Spravato® (esketamine) nasal spray
速開朗®

Bringing New Hope Through Targeting the Glutamate System

The First APPROVED MOA in 30 Years[1-6,*†]

*SPRAVATO®, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode[1].
†Following the development and approval of the SSRI fluoxetine in 1987, approved treatments (including 'atypical' antidepressants such as mirtazapine, agomelatine etc.) have either focused on, or continued to have at least some effect on, the monoaminergic system[2-5].

This booklet is intended for the use and reference by healthcare professionals only.

Facts on Depression

Ranks the 3rd among the ten leading causes of burden of disease[7]

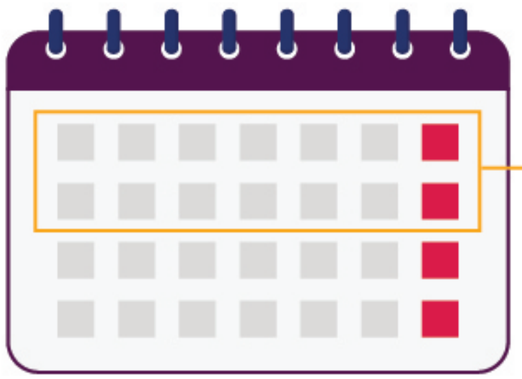
Projected to be the 1st leading disability by 2030[7,8]

More than 300,000 Hong Kong people suffer from depression[9]

What are the symptoms of depression[10]?

If the patients have 5 or more out of 9 symptoms (including at least one of depressed mood and loss of interest or pleasure) in the same 2-week period, they can be diagnosed with depression.

Within 2 weeks



At least 5 symptoms

- Depressed mood (subjective or observed)*
- Loss of interest or pleasure*
- Change in weight or appetite†
- Psychomotor retardation or agitation (observed)‡
- Insomnia or hypersomnia‡
- Loss of energy or fatigue‡
- Worthlessness or guilt‡
- Impaired concentration or indecisiveness‡
- Thoughts of death or suicidal ideation or attempt

*Most of the day, nearly every day †Appetite: Nearly every day; Weight: 5% change over 1 month ‡Nearly every day

In this booklet, "depression" means major depression.

Residual Symptoms: An Indicator of Incomplete Remission from Depression

Although many patients are receiving medical treatments, they fail to be completely relieved from depression. They are likely to have different mental and physical residual symptoms[11]. Common symptoms include[11,12]:

Effects on emotion	Effects on the body	Effects on daily activities
☐ Persistent low mood	☐ Insomnia	☐ Losing interest in things around you
☐ Feeling guilty	☐ Decreased libido	☐ Losing interest in work
☐ Anxiety	☐ Back pain	☐ Decline in work performance
☐ Feeling irritable	☐ Muscle pain	☐ Cognitive dysfunction
☐ Fatigue	☐ Stomachache	
	☐ Joint pain	

Residual symptoms greatly increase the risk of recurrence[12]

It is important for patients with residual symptoms to adjust their current depression treatment plan to prevent relapse.

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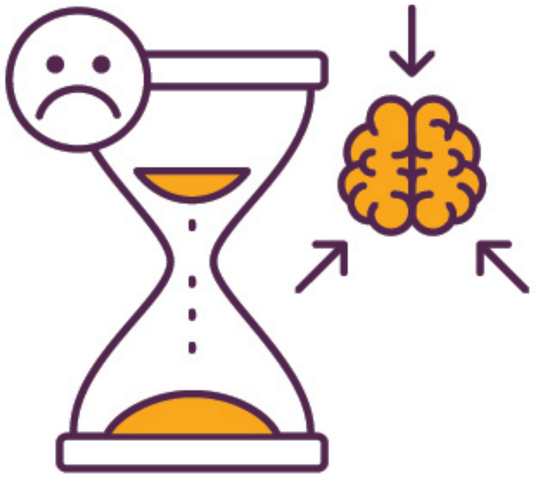
The Effects of Depression Recurrence on the Patient's Brain

Studies have shown that the brain of patients with depression is affected by chronic inflammation, which leads to changes in brain structure and function. The longer and more frequent depressive episodes appear to facilitate an accelerating and progressive illness course associated with functional decline[13,14].

Insular cortex volume and dorsolateral prefrontal cortex volume in relapsed patients significantly decreased[15]

