▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

SPRAVATO®

esketamine hydrochloride

AUSTRALIAN PRODUCT INFORMATION

WARNING: During and after SPRAVATO administration patients must be monitored for blood pressure, sedation and dissociation until clinically stable. SPRAVATO is to be provided by the Healthcare Professional for patients to administer under their direct supervision. Patients should be instructed not to drive or operate machinery until next day (see 4.2 DOSE AND METHOD OF ADMINISTRATION). There is no safety and efficacy data for the use of SPRAVATO in patients under 18 years old.

1. NAME OF THE MEDICINE

esketamine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SPRAVATO is a single use nasal spray device containing an intranasal solution inside the device. The solution contains esketamine hydrochloride equivalent to esketamine 28mg/0.2mL as the active ingredient.

Each nasal spray device delivers two actuations, one into each nostril containing a total of 32.3 mg of esketamine hydrochloride (equivalent to 28 mg of esketamine).

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Nasal spray, solution.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SPRAVATO is indicated for treatment resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current moderate to severe depressive episode).

SPRAVATO is to be initiated in conjunction with a newly initiated oral antidepressant.

4.2 DOSE AND METHOD OF ADMINISTRATION

SPRAVATO should be administered in conjunction with a newly initiated oral antidepressant (AD). During the phase III clinical program patients were assigned SNRI or SSRI as the new oral antidepressant (see section 5.1 Pharmacodynamic Properties, Clinical Trials).

SPRAVATO will be provided by the supervising healthcare professional for the patient to self-administer under their direct supervision. A treatment session consists of nasal administration of SPRAVATO and post administration observation under the supervision of a healthcare professional (see section 4.4 Special Warnings and Precautions for use).

Method of administration

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

Blood Pressure Assessment Before and After Treatment

Assess blood pressure prior to dosing with SPRAVATO (see 4.4 Special Warnings And Precautions For Use).

If baseline blood pressure is elevated (e.g., >140 mmHg systolic, >90 mmHg diastolic), consider the risks of short term increases in blood pressure and benefit of SPRAVATO treatment in patients with TRD (see 4.4 Special Warnings And Precautions For Use). Do not administer SPRAVATO if an increase in blood pressure or intracranial pressure poses a serious risk (see 4.3 Contraindications).

After dosing with SPRAVATO, reassess blood pressure at approximately 40 minutes and subsequently as clinically warranted.

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 4.4 Special Warnings and Precautions For Use).

Since some patients may experience nausea and vomiting after administration of SPRAVATO, 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 (see section 4.8 Adverse Effects (Undesirable Effects)).

Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should be advised not to administer these medications within 1 hour before administration of SPRAVATO.

For instructions to prepare the patient and for use of the nasal spray device, see also the Consumer Medicine Information and the “Instructions for Use” leaflet provided separately in the carton.

Dosage – 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
Weeks 1-4: Starting Day 1 dose: < 65 years: 56 mg ≥ 65 years: 28 mg Subsequent doses: 28 mg (≥ 65 years), 56 mg or 84 mg twice weekly	**Weeks 5-8**: 28 mg (≥ 65 years), 56 mg or 84 mg once weekly **From Week 9**: 28 mg (≥ 65 years), 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 re-examine the need for continued treatment.
* Dosing frequency should be individualised to the lowest frequency to maintain remission/response	

After depressive symptoms improve, treatment should continue for at least 6 months.

Post administration observation

During and after SPRAVATO administration at each treatment session, patients should be monitored until the patient is stable based on clinical judgment.

Before SPRAVATO administration, patients' blood pressure should be assessed and patients instructed not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery until the next day after a restful sleep (see section 4.4 Special Warnings and Precautions for Use- Effect on blood pressure; Potential for cognitive and motor impairment; Effect on driving).

After administration with SPRAVATO, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted (see section 4.4 Special Warnings and Precautions for Use- Effect on blood pressure; Potential for cognitive and motor impairment; Effect on driving).).

Due to the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored by a healthcare professional until the patient is considered clinically stable and ready to leave the healthcare setting (see section 4.4 Special Warnings and Precautions for Use- Effect on blood pressure; Potential for cognitive and motor impairment; Effect on driving).

Missed treatment session(s)

In case one or two treatment sessions are missed, schedule the next session 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 judgement, adjustment of the dose or frequency of SPRAVATO may be clinically appropriate.

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of SPRAVATO have not been established in patients aged 17 years and younger.

Elderly (65 years of age and older)

In elderly patients 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.

Hepatic impairment

No dosage adjustment is necessary in patients with mild (Child Pugh class A) or moderate (Child Pugh class B) 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 section 5.2 Pharmacokinetic Properties).

Renal Impairment

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

Race

For patients of Japanese ancestry, initial Spravato dose is 28 mg esketamine (day 1, starting dose, see Table 2). Subsequent doses should be increased in increments of 28 mg up to 56 mg or 84 mg, based on efficacy and tolerability.

Table 2: Recommended Dosing for Spravato in Adults of Japanese Ancestry

Induction phase	**Maintenance phase**
Weeks 1-4: Starting day 1 dose: 28 mg Subsequent doses: 28 mg, 56 mg or 84 mg twice a week, all dose changes should be in 28 mg increments	**Weeks 5-8**: 28 mg, 56 mg or 84 mg once weekly, all dose changes should be in 28 mg increments **From week 9:** 28 mg, 56 mg or 84 mg every 2 weeks or once weekly, all dose changes should be in 28 mg increments
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.	The need for continued treatment should be reexamined periodically.

4.3 CONTRAINDICATIONS

SPRAVATO is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.4 Special Warnings and Precautions for use):

- Patients with known aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels)
- Patients with known history of intracerebral haemorrhage

SPRAVATO is contraindicated in patients with a known hypersensitivity to esketamine, ketamine, or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 section 4.8 Adverse Effects (Undesirable Effects)). Patients with cardiovascular and cerebrovascular conditions should be carefully assessed before prescribing SPRAVATO and treatment initiated only if the benefit outweighs the risk (see section 4.3 Contraindications). Examples of conditions which should be carefully considered include:

- Unstable or poorly controlled hypertension.
- History (within 6 weeks) of cardiovascular event, including myocardial infarction (MI). Patients with a history of an MI should be clinically stable and cardiac symptom free prior to dosage administration.

