

Spravato® nasal spray, 28 mg

Each nasal spray device contains:
28 mg esketamine
Inactive and allergenic ingredients in the preparation – see section 6 “Further information”.
Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
This medicine has been prescribed for your treatment. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

In addition to this leaflet, Spravato is provided with a Patient Safety Information Card. This card contains important safety information you should be aware of and adhere to before starting and during treatment with Spravato. Read the Patient Safety Information Card and the patient leaflet before you start using the preparation. Keep the card for further reading, if necessary.

1. WHAT IS THE MEDICINE INTENDED FOR?

Spravato, in combination with antidepressants of the SSRI and SNRI groups, is intended for treatment of Major Depression Disorder in adult patients who have not responded to at least two types of treatment with antidepressants for the current episode of depression, whose level is moderate to severe.

Spravato is also used in adults to rapidly reduce symptoms of depression in situations requiring immediate intervention (also known as a psychiatric emergency).

Limitations of use – The effectiveness of Spravato in preventing suicide or in reducing suicidal thoughts or behavior has not been demonstrated. Use of Spravato does not preclude the need for hospitalisation if clinically warranted, even if the patient experiences improvement after initiation of administration of the medicine.

Therapeutic group: Other antidepressants

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are allergic to esketamine or to a similar medicine called ketamine used for anesthesia, or to any of the other ingredients contained in the medicine (as listed in section 6).
- You have ever suffered from the following conditions:
 - An aneurysm
 - Bleeding in the brain
- You recently had a heart attack (in the past 6 weeks). This is because Spravato can cause a temporary increase in blood pressure that may lead to serious complications in these conditions.

Do not use the medicine if you are suffering from any of the above conditions. If you are not sure, consult with your doctor before using the medicine – your doctor will decide whether you can use this medicine.

Special warnings regarding use of the medicine

Before beginning treatment with Spravato tell the doctor if:

- You suffer from a heart problem which is not well controlled such as: poor blood flow in the blood vessels of the heart frequently accompanied by chest pain (such as angina), high blood pressure, heart valve disease or heart failure.
 - You have ever suffered from a problem of blood supply to your brain (such as a stroke).
 - You have ever suffered from a problem of drug abuse – whether prescribed medicines or illegal drugs.
 - You have ever suffered from a condition called psychosis – where a person believes in things that are not true (delusions) or sees, feels or hears things that are not there (hallucinations).
 - You have ever suffered from bipolar disorder, or symptoms of mania (a condition where a person becomes very overactive or over excited).
 - You have ever suffered from an overactive thyroid gland that is not under control (hyperthyroidism).
 - You have ever suffered from lung problems causing breathing difficulty (pulmonary insufficiency), including Chronic Obstructive Pulmonary Disease (COPD).
 - You suffer from sleep apnea and also from extreme overweight.
 - You have ever suffered from a slow or fast heartbeat causing shortness of breath, palpitations or chest discomfort, feeling light-headed or fainting.
 - You have ever suffered from a serious brain injury or serious problems affecting the brain, particularly where there is increased pressure in the brain.
 - You suffer from severe liver problems.
- If you suffer from any of the conditions described above or if you are uncertain, consult with your doctor before using the medicine – your doctor will decide whether you should use this medicine.

Worsening of depression

Tell your doctor immediately or go to the nearest hospital straight away if you have thoughts at any time of harming or killing yourself.

If you are depressed, you may find it helpful to talk to a relative or a close friend and ask them if they think your depression has gotten worse, or if they are worried about your behavior. It is worthwhile to have them read this leaflet.

Blood pressure

Spravato may increase your blood pressure for one or two hours after you use it. Therefore, your blood pressure will be measured before you take Spravato and after you take it.

If your blood pressure is high before taking the medicine, your doctor will decide whether to start administering the medicine or wait until your blood pressure is lower. If your blood pressure goes up after the medicine is administered and stays high for more than a few hours, it is possible that you may need some more tests.

The medicine may cause a temporary increase in your blood pressure after taking a dose. Your blood pressure will therefore be checked before and after taking the medicine. Tell the medical staff right away if you start getting chest pain, shortness of breath, a sudden and severe headache, changes in vision or seizures after taking the medicine.