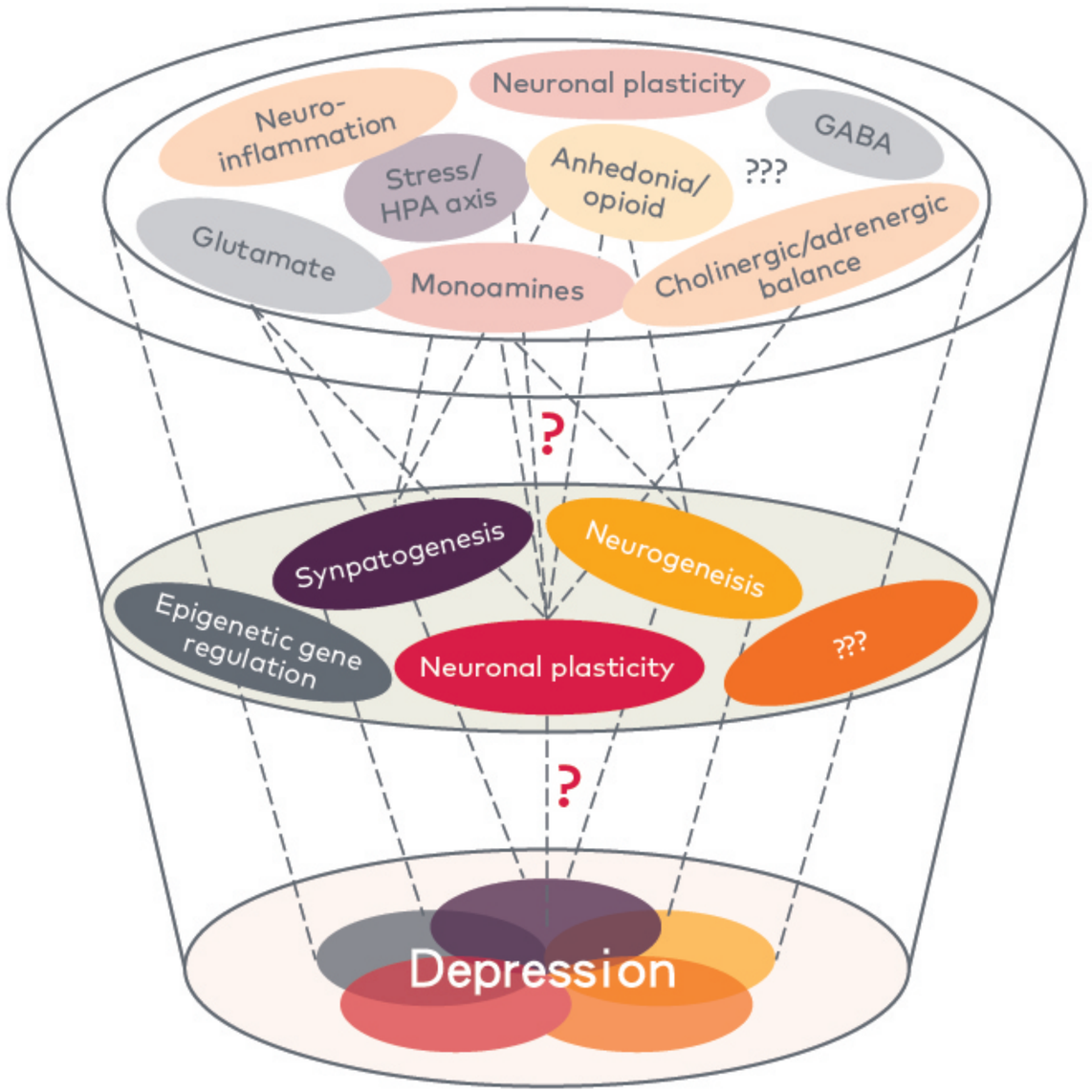


A direct correlation between increasing episode number and decreased hippocampal volume[14]

The risk of memory loss and dementia increases with the number of depressive episodes[14]

In this booklet, "depression" means major depression.

Offering More Drug Options by Targeting Different Pathways



Due to the complexity of depression, there is no single pathological mechanism that can fully explain the cause of depression in every individual patient[16].

However, the antidepressants developed in the past 30 years only targeted the monoaminergic system and failed to take other possible pathological causes into account[2-5]. Many depression patients failed to achieve remission with antidepressant treatment in the past[17,18].

Achieving complete remission and **elimination of all residual symptoms** are the treatment goals of depression[19,20]

Currently, the medical community is actively developing new antidepressant drugs that target other systems, including the glutamate system[16].