- History (within 6 months) of ischemic stroke or transient ischemic attack.
- Haemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation.
- New York Heart Association (NYHA) Class III IV heart failure of any aetiology.

Administration of SPRAVATO can temporarily raise blood pressure lasting approximately 1-2 hours. Blood pressure should be assessed prior to dosing with SPRAVATO. In patients whose blood pressures prior to dose administration are 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 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 acceptable levels. If blood pressure remains too high, assistance should promptly be sought from practitioners experienced in blood pressure management. Patients who experience symptoms of a hypertensive crisis should be referred immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants or monoamine oxidase inhibitors (MAOIs) (see 4.5 Interactions with Other Medicines And Other Forms Of Interactions).

Potential for 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 section 4.8 Adverse Effects (Undesirable Effects)). These effects may impair attention, judgment, thinking, reaction speed and motor skills. Tolerance to above effects may develop after a few treatment sessions. At each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered clinically stable (see section 4.2 Dose and Method of Administration).

Short-Term Cognitive Impairment

In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment

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 and performance remained stable.

Effect on driving

Two studies were conducted to assess the effects of SPRAVATO on the ability to drive (see section 5.1 Pharmacodynamic Properties – Pharmacodynamic effects: Effects on driving). Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor co-ordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep (see section 4.4 Special Warnings and Precautions for Use – Potential for 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 (see section 5.1 Pharmacodynamic Properties – Clinical Trials).

Drug abuse and dependence

Abuse

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO. Careful consideration is advised prior to treatment of individuals with a history of substance use disorder, including alcohol. Monitoring for signs of abuse or dependence is recommended.

The potential for abuse, misuse and diversion of SPRAVATO is minimised due to the product's design and the administration taking place under the supervision by a healthcare professional.

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. Monitoring for signs of dependence is recommended.

Use in the elderly

Of the total number (N=1601) of patients in Phase 3 clinical studies exposed to SPRAVATO, n=194 (12.1%) were 65 years of age and older, while n=25 (1.6%) were 75 years of age and older. No overall differences in the safety profile were observed between these patients and patients younger than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic analysis showed that mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients (see section 5.2 Pharmacokinetic Properties – special populations, Elderly). Therefore, the recommended initial dose of SPRAVATO in elderly patients is lower than that for younger adults (see section 4.2 Dose and Method of Administration – Special populations, Elderly).

Evidence of efficacy has been observed in patients 65 and older (see section 5.1 Pharmacodynamic Properties – Clinical Trials).

Paediatric use

The safety and efficacy of SPRAVATO have not been established in patients aged 17 years and younger.

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
- Significant pulmonary insufficiency
- Patients with known uncontrolled bradyarrhythmias or tachyarrhythmias that lead to haemodynamic instability

- History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure.

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, therefore, patients should be closely monitored. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

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 behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Effects of laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic interactions

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

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

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.

Esketamine is extensively metabolised 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 section 5.2 Pharmacokinetic Properties).

Effect of other drugs on esketamine

Hepatic enzyme inhibitors

Pre-treatment 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 pre-treatment.

Pre-treatment 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 pre-treatment.

Hepatic enzyme inducers

Pre-treatment 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. Pre-treatment of subjects with history of allergic rhinitis and pre-exposed to grass pollen with oxymetazoline administered as a nasal spray (2 actuations of 0.05% solution administered at 1 hour prior to nasal administration of esketamine) had minor effects on the pharmacokinetics of esketamine.

Pre-treatment 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. (see section 4.2 Dose and Method of Administration- Method of administration)

Effect of esketamine on other drugs

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Animal studies showed that fertility and reproductive capacities were not adversely affected by esketamine at clinically relevant doses. 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.

Use in pregnancy

Category B3

SPRAVATO should not be used during pregnancy. The risks of SPRAVATO during pregnancy have not been studied. Human data in pregnant women during clinical trials with esketamine exposure are too limited to be conclusive.

In an embryo fetal developmental toxicity study with nasally administered ketamine in rats, the offspring was not adversely affected in the presence of maternal toxicity at doses up to 150 mg/kg/day. In rats, the C_{max}- and AUC-based safety margin estimated for esketamine at the 150 mg/kg/day dose of ketamine was 80- and 12-fold compared to the maximum recommended human dose (MRHD) of esketamine of 84 mg. In an embryo fetal developmental toxicity study with nasally administered ketamine in rabbits, fetal body weight was reduced at a clinically relevant maternally toxic dose of 30 mg/kg/day. In rabbits, the estimated exposure to esketamine at the 10 mg/kg/day no effect dose of ketamine was below the maximum exposure to esketamine at 84 mg in humans.

Animal studies with ketamine showed evidence of developmental neurotoxicity. Ketamine administered intravenously at high anaesthetic dose levels to female rats on gestation day 14 caused neuronal cell abnormalities in the brains of their offspring which showed behavioural changes and impaired memory up to young adult age. When female monkeys were treated intravenously with ketamine at high anaesthetic dose levels on gestation day 123 of pregnancy, neuronal cell death was observed in the brains of their fetuses. Ketamine induced neuronal cell death was also observed with early postnatal (postnatal days 7-11 in mice and days 7-8 in rats) intraperitoneal or subcutaneous treatment of rat and mice pups, during a period of rapid brain growth.

This period of brain development translates into the third trimester of human pregnancy. In embryo fetal developmental toxicity studies in rats and rabbits, nasally administered ketamine did not induce adverse findings in the offspring other than a reduction in fetal body weight at doses of 30mg/kg/d in rabbits, 20-fold higher than the human MRHD. The potential for esketamine to have neurotoxic effects on developing fetuses cannot be excluded.

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 at this clinically relevant dose.

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 counselled about the potential risk to the fetus and clinical/therapeutic options as soon as possible.

Use in lactation

SPRAVATO should not be used in women who are breast feeding. The risks of SPRAVATO during breast feeding have not been studied in humans. There are no data available to assess the effects of esketamine on human milk production, its presence in human milk, or effects on the breastfed infant. Esketamine is expected to be excreted to human milk based on published data showing presence of ketamine in cow's milk in cows exposed to intravenously administered ketamine. Advise patients either not to undergo therapy with SPRAVATO while breast feeding or discontinue breast feeding if treatment with SPRAVATO is initiated, taking into account the importance of the drug to the mother.

