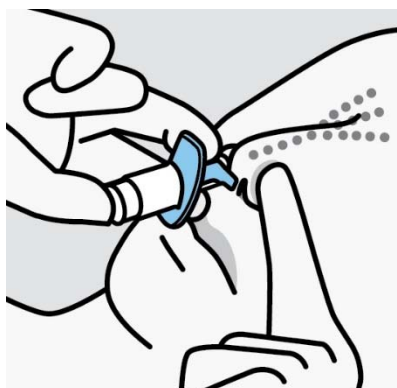
Step 4 Patient sprays once into each nostril



Patient should:

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

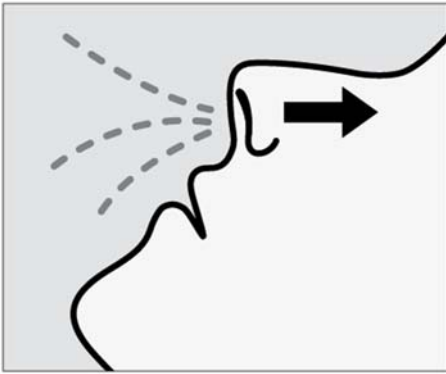
Nose rest should touch the **skin between the nostrils.**



Patient should:

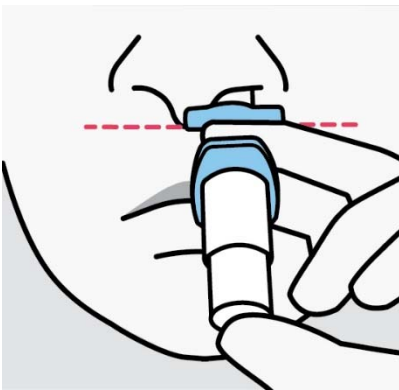
Close opposite nostril.

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.

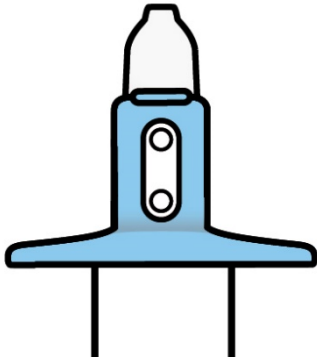


Patient should:

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:

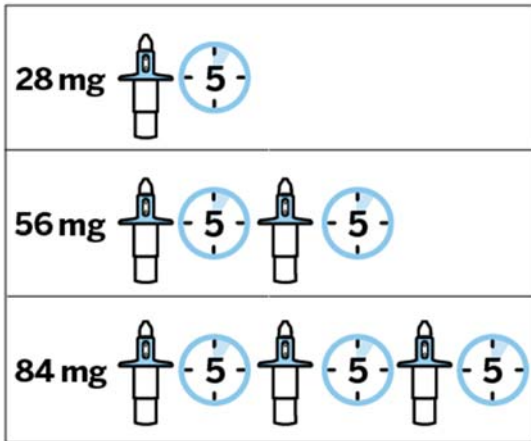
Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device**.



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.