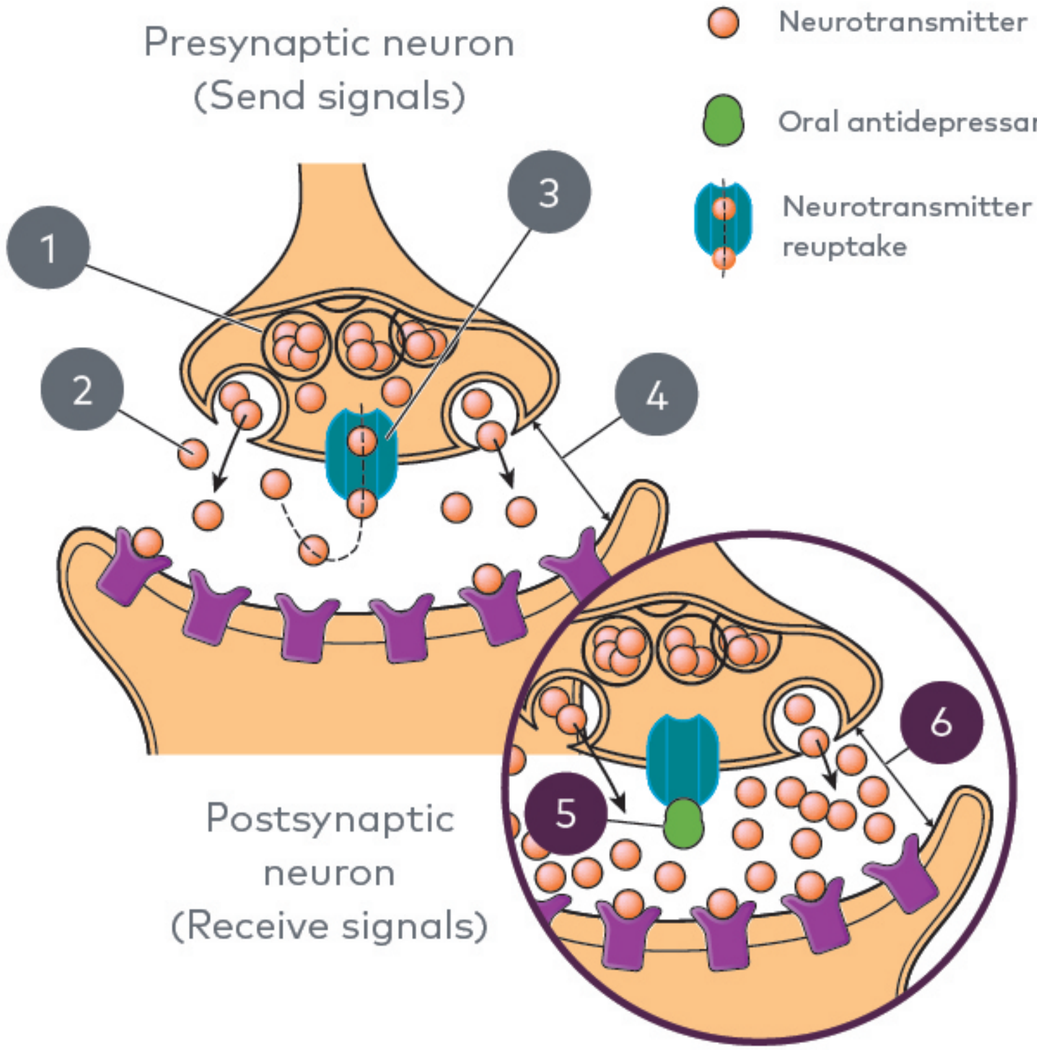
Through establishing a dual-MoA strategy, it is possible for patients to relieve symptoms in a shorter period of time[6].

In this booklet, "depression" means major depression.

Traditional Oral Antidepressants: Targeting the Monoaminergic System

Onset time
4-6 weeks[33]

In the past few decades, the monoamine hypothesis proposes that MDD patients have depleted concentrations of serotonin, norepinephrine, and dopamine[2]. Currently in the market, most of the oral antidepressants act based on the monoaminergic system, and improve the patient's condition through increasing the monoamine level[21].



Neurotransmitter

Oral antidepressant

Neurotransmitter reuptake

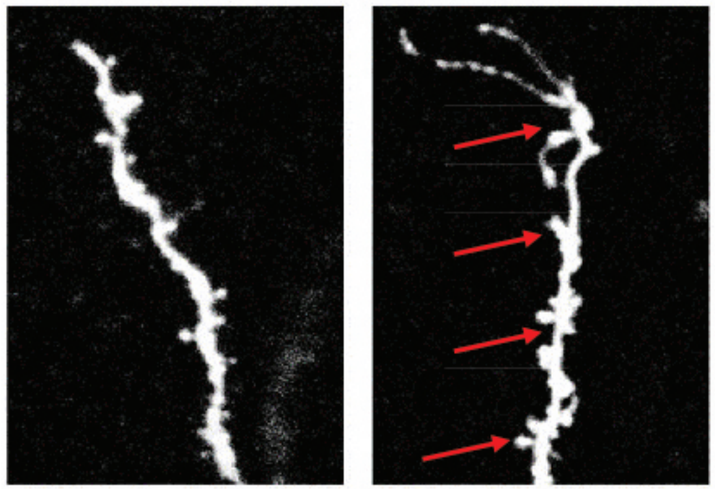
1	Neurotransmitters are located in the vesicles of nerve cells and are responsible for contacting neurons[22]
2	Neurotransmitters are released from the end of one nerve and received by the other nerve[22]
3	Among them, part of the neurotransmitter will be reabsorbed[22]
4	Because the patient's brain neurotransmitter is lower than normal, in the case of reabsorption, the neurotransmitter concentration between neurons becomes too low. This affects the transmission of messages and leads to depressive symptoms[22]
5	Oral antidepressants, such as SSRI and SNRI, use the principle of inhibition to reduce the reabsorbed neurotransmitter[22,23]
6	The concentration of neurotransmitters around the nerves of the brain is increased[22]

SSRI=serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor
In this booklet, "depression" means major depression.