4.7 EFFECTS OF ABILITY TO DRIVE AND OPERATE 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 section 4.8 Adverse Effects (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 sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties-Pharmacodynamic effects, Effect on driving).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

Summary of the safety profile

SPRAVATO was evaluated for safety in 1709 patients diagnosed with TRD (patients with MDD and were non-responders to at least two oral antidepressants (ADs), 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.

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

Table 3 shows the incidence of adverse reactions that occurred in TRD patients treated with SPRAVATO plus oral AD at any dose and greater than patients treated with oral AD plus placebo nasal spray. No differences in adverse reaction type or frequency were observed between younger and older-aged patients nor between induction and maintenance treatments.

Table 3: Adverse Reactions Occurring in TRD patients treated with SPRAVATO at any dose and greater than patients treated with oral AD and placebo nasal spray

	Double-Blind Population		Open-Label Population	
	SPRAVATO + Oral AD (N=587)	Oral AD + Placebo nasal spray (N=486)	SPRAVATO + Oral AD (N=1335)	All SPRAVATO Population (N=1709)
Psychiatric disorders				
Dissociation†	221 (37.6%)	30 (6.2%)	511 (38.3%)	690 (40.4%)
Anxiety†	63 (10.7%)	28 (5.8%)	155 (11.6%)	220 (12.9%)
Euphoric mood	20 (3.4%)	3 (0.6%)	51 (3.8%)	73 (4.3%)
Nervous system disorders				
Dizziness†	175 (29.8%)	33 (6.8%)	490 (36.7%)	628 (36.7%)
Sedation†	124 (21.1%)	35 (7.2%)	321 (24.0%)	434 (25.4%)
Headache†	115 (19.6%)	60 (12.3%)	293 (21.9%)	410 (24.0%)
Dysgeusia†	113 (19.3%)	54 (11.1%)	207 (15.5%)	293 (17.1%)
Hypoesthesia†	103 (17.5%)	7 (1.4%)	204 (15.3%)	285 (16.7%)
Lethargy†	47 (8.0%)	21 (4.3%)	95 (7.1%)	148 (8.7%)
Dysarthria†	18 (3.1%)	1 (0.2%)	37 (2.8%)	56 (3.3%)
Mental impairment	14 (2.4%)	4 (0.8%)	26 (1.9%)	41 (2.4%)
Tremor†	13 (2.2%)	2 (0.4%)	27 (2.0%)	45 (2.6%)
Ear and labyrinth disorders				
Vertigo†	115 (19.6%)	16 (3.3%)	211 (15.8%)	303 (17.7%)
Cardiac disorders				
Tachycardia†	6 (1.0%)	2 (0.4%)	19 (1.4%)	27 (1.6%)
Respiratory, thoracic and mediastinal disorders				
Nasal discomfort†	43 (7.3%)	21 (4.3%)	96 (7.2%)	133 (7.8%)
Gastrointestinal disorders				
Nausea	144 (24.5%)	28 (5.8%)	321 (24.0%)	458 (26.8%)
Vomiting	49 (8.3%)	6 (1.2%)	123 (9.2%)	177 (10.4%)
Dry mouth	23 (3.9%)	8 (1.6%)	42 (3.1%)	68 (4.0%)
Salivary hypersecretion	5 (0.9%)	1 (0.2%)	5 (0.4%)	9 (0.5%)
Skin and subcutaneous tissue disorders				
Hyperhidrosis	21 (3.6%)	5 (1.0%)	52 (3.9%)	77 (4.5%)
Renal and urinary disorders				
Pollakiuria†	13 (2.2%)	2 (0.4%)	26 (1.9%)	40 (2.3%)
General disorders and administration site conditions				
Feeling abnormal	24 (4.1%)	3 (0.6%)	53 (4.0%)	72 (4.2%)
Feeling drunk	23 (3.9%)	1 (0.2%)	31 (2.3%)	51 (3.0%)
Investigations				
Blood pressure increased†	68 (11.6%)	19 (3.9%)	165 (12.4%)	220 (12.9%)

* Note: The following studies are included in the Double-Blind Population: TRD2003 (Double-Blind Phase), TRD3001, TRD3002, TRD3003 (Maintenance Phase), TRD3005. The following studies are included in the Open-Label Population: TRD2003 (Open-Label Phase), TRD3003 (Induction and Optimisation Data from Direct-Entry patients), TRD3004. The 'All SPRAVATO Population' includes all patients in the SPRAVATO arm in any phase in TRD2003, TRD3001, TRD3002, TRD3003, TRD3004, TRD3005.

† The following terms were combined:
Dissociation includes: dissociation; depersonalisation/derealisation disorder; derealisation; dissociative disorder; flashback; hallucination; hallucination, auditory; hallucination, visual; illusion; somatic hallucination; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; paraesthesia; paraesthesia oral; pharyngeal paraesthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change.
Anxiety includes: anxiety; anticipatory anxiety; anxiety disorder; generalised anxiety disorder; agitation; fear; nervousness; tension; panic attack; panic disorder; panic reaction; feeling jittery; irritability; psychogenic tremor.
Dizziness includes: dizziness; dizziness postural; procedural dizziness; dizziness exertional.
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; hypoesthesia oral; hypoesthesia teeth; pharyngeal hypoesthesia; intranasal hypoesthesia.
Lethargy includes: lethargy; fatigue; listless.
Dysarthria includes: dysarthria; speech disorder; slow speech.
Tremor includes: tremor; intention tremor.
Vertigo includes: vertigo; vertigo positional.
Tachycardia includes: sinus tachycardia; tachycardia; heart rate increased; extra-systole.
Nasal discomfort includes: nasal discomfort; nasal crusting; nasal dryness; nasal pruritus
Pollakiuria includes: pollakiuria; micturition disorder.
Blood pressure increased includes: blood pressure increased; blood pressure systolic increased; blood pressure diastolic increased; hypertension; hypertensive heart disease; hypertensive crisis.