Tell your doctor if you begin to suffer from any of the following during treatment with the medicine:

- Difficulty in concentration, judgment and thinking (see also “Driving and operating machinery” and section 4 “Side effects”). During and after each use of the medicine, the doctor will check your condition and will decide for how long you need to be kept under observation.
- Sleepiness (sedation), fainting, dizziness, spinning sensation, anxiety, or feeling disconnected from yourself, from your thoughts and your feelings, feeling disconnected from place and time (dissociation), difficulty breathing (respiratory depression). Tell the medical staff right away if you feel that you cannot stay awake or if you feel that you are about to faint.
- Pain when urinating or appearance of blood in the urine – these could be signs of bladder problems. These can occur with high doses of a similar medicine (called ketamine) used over a long period.

Tell the doctor if you begin to suffer from any of the above effects during treatment with Spravato.

Elderly (above 65)

If you are elderly (above 65), you will be carefully monitored as you may be at increased risk of falling when you start moving around after the treatment.

Children and adolescents

The medicine is not intended for children and adolescents under 18 years of age. This is because the medicine has not been tested in this age group for treatment of resistant depression.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular if you are taking:

- Medicines used for treatment of mood disturbances or for treatment of severe pain (for example, benzodiazepines, opioids), or medicines or beverages containing alcohol.
- Stimulants such as those used for treatment of narcolepsy or medicines for treatment of attention deficit hyperactivity disorder (ADHD) (for example, amphetamines, methylphenidate, modafinil, armodafinil).
- Medicines that could increase your blood pressure, such as thyroid hormones, medicines for the treatment of asthma, such as xanthine derivatives, medicines for treatment of bleeding after childbirth (ergometrine) and heart medicines, such as vasopressin.
- Medicines for treatment of depression or Parkinson's disease – monoamine oxidase inhibitors (MAOIs) (for example, tranylcypromine, selegiline, phenelzine).

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, consult your doctor before receiving the treatment.

Contraception:

- If you are of childbearing age and capable of becoming pregnant, you must use contraceptives during treatment. Talk with your doctor about suitable methods of contraception.

Pregnancy:

- Do not take Spravato if you are pregnant.
- You must inform your doctor immediately if you become pregnant while being treated with Spravato, in order to decide whether to stop treatment with the medicine and to examine other options for treatment.

Breast-feeding:

- Do not take Spravato if you are breast-feeding. Consult with your doctor before using Spravato if you are breast-feeding. Your doctor will discuss with you the option of stopping breast-feeding or stopping use of the medicine. The doctor will take into account the benefit of breast-feeding for you and your child, against the benefit you would gain from treatment with the medicine.

Driving and operating machinery

Spravato can make you feel sleepy, dizzy, and have other side effects that can temporarily affect your ability to drive, operate dangerous machinery or undertake any activity that requires you to be completely alert. After treatment with Spravato, do not undertake these activities until the next day, following a good night's sleep.

3. HOW SHOULD THE MEDICINE BE USED?

Always use according to the doctor's instructions.

Check with the doctor or pharmacist if you are uncertain.

You will use the Spravato nasal spray yourself under the supervision of your doctor or a healthcare professional in a healthcare setting, such as a clinic or doctor's office. Your doctor or a healthcare professional will show you how to use the Spravato spray device (see also **Instructions for use**).

The dosage and treatment regimen will be determined by the doctor only, and s/he will decide how often you should come to the clinic or the doctor's office for treatment.

- Each nasal spray device delivers two sprays (one spray per nostril).
- Spravato is administered twice a week for the first 4 weeks of treatment.

If your treatment is continued:

- Spravato is usually administered once a week for 4 weeks.
- After that, Spravato may be given either once a week or once every two weeks.

You must adhere and strictly follow the dosage regimen and treatment times with Spravato as determined by your doctor.

During and after each treatment with Spravato nasal spray, you will be examined by your doctor and your condition will be monitored for at least two hours. The doctor will decide when you are ready to be released from the clinic/hospital.

Food and drink:

Some patients who take Spravato experience nausea and vomiting. Do not eat for at least two hours before treatment with

Spravato. Do not drink for at least 30 minutes before treatment with Spravato.

Nasal sprays:

If you need to use nasal corticosteroids or decongestants, do not use these medicines for an hour before treatment with Spravato.