Targeting the Glutamate System, Bringing New Hope to Patients

Glutamate is the main excitatory neurotransmitter in the central nervous system and plays an important role in more than half of the neuronal connections in the brain[24].

In recent years, studies have found that the abnormal transmission of glutamate signals in patients with depression reduces the amount and strength of brain connections between neurons in some key regions of the brain, which in turn affects emotional control[25].



Control treatment

Glutamate receptor modulator

By blocking a type of glutamate receptor called NMDA receptor, SPRAVATO® is believed to create a surge of glutamate increase which may eventually help increase synaptic plasticity[25].

Increased synaptic protein synthesis and spine synapse number detected within 24 hours post-treatment[26,‡].

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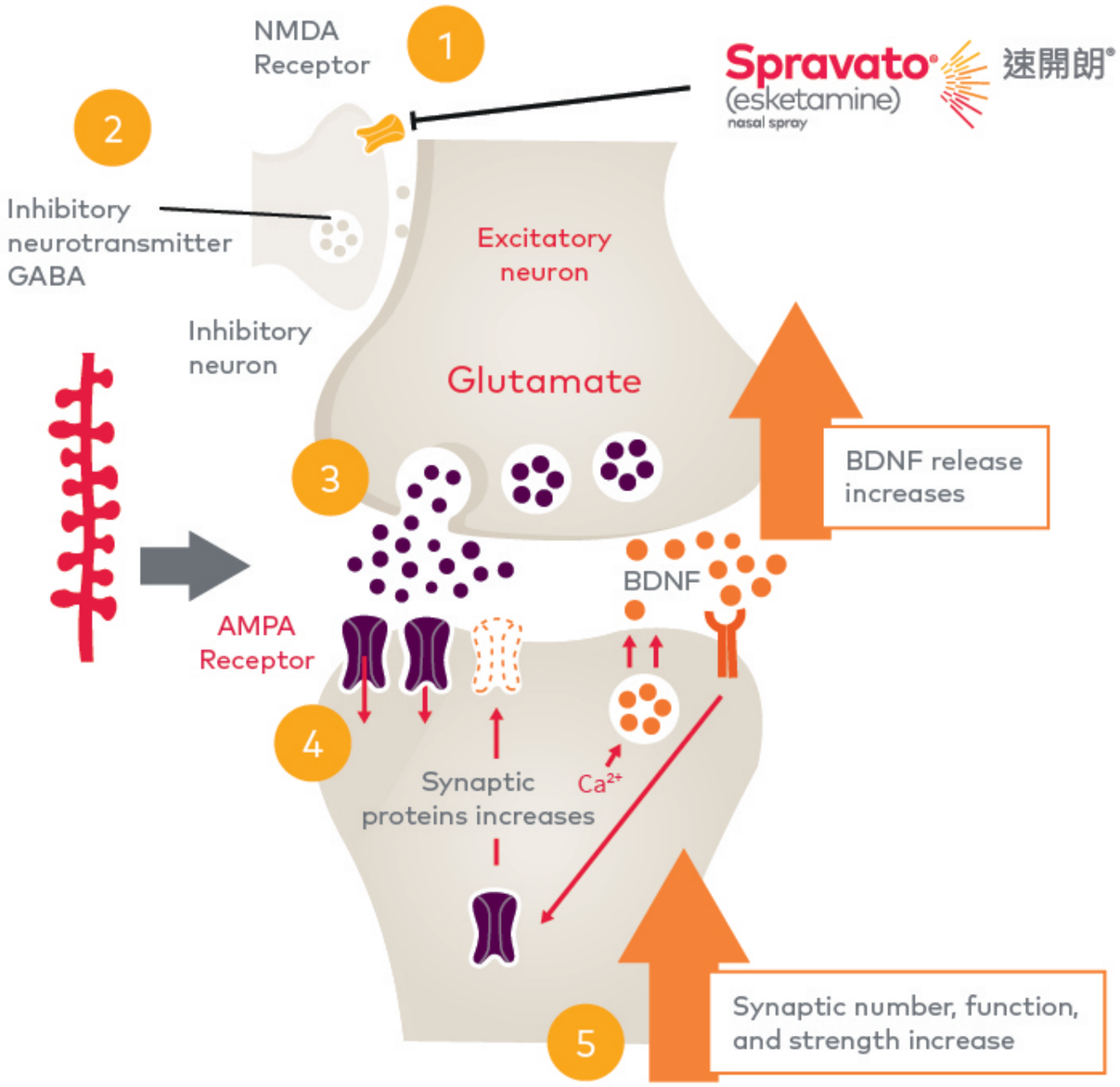
†Following the development and approval of the SSRI fluoxetine in 1987, approved treatments (including 'atypical' antidepressants such as mirtazapine, agomelatine etc.) have either focused on, or continued to have at least some effect on, the monoaminergic system[2-5].
‡Preclinical data.

Mechanism of Action of SPRAVATO®

SPRAVATO® contains the active substance esketamine, which is an NMDA receptor antagonist, and its mechanism of action is based on the glutamate system[1].