Table 4 shows the adverse reactions that occurred in TRD patients treated with SPRAVATO plus oral AD at any dose and greater than patients treated with oral AD plus placebo nasal spray from the five Phase 3 studies (3 short term and 2 long term studies) and one Phase 2 dose ranging study. Within the designated system organ classes, adverse reactions are listed under headings of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 4: Adverse Reactions Occurring in TRD patients treated with SPRAVATO at any dose and greater than patients treated with oral AD and placebo nasal spray

System Organ Class	Adverse Drug Reaction		
	Frequency		
	Very common	Common	Uncommon
Psychiatric disorders	dissociation[a], anxiety[a]	euphoric mood	
Nervous system disorders	dysgeusia[a], dizziness[a], sedation[a], hypoaesthesia[a], headache[a]	mental impairment, tremor, lethargy, dysarthria[a]	
Ear and labyrinth disorders	vertigo[a]		
Cardiac disorders		tachycardia[a]	
Respiratory, thoracic and mediastinal disorders		nasal discomfort[a]	
Gastrointestinal disorders	nausea, vomiting	dry mouth	salivary hypersecretion
Skin and subcutaneous tissue disorders		hyperhidrosis	
Renal and urinary disorders		pollakiuria[a]	
General disorders and administration site conditions		feeling abnormal, feeling drunk	
Investigations	blood pressure increased[a]		

[a] The following terms were combined:
Tachycardia includes: sinus tachycardia; tachycardia; heart rate increased; extrasystole.
Vertigo includes: vertigo; vertigo positional.
Blood pressure increased includes: blood pressure increased; blood pressure systolic increased; blood pressure diastolic increased; hypertension; hypertensive heart disease; hypertensive crisis.
Dizziness includes: dizziness; dizziness postural; procedural dizziness; dizziness exertional.
Dysarthria includes: dysarthria; speech disorder; slow speech.
Dysgeusia includes: dysgeusia; hypogeusia.
Hypoaesthesia includes: hypoaesthesia; hypoaesthesia oral; hypoaesthesia teeth; pharyngeal hypoaesthesia; intranasal hypoaesthesia.
Headache includes: headache; sinus headache.
Lethargy includes: lethargy; fatigue; listless.
Sedation includes: sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor.
Tremor includes: tremor; intention tremor.
Anxiety includes: anxiety; anticipatory anxiety; anxiety disorder; generalised anxiety disorder; agitation; fear; nervousness; tension; panic attack; panic disorder; panic reaction; feeling jittery; irritability; psychogenic tremor.
Dissociation includes: dissociation; depersonalisation/derealisation disorder; derealisation; dissociative disorder; flashback; hallucination; hallucination, auditory; hallucination, visual; illusion; somatic hallucination; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysaesthesia; oral dysaesthesia; paraesthesia; paraesthesia oral; pharyngeal paraesthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change.
Pollakiuria includes: pollakiuria; micturition disorder.
Nasal discomfort includes: nasal discomfort; nasal crusting; nasal dryness; nasal pruritus.

Description of selected adverse reactions

Dissociation/perceptual changes

The most common psychological effects of esketamine have been dissociative/perceptual changes (including distortion of time and space and illusions), derealisation and depersonalisation. These adverse reactions were reported as transient and self-limited and occurred on the day of dosing. Dissociation was reported as severe in intensity at the incidence of less than 4% across studies. Dissociation symptoms typically resolved by 1.5 hours post dose and the severity tended to reduce over time with repeated treatments.

Sedation/Somnolence

Adverse reactions of sedation and somnolence were primarily mild or moderate in severity, occurred on the day of dosing and resolved spontaneously the same day. 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 haemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges.

Impaired Cognition

In the short-term studies, treatment with SPRAVATO plus oral AD did not influence any aspect of cognition studied in adult patients with TRD and was not associated with any systematic changes in cognition in the elderly patients. Consistently, in long term studies, performance on each of the cognitive tests relative to baseline showed slight improvement or remained stable in each treatment phase. In the elderly subgroup (≥65 years of age) slowing of reaction time starting at Week 20 and through the end of the study was observed, however, performance on other cognitive tests remained stable.

Changes in Blood Pressure

The mean placebo-adjusted increases in systolic and diastolic blood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving SPRAVATO plus oral antidepressants (Table 5).

Table 5: 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%)

Nausea and Vomiting

SPRAVATO can cause nausea and vomiting (Table 6). Most of these events occurred on the day of dosing and resolved the same day, with the median duration not exceeding 1 hour in most subjects across dosing sessions. Rates of reported nausea and vomiting decreased over time across dosing sessions from the first week of treatment in the short-term studies, as well as over time with long-term treatment (Table 6).

Table 6: Incidence and Severity of Nausea and Vomiting in Double-blind, Randomized-controlled, Fixed-dose Study

Treatment (+ Oral AD)		**Nausea**		**Vomiting**	
	N	**All**	**Severe**	**All**	**Severe**
SPRAVATO 56 mg	115	31 (27%)	0	7 (6%)	0
SPRAVATO 84 mg	116	37 (32%)	4 (3%)	14 (12%)	3 (3%)
Placebo Nasal Spray	113	12 (11%)	0	2 (2%)	0

Nasal Tolerability and Sense of Smell

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

Body Weight

SPRAVATO had no clinically meaningful effect on body weight over short- or long-term administration. In the double-blind maintenance phase of TRD3003, the proportion of patients with an increase in body weight of ≥7% was comparable for the SPRAVATO plus oral AD vs. oral AD plus placebo nasal spray groups (13.9% and 13.3%). In the open label, long term study TRD3004, a similar percentage of patients exhibited an increase or decrease in body weight of ≥7% (7.4% and 9.1%, respectively). In TRD3004, mean body weight remained stable during treatment with SPRAVATO plus oral AD both in the induction phase and maintenance phase (mean change from baseline ± standard deviation of -0.29±2.15 kg at Day 28 and 0.44±5.83 kg at Week 48).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No cases of overdose were reported in clinical studies with SPRAVATO. The potential for overdose of SPRAVATO by the patient is minimised due to the product's design and the administration taking place under the supervision of a healthcare professional (see section 4.2 Dose and Method of Administration).

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 adverse reactions including dizziness, hyperhidrosis, somnolence, hypoaesthesia, feeling abnormal, nausea and vomiting.

Management of overdose

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. Management of SPRAVATO overdose should consist of treating clinical symptoms and relevant monitoring. Close supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 aetiological 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 behaviour. Evidence within the literature suggests that through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling 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.

Pharmacodynamic effects

Effect on driving

Two studies were conducted to assess the effects of SPRAVATO on driving skills.

In a controlled study in 25 adult subjects with major depressive disorder, driving performance was assessed the day after administration of a single 84 mg dose. Treatment with esketamine nasal spray at this dose did not affect driving performance in a standard driving test.