If you took a higher dose than you should:

You will receive the treatment with Spravato under the supervision of your doctor or a healthcare professional in a healthcare setting, such as a clinic or doctor's office. It is therefore unlikely that you will receive too high a dose.

If you did receive too high a dose of Spravato, you are more likely to suffer from side effects (see section 4 “Side effects”).

If you stop treatment with the medicine:

It is important to make sure you come in for your scheduled appointments, so that this medicine is effective for you. Even if there is an improvement in the state of your health, do not stop treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult a doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Spravato may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Inform the doctor if one of the following side effects appears:

Very common side effects (appear in more than 1 patient in 10)

- Feeling disconnected from yourself, your thoughts, feelings and things around you
- Feeling dizzy
- Headache
- Change in sense of taste
- Feeling sleepy
- Decreased feeling or sensitivity, including the area around the mouth
- Spinning sensation (“vertigo”)
- Vomiting
- Nausea
- Increased blood pressure

Common side effects (appear in 1-10 patients in 100)

- Exaggerated sense of happiness (“euphoria”)
- Feeling confused
- Feeling restless (“agitation”)
- Feeling anxious
- Distorted sense of sight, hearing, touch
- Feeling of irritability/disquiet
- Panic attacks
- Change in perception of time
- Seeing, feeling, smelling or hearing things that are not there (hallucinations)
- Feeling detached from reality
- Problems with thinking
- Muscle tremors
- Feeling sleepy with low energy
- Speech difficulties
- Difficulty concentrating
- An unusual feeling in the mouth (such as tingling or a crawling feeling)
- Increased sensitivity to noise or sounds
- Tinnitus – persistent ringing in the ears
- Blurred vision
- Fast heartbeat
- Nasal discomfort
- Irritated throat
- Sore throat
- Nasal dryness including dry crusts in the nose
- Itchy nose
- Dry mouth
- Decreased feeling or sensitivity in the mouth
- Excessive sweating
- Frequent need to pass urine
- Pain when passing urine
- Urgent need to pass urine
- Feeling abnormal
- Feeling drunk
- Feeling weak
- Crying
- A feeling of body temperature change
- High blood pressure

Uncommon side effects (appear in 1-10 patients in 1,000)

- Thoughts, speech and physical movements slow down
- Emotional distress
- Feeling uneasy or tense
- Fast eye movements that you cannot control
- Hyperactivity
- Increased salivation
- Cold sweats
- Problems walking

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, you must consult the doctor.

Reporting of side effects

Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: <https://sideeffects.health.gov.il>.

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (Exp. Date) that appears on the package. The expiry date refers to the last day of that month.
- Storage – There are no special storage instructions. It is recommended to store at room temperature.
- Discard the used spray device in accordance with local requirements.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
citric acid monohydrate, edetate disodium, sodium hydroxide, water for injection

What the medicine looks like and the contents of the package:

A nasal spray device for single use containing 28 mg esketamine. Each spray device contains two sprays, one for each nostril. The solution in the spray device is clear, colorless or slightly yellowish.

Approved pack sizes: a pack containing two 28 mg spray devices, a pack containing three 28 mg spray devices.

Each spray device is individually packaged in a sealed blister.

Not all pack sizes may be marketed.

License holder and address: J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel.

Manufacturer: Renaissance Lakewood LLC, 1200 Paco Way, Lakewood, New Jersey (NJ) 08701, U.S.A.

Approved by the MOH in 08/2021.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 164-65-36113-00

The following information is for medical personnel only:

Instructions for use
Spravato
(esketamine)
Nasal Spray Device



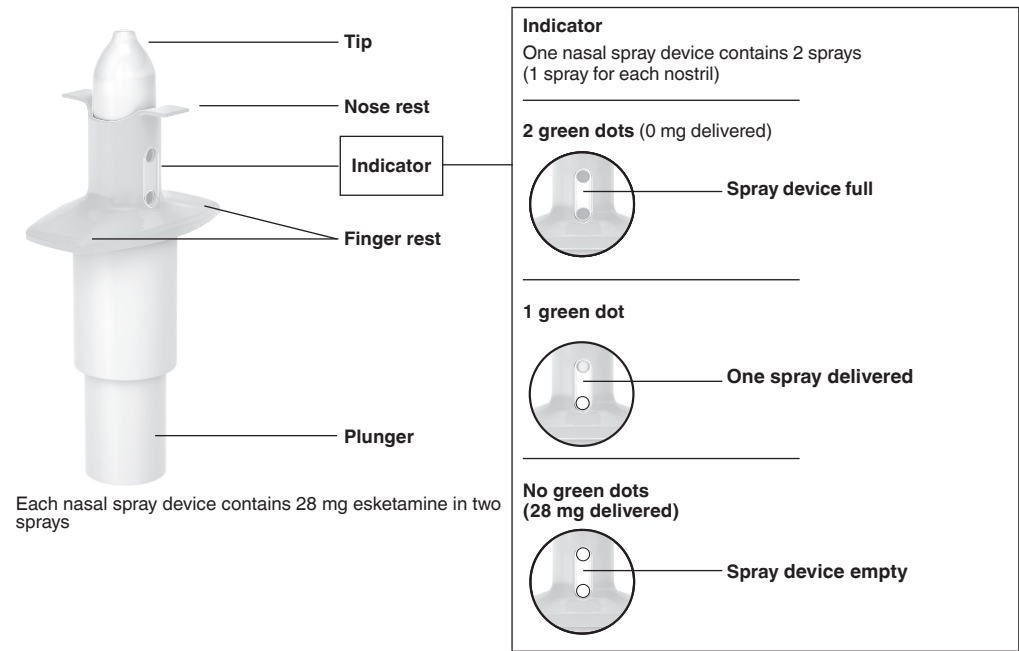
28 mg per spray device

Each nasal spray device contains 28 mg esketamine in two sprays

Important

The spray device is intended to be used by the patient, **under the supervision of a healthcare professional**. Read the instructions for use in their entirety before instructing and supervising the patient.

Nasal Spray Device



Step 1 – Preparation

Before use of the first spray device only:

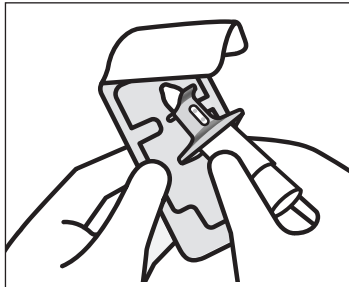
Instruct patient to blow nose **before first spray only**.



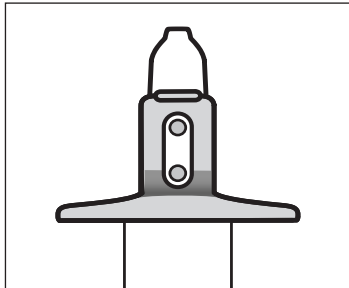
Confirm the required number of nasal spray devices needed for the patient.

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

Step 2 – Preparing the nasal spray device

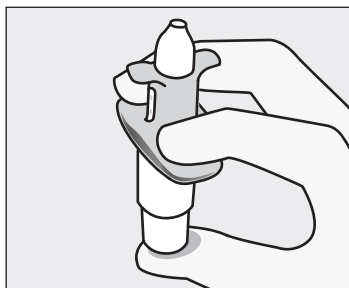


- Check the expiry date (“EXP”). If it has expired, get a new spray device.
- Peel off the blister cover and remove the spray device.



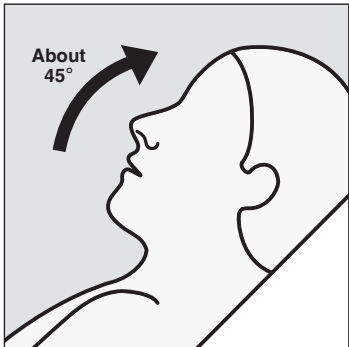
- Do not press on the plunger to load the medicine. This will cause a loss of medicine.
- Check that the indicator **shows two green dots**. If not, discard the spray device and take a new one.
- Give the spray device to the patient.

Step 3 – Prepare the patient



Instruct the patient:

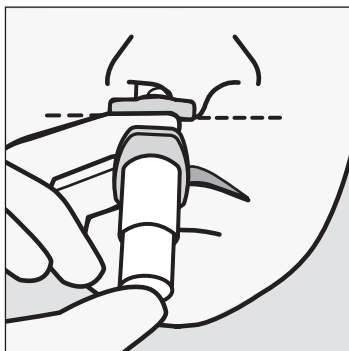
- To hold the spray device as in the illustration, with the thumb gently supporting the plunger.
- Do not** press the plunger.