1	SPRAVATO® binds to and inhibits the NMDA receptor[25]
2	This prevents the release of the chemical messenger GABA, which originally interrupted glutamate release[25]
3	A surge of glutamate releases into the synaptic cleft[25]
4	The stimulation of AMPA receptors triggers a number of intracellular processes, resulting in the release of protein factors that encourage synaptic growth[25]
5	As a result, synapses could be restored with increased activity and strength[25]

How Does SPRAVATO® Help Patients with Treatment-Resistant Depression?

SPRAVATO® is indicated for patients who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode[1].

The first approved MOA in 30 years[1-6,*,†]

SPRAVATO® is the first anti-depressant drug with glutamate-based system in 30 years. The mechanism of action is different from that of drugs targeting the monoaminergic system in the past few decades[1-6,*,†].

Dual mechanism of action treatment plan

SPRAVATO® is used in combination with oral antidepressants. The two target different pathological causes of depression to achieve better therapeutic effects[1].

Unique nasal administration

SPRAVATO® is a nasal spray. The form of nasal spray allows the drug to be quickly absorbed by the vascular bed of the nasal mucosa, thus a faster onset time[27].

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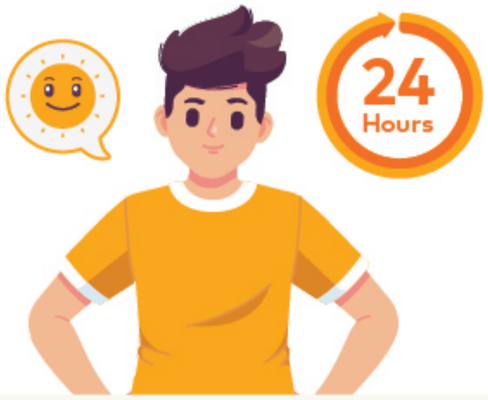

Onset as early as **24 hours**[6,*]

(Depressive symptoms reduction within 24 hours in patients with SPRAVATO® + oral antidepressant)

More than half of patients reach remission on day 28[6]

(SPRAVATO® + oral antidepressant: 52.5% vs placebo + oral antidepressant: 31.0%)

Long-term reduction of **70%** risk of relapse[28]

(Stable responders, HR=0.30, 95% CI 0.16-0.55; P<0.001)

One year later, **58.2%** of patients are still in remission[29]

(n=351/603)

Response: After continuing to take the appropriate amount of antidepressants, the MADRS score decreases by ≥50%; Remission: After continuing to take appropriate doses of antidepressants, the MADRS score ≤12[28].

*The difference in least square mean MADRS score between treatment groups at 24 hours after a single dose was -3.3 points[6]. The minimum clinically meaningful difference from placebo is defined as a ≥ 1.6 reduction in total MADRS score[30]. The TRANSFORM-2 was a phase 3, double-blind, active-controlled, multicenter study involving 227 adults with moderate to severe depression and a history of nonresponse to at least two antidepressants in the current episode. Confirmed nonresponders were randomly assigned to treatment with SPRAVATO® (56 or 84 mg twice weekly)+an antidepressant or an antidepressant+placebo nasal spray for 4 weeks. The primary efficacy endpoint was change in MADRS score from baseline to day 28[6].

Recommended Dosing for SPRAVATO®

- SPRAVATO® dosing should be individualised if necessary, and dose adjustments could be made to maintain the treatment response[1].
- In case one or two treatment sessions are missed, the next session should be scheduled when the next 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[1].

*Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.
†Dose adjustments should be made based on efficacy and tolerability to the previous dose. During the maintenance phase, SPRAVATO® dosing should be individualised to the lowest frequency to maintain remission/response.

Precautions for patients receiving SPRAVATO® treatment[1]

Do not eat for at least 2 hours before administration

Do not administer using nasal corticosteroid or nasal decongestant within 1 hour before administration

Do not drink liquids at least 30 minutes prior to administration

Before SPRAVATO® administration, patients should be instructed not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a vehicle or operating machinery, until the next day following a restful sleep. Patients should be reminded to arrange for the carer to pick up and drop off in advance or consider taking public transportation to leave the treatment center.

Procedures of Using SPRAVATO®

User guide video

Step 1 Get ready[1]

Before first device only:

- Instruct patient to blow nose **before first device only**

- Confirm required number of devices (56 mg = 2 devices; 84 mg = 3 devices)*

Step 2 Prepare the device[1]

- 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 the patient[1]

Instruct the patient to:

- Hold device as shown with the thumb gently supporting the plunger
- **Do not** press the plunger

Instruct the patient to:

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

*28mg (1 device) is a possible dose for adults ≥65 years.