In a healthy volunteer study (N = 23 subjects), driving performance was assessed 8 hours after administration of a single dose of 84 mg of esketamine nasal spray, mirtazapine, or placebo. The effect of esketamine nasal spray administration on driving was similar to placebo. However, two subjects discontinued the driving test after receiving esketamine because of a perceived inability to drive.

Effect on QT/QTc interval and cardiac electrophysiology

Esketamine did not prolong the QT/QTc interval when nasally administered as an 84 mg dose or when intravenously infused as a 0.8 mg/kg dose over 40 minutes.

Clinical trials

The efficacy and safety of SPRAVATO nasal spray was evaluated 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 antidepressants (ADs) treatments, of adequate dosage and duration, in the current major depressive episode. 1833 adult patients were enrolled, of which 1601 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, multicentre, active-controlled studies in patients with TRD. Studies TRANSFORM-1 (TRD3001) and TRANSFORM-2 (TRD3002) were conducted in adults (18 to <65 years) and Study TRANSFORM-3 (TRD3005) was conducted in adults ≥65 years of age. Patients in TRD3001 and TRD3002 initiated treatment with SPRAVATO 56 mg plus a newly initiated daily oral AD or a newly initiated daily oral AD plus placebo nasal spray on Day 1 and SPRAVATO dosages were then maintained on 56 mg or titrated to 84 mg 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) which was maintained or titrated to 56 mg or 84 mg dose administered twice-weekly during a 4-week double-blind induction phase. 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.

The baseline demographic and disease characteristics of patients in TRD3001 and TRD3002 studies were similar between the SPRAVATO plus oral AD and oral AD plus placebo nasal spray groups. The median subject age was 47 years (range 18 to 64 years), 67% were female; 83% Caucasian and 5% of African descent and mean duration of prior AD treatment was approximately 425 days. At the time of screening, the mean duration of the current episode of depression was 168 weeks. At the time of screening, 90% of patients had non-response to ≥2 oral ADs with the remainder requiring confirmation of non-response to the second AD during the 4-week screening prospective phase. The new open label oral AD initiated during the 4-week double blind induction phase was an SSRI in 38% of patients and an SNRI in 62% of patients. In TRD3005, the median subject age was 69 years (range 65 to 86 years) of which, 85% of patients were 65-74 years of age, 62% were female and 95% were Caucasian and mean duration of prior AD treatment was approximately 727 days. At the time of screening, the mean duration of the current episode of depression was 216 weeks in TRD3005. At the time of screening, 85% of patients had non-response to ≥2 oral ADs with the remainder requiring confirmation of non-response to the second AD during the 4-week screening prospective phase. The new open label AD initiated during the 4-week double blind induction phase was an SSRI in 55% of patients and an SNRI in 45% of patients.

The primary efficacy measure was change from baseline in the Montgomery Åsberg Depression Rating Scale (MADRS) total score at the end of the 4-week double blind induction phase. The MADRS is a ten-item, clinician-rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression.

In the flexible dose study TRD3002, for the primary efficacy measure of improvement in depressive symptoms (change in MADRS total scores from baseline at the end of the 4-week induction phase), SPRAVATO plus a newly initiated oral AD demonstrated clinically meaningful and statistical superiority compared to standard of care (newly initiated oral AD) plus placebo nasal spray. In studies TRD3001 and TRD3005, a clinically meaningful treatment effect in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed favouring SPRAVATO plus newly initiated oral AD compared with standard of care (newly initiated oral AD) plus placebo nasal spray (Table 7). In TRD3002, improvements in the Sheehan Disability Scale (SDS) total score assessing global functional impairment and Patient Health Questionnaire 9 (PHQ 9) total score assessing symptoms of depression numerically favoured SPRAVATO plus a newly initiated oral AD compared to standard of care (newly initiated oral AD) plus placebo nasal spray.

Table 7: 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)[†]
TRD3001	SPRAVATO 56 mg + oral AD	115	37.4 (4.8)	-18.7 (1.3)	-4.1 (-7.5, -0.6)[#]
	SPRAVATO 84 mg + oral AD	114	37.8 (5.6)	-17.3 (1.3)	-2.0 (-5.5, 1.4)[#]
	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)[‡]
	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)[#]
	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

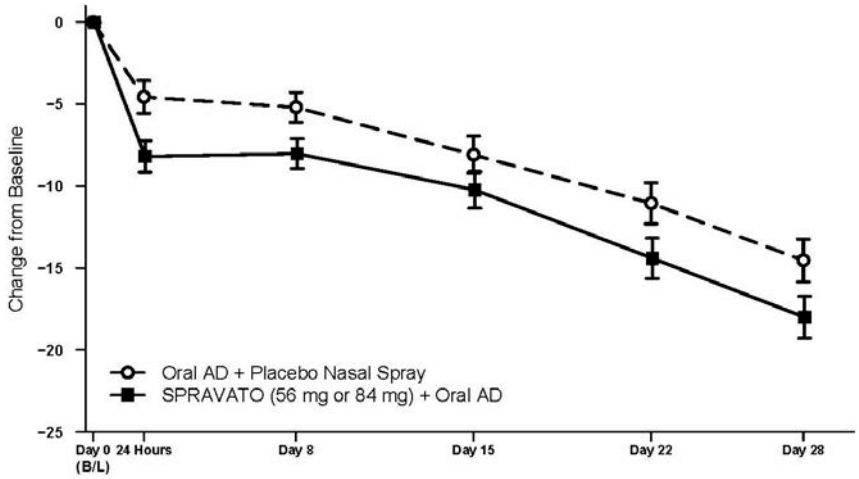
[‡] Treatment groups that were statistically significantly superior to oral AD + placebo nasal spray

[#] 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

Time Course of Treatment Response

In Study TRD3002, an effect of SPRAVATO on symptom reduction was observed as early as 24 hours post-dose and increased in subsequent weeks with the full antidepressant effect of SPRAVATO seen by Day 28. Throughout the 4-week double blind induction phase of Study TRD3002, the mean change in MADRS total score for flexibly dosed SPRAVATO (56 mg or 84 mg) plus oral AD was greater than for oral AD plus nasally-administered placebo. At Day 28, 67% of the patients randomised to SPRAVATO were on 84 mg. Figure 1 depicts time course of response in the primary efficacy measure (MADRS) in Study TRD3002. A consistent treatment effect was observed in Studies TRD3001 and TRD3005.