Instruct the patient:

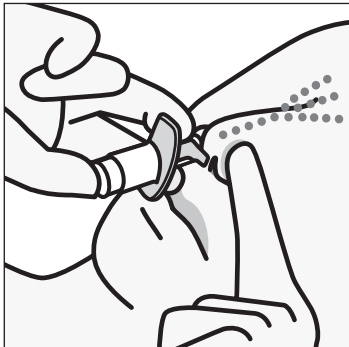
- To recline the head at an angle of about 45 degrees during administration of the medicine in order to keep the medicine inside the nose.

Step 4 – Patient sprays once into each nostril



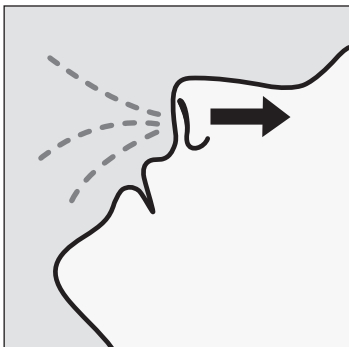
Instruct the patient:

- To insert the tip of the spray device straight into **the first nostril**.
- The nose rest should touch **the skin between the nostrils**.



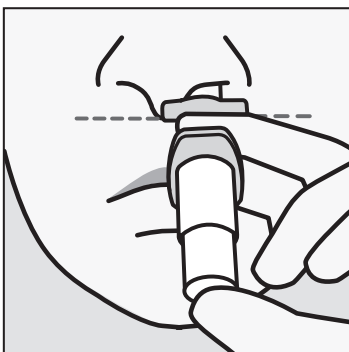
Instruct the patient:

- To close the opposite nostril.
- To breathe in through the nose** while pushing the plunger all the way up until it stops.



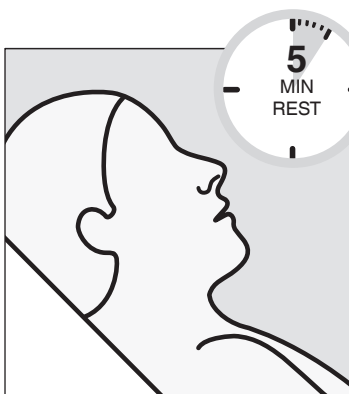
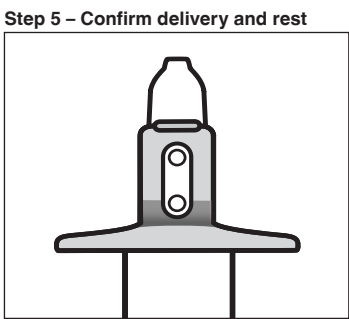
Instruct the patient:

- To sniff gently** after spraying to keep the medicine inside nose.



Instruct the patient:

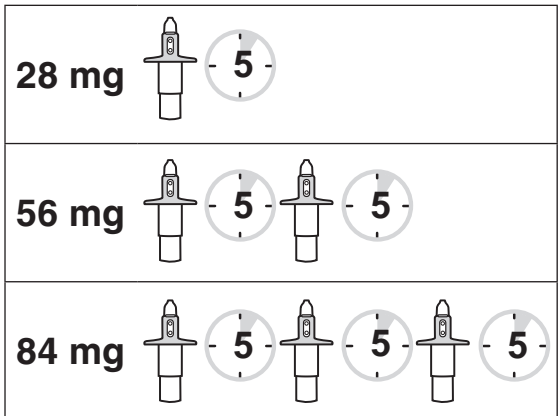
- To transfer the spray device to the other hand in order to insert the **tip** of the spray device into the **second nostril**.
- To repeat Step 4 to deliver the second spray.



Instruct the patient:

- To rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each nasal spray device**.
- If liquid drips out, dab the nose gently with a tissue.
- Do not blow the nose.

Next nasal spray device (if required)



- Repeat Steps 2-5** if more than one nasal spray device is required.
- IMPORTANT:** Ensure that the patient waits 5 minutes after each spray device in order to allow for the medicine to be absorbed.
- Discard used spray devices in accordance with local requirements.