Step 4 Patient sprays once into each nostril[1]

Before first device only:

- Insert tip straight into the **first nostril**
- Nose rest should touch the **skin between the nostrils**

Instruct the patient to:

- **Sniff gently** after spraying to keep medication inside nose

Instruct the patient to:

- Close opposite nostril
- **Breathe in through nose** while pushing plunger all the way up until it stops

Instruct the patient to:

- Switch hands to insert **tip** into the **second nostril**
- Repeat Step 4 to deliver second spray

Step 5 Confirm delivery and rest[1]

- Take device from patient
- Check that indicator panel shows **no green dots**. If you see a green dot, have patient spray again into the second nostril
- Check indicator again to confirm device is empty

Instruct the patient to:

- Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device**
- If liquid drips out, dab nose with a tissue

⚠ **Do not** blow nose

- **Repeat Steps 2-5** for the next device

Ensure that the patient waits 5 minutes after each device to allow medication to absorb

How Tolerable is SPRAVATO®?

Proven Tolerability

In clinical studies, among patients who used SPRAVATO® + oral antidepressants

- Only 3.8% (n=23/603) of patients discontinued the drug at 48 weeks due to side effects[29]
- No evidence of AEs related to abuse or misuse[28]
- No evidence of withdrawal syndrome in the first 2 weeks following SPRAVATO® cessation[28]

Common adverse reactions:

Dizziness

Nausea

Dissociation

Headache

Somnolence

Dizziness

Dysgeusia

Hypoaesthesia

Vomiting

These side effects generally only last for a short period of time[1,6].

How Tolerable is SPRAVATO®?

Proper risk management

- After receiving SPRAVATO®, the patient may experience somnolence and dissociation. The medical staff should monitor the patient until the patient is deemed to be clinically stable and can be allowed to leave the clinic[1].

- SPRAVATO® can cause blood pressure to rise, but this is only a short-term phenomenon, generally lasting about 1-2 hours[1].
- Before starting the treatment, the doctor should make sure that the patient's blood pressure is within the normal range[1].
- The medical staff should measure the blood pressure of the patient 40 minutes after the medication, and then measure it regularly according to clinical needs until the blood pressure returns to normal[1].

SPRAVATO® Q & A

Is there any patient who is not suitable to use SPRAVATO®[1]?

If the patient has the following conditions, please do not use SPRAVATO®

- Hypersensitivity to the active substance, ketamine, or to any of the excipients
- An increase in blood pressure or intracranial pressure poses a serious risk, including patients with aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels), history of intracerebral haemorrhage and recent (within 6 weeks) cardiovascular event, including myocardial infarction (MI)

SPRAVATO® is not recommended if the patient is currently pregnant

- If a woman becomes pregnant while being treated with SPRAVATO®, treatment should be discontinued, and the patient should be counselled about the potential risk to the foetus and clinical/therapeutic options as soon as possible

If the patient has any of the following symptoms, they should only use SPRAVATO® when the benefits outweigh the risks

- Haemodynamically significant valvular heart disease or heart failure
- Ever had uncontrolled brady- or tachyarrhythmias that lead to shortness of breath and haemodynamic instability
- Ever had problems with the blood supply to your brain (such as a stroke)
- History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure
- Ever had problems with drug abuse – prescribed medicines or illegal drugs - or a problem with alcohol
- Ever had a condition called psychosis - where you believe in things that are not true (delusions) or see, feel, or hear things that are not there (hallucinations)
- Ever had a condition called bipolar disorder, or symptoms of mania (where you become very over-active or over excited)
- Ever had hyperthyroidism that has not been sufficiently treated
- Ever had lung problems causing breathing difficulty (pulmonary insufficiency), including Chronic Obstructive Pulmonary Disease (COPD)
- Sleep apnoea with morbid obesity

SPRAVATO® Q & A

What mechanisms are there to ensure that SPRAVATO® can be used under safe conditions and reduce the risk of accidents?

Chemical structure

It is esketamine (left exosome), which has a higher affinity for NMDA receptors than arketamine[31]

Appoved

It has been verified by multiple clinical studies and approved by the Hong Kong Hospital Authority for the treatment of depression[6,28,29,32]

Low dosage

The dosage is low and infrequent; in the most frequent induction phase, patients are only recommended to take the drug twice a week, 28-84 mg each time[1]

Proper supervision

As a prescription drug, patients can only use SPRAVATO® in the clinic under the supervision of medical staff, and cannot use it at home by themselves[1]

SPRAVATO® Q & A

Can patients with hypertension use SPRAVATO®[1]?

In patients whose blood pressure prior to dose administration 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), SPRAVATO® therapy should only be prescribed when benefit is greater than risk in individual patients. Doctors may advise patients with hypertension to lower their blood pressure by improving their lifestyle habits to ensure that their condition is suitable for SPRAVATO® treatment.

Can I go to work after receiving SPRAVATO® treatment[1]?

After the medication, the doctor will observe the patient for a period of time to see if the patient is affected by side effects. In clinical trials, most people can leave the clinic 90 minutes after using SPRAVATO®. After receiving the treatment, the patient is not suitable to drive, use machines or performing any activities that require high concentration. The patient may depend on the nature of the job, consult the doctor whether his/her condition is suitable for work.

Are SPRAVATO® users at high risk of abuse or bladder problems[28,29]?