Figure 1: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Study TRD3002* (Full Analysis Set) – ANCOVA LOCF Analysis with Standard Error Bars



* Note: In this flexible-dose study, dosing was individualised based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO™ dose from 84 mg to 56 mg, and almost all remained on the lower dose for the duration of the induction phase.

Response and remission rates

Response was defined as ≥50% reduction in the MADRS total score from baseline of the induction phase. Based on the reduction in MADRS total score from baseline, the proportion of patients in Studies TRD3001, TRD3002 and TRD3005 who demonstrated response to SPRAVATO plus oral AD treatment was greater than for oral AD plus placebo nasal spray throughout the 4-week double blind induction phase (Table 8)

Remission was defined as a MADRS total score ≤12. In all three studies, a greater proportion of patients treated with SPRAVATO plus oral AD were in remission at the end of the 4-week double blind induction phase than for oral AD plus placebo nasal spray (Table 8).

Table 8: Response and Remission Rates in 4 Week Clinical Trials Based on LOCF Data

		Number of Patients (%)					
		Response Rate†					**Remission Rate‡**
Study No.	**Treatment Group§**	**24 hours**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 4**
TRD3001	SPRAVATO 56 mg + oral AD	20 (19.0%)	21 (18.3%)	30 (26.1%)	52 (45.2%)	61 (53.0%)	40 (34.8%)
	SPRAVATO 84 mg + oral AD	17 (16.3%)#	16 (14.3%)	26 (23.2%)	35 (31.0%)	54 (47.8%)	40 (35.4%)
	Oral AD + Placebo nasal spray	8 (7.9%)	5 (4.4%)	15 (13.3%)	27 (23.9%)	42 (37.2%)	33 (29.2%)
TRD3002	SPRAVATO 56 mg or 84 mg + oral AD	18 (16.5%)	15 (13.4%)	29 (25.9%)	54 (48.2%)	71 (63.4%)	54 (48.2%)
	Oral AD + placebo nasal spray	11 (10.8%)	13 (11.9%)	23 (21.1%)	36 (33.0%)	54 (49.5%)	33 (30.3%)
TRD3005 (≥65 years)	SPRAVATO 28 mg, 56 mg or 84 mg + oral AD	NA	4 (6.1%)	4 (5.6%)	9 (12.7%)	17 (23.9%)	11 (15.5%)
	Oral AD + placebo nasal spray	NA	3 (4.8%)	8 (12.5%)	10 (15.6%)	8 (12.5%)	4 (6.3%)

AD=antidepressant; NA=not available
§ Nasally administered SPRAVATO or placebo; oral AD=standard of care (newly initiated AD)
† Response was defined as ≥50% reduction in the MADRS total score from baseline
‡ Remission was defined as MADRS total score ≤12
# First dose was SPRAVATO 56 mg + oral AD

Treatment resistant depression – Long term studies

Relapse prevention study

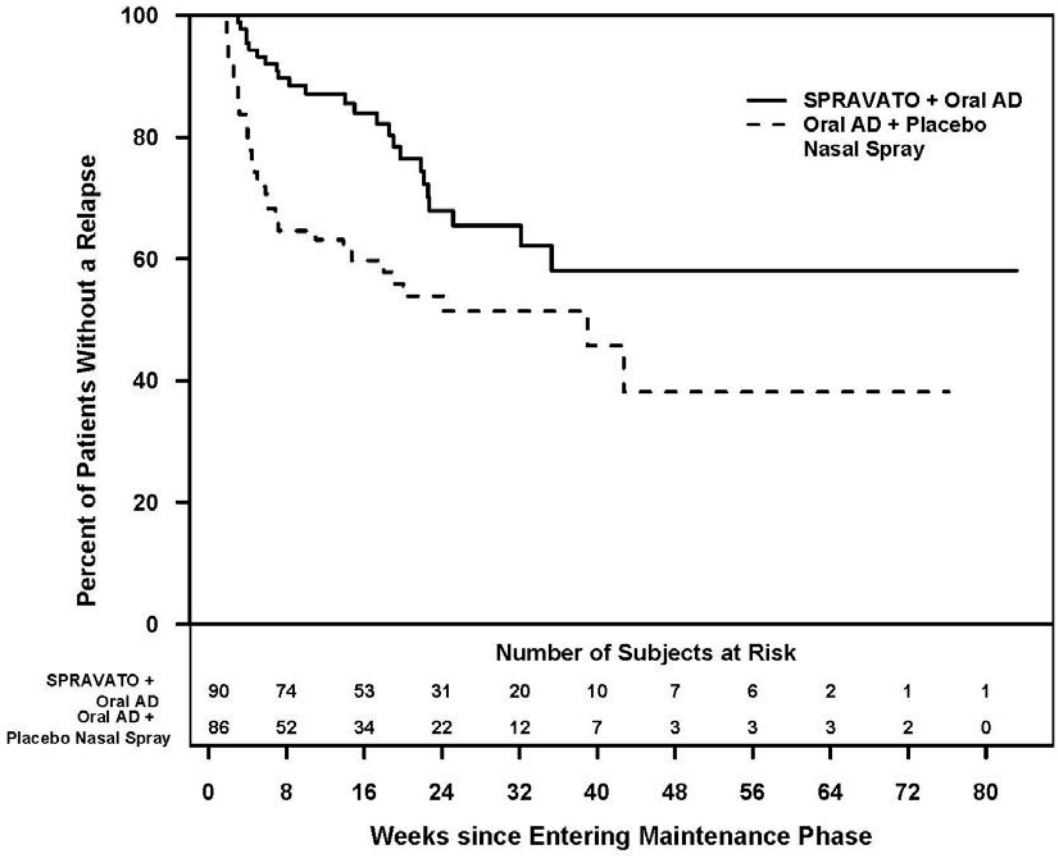
Study SUSTAIN-1 (TRD3003) was a long-term randomised, double-blind, parallel-group, active-controlled, multicentre, relapse prevention study. Overall a total of 705 patients were enrolled; 437 directly enrolled; 150 transferred from TRD3001, and 118 transferred from TRD3002. Patients directly enrolled were administered SPRAVATO (56 mg or 84 mg twice weekly) plus oral AD in a 4-week open label induction phase. Patients who were responders (MADRS total score reduction ≥50% from baseline), continued receiving treatment with SPRAVATO plus oral AD in a 12-week optimisation phase. At the end of the open label induction phase, 52% of patients were in remission (MADRS total score ≤12) and 66% of patients were responders (≥50% improvement in MADRS total score). Four hundred fifty-five (455) esketamine-treated patients entered the optimisation phase, patients in stable remission or stable response were randomised to continue with SPRAVATO or stop SPRAVATO and switch to placebo nasal spray. After an initial 16 weeks of treatment with SPRAVATO plus oral AD, 176 (39%) patients were in stable remission and 121 (27%) patients were in stable response (but not in stable remission). Stable remission was defined as MADRS total score ≤12 in at least 3 of the last 4 weeks of the optimisation phase and stable response was defined as ≥50% reduction in the MADRS total score from baseline for the last 2 weeks of the optimisation phase, but not in stable remission.

The baseline demographic and disease characteristics of the patients randomised to the double-blind maintenance phase were similar between the SPRAVATO plus oral AD and oral AD plus placebo groups, median patient age was 48 years (range 19 to 64 years), 66% were female; 90% Caucasian and 4% of African descent.

Stable Remission

Patients in stable remission who continued treatment with SPRAVATO plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on standard of care (oral AD) plus placebo nasal spray (Figure 2). Relapse was defined as a MADRS total score ≥22 for 2 consecutive weeks or hospitalisation for worsening depression or any other clinically relevant event indicative of relapse. The median time to relapse for standard of care (oral AD) plus placebo nasal spray group was 273 days, whereas the median was not estimable for SPRAVATO plus oral AD, as this group never reached 50% relapse rate.

Figure 2: Time to Relapse in Patients in Stable Remission in Study TRD3003 (Full Analysis Set)

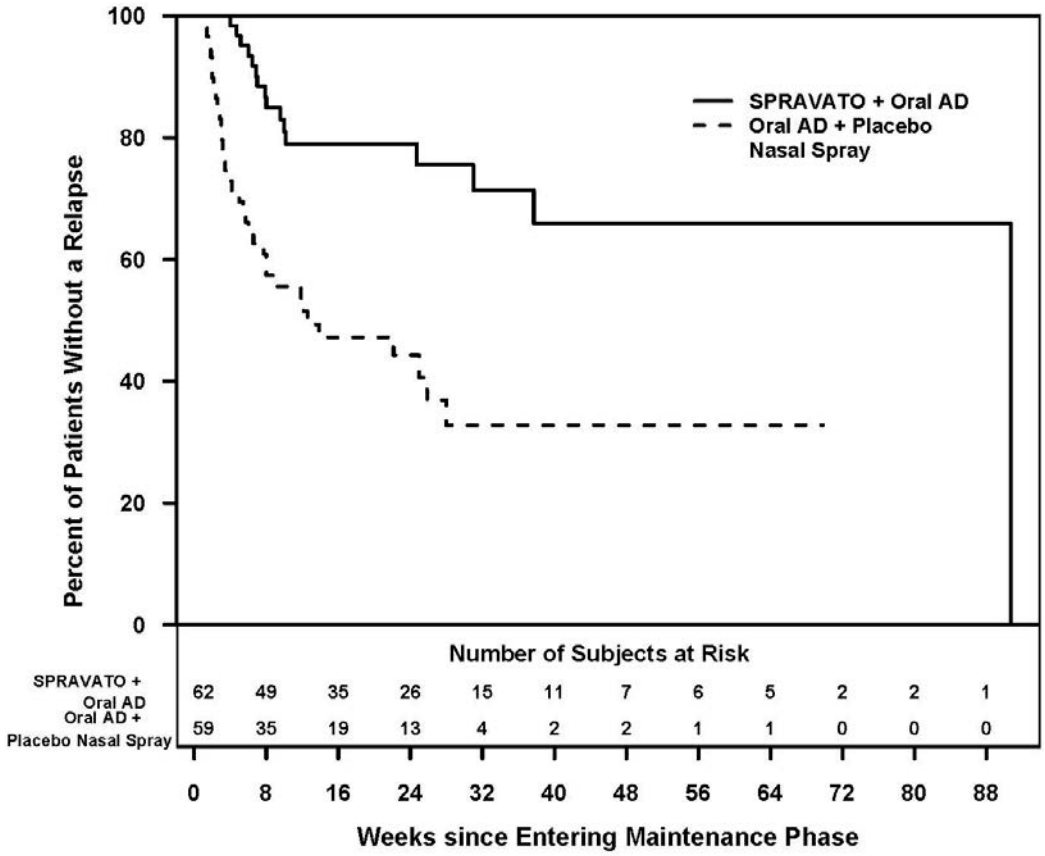


For patients in stable remission, the estimated hazard ratio (95% CI) of SPRAVATO plus oral AD relative to standard of care (oral AD) plus placebo nasal spray based on weighted estimates was 0.49 (95% CI: 0.29, 0.84), indicating that, patients who were in stable remission and continued treatment with SPRAVATO plus oral AD group were on average 51% less likely to relapse than patients who switched to standard of care (oral AD) plus placebo nasal spray.

Stable Response

The efficacy results were also consistent for patients in stable response who continued treatment with SPRAVATO plus oral AD; patients experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on standard of care (oral AD) plus placebo nasal spray (Figure 3). The median time to relapse for standard of care (oral AD) plus placebo nasal spray group (88 days) was shorter compared to SPRAVATO plus oral AD group (635 days).

Figure 3: Time to Relapse in Patients in Stable Response in Study TRD3003 (Full Analysis Set)



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

Enrolment in TRD3003 was staggered over approximately 2 years. The maintenance phase was of variable duration and continued until the individual patient had a relapse of depressive symptoms or discontinued for any other reason, or the study ended because the required number of relapse events occurred. Exposure numbers were influenced by the study stopping at a pre-determined number of relapses based on the interim analysis. After an initial 16 weeks of treatment with SPRAVATO plus oral AD, the median duration of exposure to SPRAVATO in the maintenance phase was 4.2 months (range: 1 day to 21.2 months) in SPRAVATO -treated patients (stable remission and stable response). In this study, 31.6% of patients received SPRAVATO for greater than 6 months and 7.9% of patients received SPRAVATO for greater than 1 year in the maintenance phase.