- In clinical trials, there is no evidence that patients have abused SPRAVATO® or developed withdrawal syndrome two weeks after treatment cessation.
- No patient requested an increase in dosage or dosing frequency.
- In the 48-week clinical trial, there were no cases of interstitial cystitis. The incidence of urinary system symptoms was low, and was generally mild-to-moderate, and resolved within 2 weeks.
- Before prescribing SPRAVATO®, doctors should assess each patient's risk of abuse or misuse, including whether they have a history of drug abuse or dependence.

References: 1. SPRAVATO® Hong Kong Prescribing Information P02. 2. Hillhouse TM, et al. Exp Clin Psychopharmacol. 2015;23:1-21. 3. Li YF. Pharmacol Ther. 2020;208:107494. 4. Whiting DW, et al. Psychiatrist. 2013;37:356–358. 5. Harmer CJ, et al. Lancet Psychiatry. 2017;4: 409–418. 6. Popova V, et al. Am J Psychiatry. 2019;176:428-438. 7. WHO. Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level. 2012. Available at: https://apps.who.int/iris/bitstream/handle/10665/78898/A65_10-en.pdf?sequence=1&isAllowed=y. Accessed: Nov 2020. 8. WHO. The global burden of disease: 2004 update. Available at: https://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed: Nov 2020. 9. Hospital Authority. Depression. Smart Patient. Available at: https://www21.ha.org.hk/smartpatient/SPW/zh-hk/Disease-Information/Disease/?guid=deee56b4-cec7-4d51-9460-1d071856856f. Accessed: 25 Oct 2021.10. Uher R, et al. Depress Anxiety. 2014;31:459-71. 11. Wang Y. Compr Psychiatry. 2020;98:152164. 12. Israel JA. Pharmaceuticals (Basel).2010;3:2426-2440. 13. Setiawan E, et al. Lancet Psychiatry. 2018;5:339-347. 14. Moylan S, et al. Mol Psychiatry. 2013;18:595-606. 15. Zaremba D, et al. JAMA Psychiatry. 2018;75:484-492. 16. Dale E, et al. Biochem Pharmacol. 2015;95:81-97. 17. Kudlow PA, et al. CNS Drugs. 2014;28:601-609. 18. Rush AJ, et al. Am J Psychiatry. 2006;163:1905-17. 19. Harada E, et al. Neuropsychiatr Dis Treat. 2016 Jun 30;12:1599-607. 20. Fekadu A, et al. Can J Psychiatry. 2011;56:549-57. 21. Ates-Alagoz Z, et al. Pharmaceuticals. 2013;6:480-499. 22. Khushboo, Sharma B. J Appl Biotechnol Bioeng. 2017;3:437-448. 23. Van Rensburg R, et al. South African Family Practice. 2019;61:59-62. 24. Ch´avez-Castillo M, et al. Hindawi. Advances in Pharmacological Sciences. 2019;2019. 25. Duman RS, et al. Nat Med. 2016;22:238-49. 26. Li N, et al. Science. 2010;329:959-64. 27. Andrade C. J Clin Psychiatry. 2015;76:e628-31. 28. Daly E, et al. JAMA Psychiatry. 2019;76:893-903. 29. Wajs E, et al. J Clin Psychiatry. 2020;81:19m12891. 30. Duru G, et al. Curr Med Res Opin 2008;24:1329-1335. 31.Molero P, et al. CNS Drugs 2018; 32:411–420. 32.Spravato. Hong Kong Drug Ofice. 33. Bahr R, et al. P T. 2019;44:340-75.