Dosing Frequency

Starting from week 8, an algorithm (based on the MADRS) was used to determine the dosing frequency; patients in remission (i.e., MADRS total score was ≤12) were dosed every other week, however, if the MADRS total score increased to >12, then the frequency was increased to weekly dosing for the next 4 weeks; with the objective of maintaining the patient on the lowest dosing frequency to maintain response/remission. The dosing frequency used the majority of the time during the maintenance phase is shown in Table 9. Of the patients randomised to SPRAVATO, 60% received 84 mg and 40% received 56 mg dose.

Table 9: Dosing Frequency Used the Majority of the Time; Maintenance Phase (Study TRD3003)

	Stable Remission		Stable Responders	
	SPRAVATO + Oral AD (N=90)	Oral AD + Placebo Nasal Spray (N=86)	SPRAVATO + Oral AD (N=62)	Oral AD + Placebo Nasal Spray (N=59)
Majority dosing frequency				
Weekly	21 (23.3%)	27 (31.4%)	34 (54.8%)	36 (61.0%)
Every other week	62 (68.9%)	48 (55.8%)	21 (33.9%)	19 (32.2%)
Weekly or every other week	7 (7.8%)	11 (12.8%)	7 (11.3%)	4 (6.8%)

Open-label Long-term Safety and Efficacy Study

Study SUSTAIN-2 (TRD3004) was an open-label, long-term study of SPRAVATO plus oral AD in patients with TRD.

The primary objective was to evaluate the long-term (up to 52 weeks) safety and efficacy of SPRAVATO. SPRAVATO was not associated with effects on cognitive function or treatment-emergent symptoms of interstitial cystitis. In the elderly subgroup (≥65 years of age) slowing of reaction time starting at Week 20 and through the end of the study was observed, however, performance on other cognitive tests remained stable.

In addition, there was no evidence of withdrawal and/or rebound symptoms following cessation of SPRAVATO treatment. No cases of respiratory depression were reported and there was no evidence of treatment related changes in lab parameters.

Mean body weight remained stable during treatment with SPRAVATO plus oral AD both in the induction phase and maintenance phase (mean change from baseline ± standard deviation of -0.29±2.15 kg at Day 28 and 0.44±5.83 kg at Week 48).

TRD3004 also evaluated long-term efficacy, including effects on depressive symptoms. At the end of the 4-week induction phase, the response rate (≥50% improvement from Baseline in the MADRS total score) was 78.4% (593/756) and remission rate (MADRS total score ≤12) was 47.2% (357/756); of the responders proceeding to the maintenance phase, 76.5% (461/603) were in response and 58.2% (351/603) were in remission at endpoint.

Dose-response study in treatment-resistant depression

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

Response rates at Day 8 of Period 1 for the double-blind phase are shown below (Table 10).

Table 10: Response Rates in TRD2003 (Double Blind Phase – Period 1)

		Number of Patients (%)		
	Treatment Group[§]	Response Rate[†] 2 hours	24 hours	Day 8
Panel A	SPRAVATO 28mg	6 (54.5%)	4 (36.4%)	1 (9.1%)
	SPRAVATO 56 mg	4 (36.4%)	3 (27.3%)	2 (18.2%)
	SPRAVATO 84 mg	7 (58.3%)	5 (41.7%)	5 (41.7%)
	Placebo Nasal Spray	6 (18.2%)	1 (3.0%)	2 (6.1%)
Panel B	SPRAVATO 14mg	4 (36.4%)	4 (36.4%)	2 (18.2%)
	SPRAVATO 56 mg	4 (44.4%)	4 (44.4%)	2 (22.2%)
	Placebo Nasal Spray	7 (33.3%)	6 (28.6%)	5 (23.8%)

§ Nasally administered SPRAVATO or placebo

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

5.2 PHARMACOKINETIC PROPERTIES

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 actuation of a treatment session (see section 4.2 Dose and Method of Administration).

Dose-dependent, linear increases in the plasma C_{max} and AUC_{∞} of esketamine nasal spray were produced by doses of 28 mg, 56 mg and 84 mg.

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.

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. Esketamine does not inhibit these transporters or multi drug and toxin extrusion 1 (MATE1) and MATE2 K, or organic cation transporter 2 (OCT2), OAT1, or OAT3.

Metabolism

Esketamine is extensively metabolised 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 metabolised via CYP dependent pathways to other metabolites, some of which undergo glucuronidation.

Excretion

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 faeces, respectively. Following oral administration of radiolabelled esketamine, approximately 86% and 2% of administered radioactivity was recovered in urine and faeces, 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.

Special Populations

Elderly (65 years of age and older)

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.

Renal Impairment

Relative to the subjects with normal renal function (creatinine clearance [CLCR], 88 to 140 mL/min), the C_{max} of esketamine was on average 20 to 26% higher in subjects with mild (CLCR, 58 to 77 mL/min), moderate (CLCR, 30 to 47 mL/min), or severe (CLCR, 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.

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.

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.

5.3 PRECLINICAL SAFETY DATA

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 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

The weight of evidence indicates that esketamine lacks genotoxic and carcinogenic potential in vivo.

Once daily nasal administration of esketamine did not increase the incidence of tumours in a 2-year rat carcinogenicity study at doses up to 9 mg/day. At this dose, the exposure to esketamine resembled 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 C_{max}-and AUC- based exposure ratios for esketamine were approximately 35- and 6-fold, respectively, compared to the MRHD of 84 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Citric acid monohydrate

Disodium edetate

Sodium hydroxide

Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Clear and colourless to slightly yellowish solution free from visible particles in a type-I glass vial with rubber stopper assembled into a single-use nasal spray device.

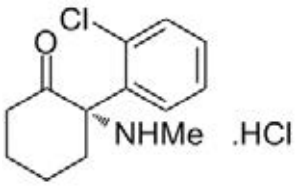
SPRAVATO is provided in cartons containing 1, 2 or 3 single-use nasal spray devices.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material including the device, should be disposed of by the pharmacy as arranged by the treatment clinic. The patient must never be in direct possession of this medicine, at any time outside of the treatment site.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Esketamine HCl

Molecular Formula

$C_{13}H_{16}ClNO.HCl$

CAS number

33795-24-3

7. MEDICINE SCHEDULE (POISON STANDARD)

S8 Controlled Drug

8. SPONSOR

Janssen-Cilag Pty Ltd
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Macquarie Park,
NSW, 2113, AUSTRALIA
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9. DATE OF FIRST APPROVAL

09 March 2021