SPRAVATO®

ABBREVIATED PRESCRIBING INFORMATION

ACTIVE INGREDIENT(S): esketamine (as hydrochloride) INDICATION(S): Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode. Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency. DOSAGE & ADMINISTRATION: The decision to prescribe Spravato should be determined by a psychiatrist. Spravato is intended to be self-administered by the patient under the direct supervision of a healthcare professional. Assessment before treatment - Prior to dosing with Spravato blood pressure should be assessed. Post-administration observation - After dosing with Spravato, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted. Recommended dosing for Spravato in adults <65 years with treatment-resistant Major Depressive Disorder - Induction phase, Weeks 1-4: Starting day 1 dose: 56 mg; Subsequent doses: 56 mg or 84 mg twice a week); Maintenance phase, Weeks 5-8: 56 mg or 84 mg once weekly; From Week 9: 56 mg or 84 mg every 2 weeks or once weekly. Recommended dosing for Spravato in adults ≥65 years with treatment-resistant Major Depressive Disorder - Induction phase, Weeks 1-4: Starting day 1 dose: 28 mg; Subsequent doses: 28 mg, 56 mg or 84 mg twice a week* ; Maintenance phase, Weeks 5-8: 28 mg, 56 mg or 84 mg once weekly* ; 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. After depressive symptoms improve, treatment is recommended for at least 6 months. Acute short-term treatment of psychiatric emergency due to Major Depressive Disorder - Recommended dosage of Spravato for adult patients (<65 years) is 84 mg twice per week for 4 weeks. Dosage reduction to 56 mg should be made based on tolerability. After 4 weeks of treatment with Spravato, the oral antidepressant (AD) therapy should be continued, per clinical judgement. 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. Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should be advised not to administer these medicinal products within 1 hour before Spravato administration. Patients who have missed treatment session(s) during the first 4 weeks of treatment should continue with their current dosing schedule. For patients with treatment-resistant Major Depressive Disorder who miss treatment session(s) during maintenance phase and have worsening of depression symptoms, per clinical judgement, consider returning to the previous dosing schedule. Efficacy of Spravato in Japanese patients has been studied, but not established. Method of administration - For nasal use only. Do not prime before use. CONTRAINDICATIONS: Hypersensitivity to the active substance, ketamine, or to any of the excipients listed in the full prescribing information. Patients for whom an increase in blood pressure or intracranial pressure poses a serious risk: Patients with aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels); Patients with history of intracerebral haemorrhage; Recent (within 6 weeks) cardiovascular event, including myocardial infarction (MI). SPECIAL WARNINGS & PRECAUTIONS: Suicide/suicidal thoughts or clinical worsening - Effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated. Use of Spravato does not preclude the need for hospitalisation if clinically warranted, even if patients experience improvement after an initial dose of Spravato. Close supervision of patients especially in early treatment and following dose changes. Patients and caregivers 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. 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. Neuropsychiatric and motor impairments - Spravato has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety during the clinical trials. At each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered stable based on clinical judgement. Respiratory depression - Respiratory depression may occur at high doses following rapid intravenous injection of esketamine or ketamine when used for anaesthesia. Close monitoring 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 administration of the medicinal product and last approximately 1-2 hours. 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. 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 pressure prior to dose administration is judged to be elevated, it is appropriate to adjust lifestyle and/or pharmacologic therapies to reduce blood pressure before starting treatment with Spravato. If blood pressure is elevated prior to Spravato administration a decision 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. Blood pressure should be measured around 40 minutes post-dose and subsequently as clinically warranted until values decline. If blood pressure remains elevated for a prolonged period of time, 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. 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. Spravato should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available. Refer to the full prescribing information for examples of conditions. Drug abuse, dependence, withdrawal - Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of Spravato. Prior to prescribing Spravato, each patient's risk for abuse or misuse should be assessed and patients receiving esketamine should be monitored for the development of behaviours or conditions of abuse or misuse, including drug seeking behaviour, while on therapy. Dependence and tolerance have been reported with prolonged use of ketamine. In individuals who were dependent on ketamine, withdrawal symptoms of cravings, anxiety, shaking, sweating and palpitations have been reported upon discontinuing ketamine. Ketamine, the racemic mixture of arketamine and esketamine, is a medicinal product that has been reported to be abused. The potential for abuse, misuse and diversion of Spravato is minimised due to the administration taking place under the direct supervision of a healthcare professional. Spravato contains esketamine and may be subject to abuse and diversion. Other populations at risk - Use 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: (i) Presence or history of psychosis; (ii) Presence or history of mania or bipolar disorder; (iii) Hyperthyroidism that has not been sufficiently treated; (iv) History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure. Elderly (65 years of age and older) - May have a greater risk of falling once mobilised, therefore, these patients should be carefully monitored. Severe hepatic impairment - Due to expected increase in exposure and lack of clinical experience, Spravato is not recommended in patients with Child-Pugh class C (severe) hepatic impairment. Hepatotoxicity has been reported with chronic ketamine use, so the potential for such an effect due to long-term use of Spravato cannot be excluded. Urinary tract symptoms - Urinary tract and bladder symptoms have been reported with Spravato use. Recommended to monitor for urinary tract and bladder symptoms during the course of treatment and refer to an appropriate healthcare provider when symptoms persist. SIDE EFFECTS: The most commonly observed adverse reactions in treatment resistant depression patients treated with Spravato were dizziness, nausea, dissociation, headache, somnolence, vertigo, dysgeusia, hypoaesthesia, and vomiting. Refer to the full prescribing information for other side effects. PREGNANCY & LACTATION: Spravato is not recommended during pregnancy and in women of childbearing potential not using contraception. There are no or limited data on the use of esketamine in pregnant women. If a woman becomes pregnant while being treated with Spravato, treatment should be discontinued, and the patient should be counselled about the potential risk to the foetus and clinical/therapeutic options as soon as possible. It is unknown whether esketamine is excreted in human milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Spravato therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. INTERACTIONS: Concomitant use of Spravato with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation, which therefore should be closely monitored. Blood pressure should be closely monitored when Spravato is used concomitantly with psychostimulants (e.g., amphetamines, methylphenidate, modafanil, armodafinil) or other medicinal products that may increase blood pressure (e.g. xanthine derivatives, ergometrine, thyroid hormones, vasopressin, or MAOIs, such as, tranylcypromine, selegiline, phenelzine). PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING. Spravato aPI ver.2.0

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