B. PACKAGE LEAFLET

Package leaflet: Information for the user

Esketamine IDD 5 mg/ml, oplossing voor injectie/infusie
Esketamine IDD 25 mg/ml, oplossing voor injectie/infusie
esketamine

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Esketamine IDD and what it is used for

Esketamine IDD belongs to one of a group of medicines called general anaesthetics, which is used to put you to sleep during an operation.

Esketamine IDD is used:
- to initiate and perform general anaesthesia, as the only anaesthetic or possibly in combination with sleeping pills (hypnotics),
- to supplement regional anaesthesia (local anaesthesia),
- for anaesthesia and pain relief (analgesia) in emergency situations,
- for pain control in artificial respiration (intubation).

2. What you need to know before you are given Esketamine IDD

Esketamine IDD must not be used:
- if you are allergic to esketamine or any of the other ingredients of this medicine (listed in section 6),
- if high blood pressure or increased pressure in the brain is a serious risk for you,
- if you have poorly controlled or untreated high blood pressure,
- if you have a condition called eclampsia or pre-eclampsia (which is a complication of pregnancy that causes high blood pressure),
- if you have an overactive thyroid (insufficiently treated hyperthyroidism),
- in situations during childbirth which require relaxed uterus muscle, (e.g. threat of a uterus rupture, prolapsed umbilical cord),
- if you suffer from an existing heart disease with reduced blood flow and get esketamine as the only remedy for anaesthesia.
- in combination with xanthine derivatives (e.g. aminophylline or theophylline) (the convulsion threshold may become lower),
- in combination with ergometrine (used during or after childbirth and to inhibit milk production).

Warnings and precautions
Talk to your doctor or nurse before you are given Esketamine IDD:

- in the case of chest pain (angina pectoris) or in the case of heart attack (myocardial infarction) during the last 6 months,
- in the case of a weak heart (cardiac insufficiency),
- if you have an increased brain pressure, except under appropriate ventilation, and in the case of damage or diseases of the central nervous system,
- if you have or have had severe psychiatric problems,
- if you have an increased eye pressure (glaucoma) and eye injuries, as well as if you need an eye examination or eye surgery in which eye pressure must not be increased,
- in the case of surgery in the upper respiratory tract,
- if you are under the influence of alcohol (chronic or acute alcohol),
- if you have liver disease,
- if you have a history of drug abuse or addiction.

Out-patient treatment
Adequate continuous monitoring of the patient must be ensured until discharge.
You should be accompanied home after out-patient anaesthesia and you should not drink alcohol within the next 24 hours.
You are not allowed to drive, operate machinery or operate dangerous activities for at least 24 hours following esketamine administration.

In diagnostic and therapeutic procedures of the upper respiratory tract , laryngeal spasms (laryngospasms) are possible, especially in children. Controlled ventilation may be necessary.

Long-Term Use
In patients who used ketamine during long term therapy (1 month to several year), cases of urinary disorders (such as bladder inflammation) and liver toxicity have been reported. Similar effects may also occur following esketamine abuse.

Drug Abuse and Dependence
There are reports of drug abuse with ketamine which suggest that ketamine abuse causes a variety of symptoms such as flashbacks, hallucinations, anxiety, dissatisfaction feeling, insomnia or disorientation. Urinary symptoms such as bladder inflammation and disorders of the liver were also reported after use of ketamine. Same symptoms may occur with Esketamine in individuals with a history of drug abuse or dependence. Therefore esketamine should be prescribed and administered with caution only under the supervision of a doctor.

Other medicines and Esketamine IDD
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

- Xanthine derivatives (for example aminophylline, theophylline) Ergometrine (used during or after childbirth and to inhibit milk production)
- Sympathomimetics (for example adrenaline or noradrenaline), thyroid hormones and vasopressin may lead to an increase in blood pressure and in heart rate or heart rhythm disorders.
- - In combination with sleeping pills (hypnotics), benzodiazepines (for example diazepam) or neuroleptics used for mental disorders, as the duration of effect of Esketamine IDD may be prolonged.
- Barbiturates and opiates (such as morphine) given together with Esketamine IDD may prolong the recovery phase after the application of esketamine .
- The anaesthetic effect of some gas anaesthetics (for example, isoflurane, desflurane, sevoflurane) is increased by administration of Esketamine IDD so lower doses may be needed.
- The effect of muscle relaxants such as pancuronium-or suxamethonium- may be prolonged due to the use of Esketamine IDD.
- Concomitant administration of esketamine with medicines that inhibit the enzyme CYP3A4 may require a reduced dose of esketamine to achieve the desired clinical outcome.
- Concomitant administration of esketamine with medicines that induce the enzyme CYP3A4 may require an increased dose of esketamine to achieve the desired clinical outcome.

Esketamine IDD with alcohol
You should not drink alcohol within 24 hours after receiving this anaesthetic.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.

Pregnancy
This medicine will not be used during pregnancy unless your doctor comes to the conclusion that the therapeutic benefit for you outweighs any possible hazard for the child. It may negatively affect the baby's breathing rate (respiratory depression) if used during delivery.

Breast-feeding
Esketamine can pass into breast-milk, however, it is unlikely to affect the baby when it is used at the recommended doses.

Driving and using machines
You should not drive or operate machinery for at least 24 hours after receiving this medicine. Esketamine IDD results in reduced response times which are important in situations requiring special alertness, e.g., when driving a car.
You should only go home if you are accompanied.

Esketamine IDD contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

3. How to use Esketamine IDD

For hospital use only. Esketamine IDD will only be given to you by or under the supervision of an anaesthetist.

You will be asked to fast for 4 to 6 hours before you are due to receive Esketamine IDD.

Method of administration
Esketamine is given as a slow injection into your vein (intravenous) or muscle (intramuscular). If necessary, the injection can be repeated or it can be given as an infusion.

If you are given more Esketamine IDD than you should
At very high doses, life-threatening symptoms such as seizures abnormal heart rhythm a respiratory arrest are to be expected but as the product is given only by trained specialists, those overdoses with these symptoms are very unlikely.

If you have further questions on the use of this medicine ask your doctor, anaesthetist, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects usually depend on the dose and speed of injection and usually get better without treatment..

Very common side effects (may affect more than 1 in 10 patients) are:
- recovery reactionsincluding vivid dreams, including nightmares, dizziness and restlessness;
- increase in blood pressure and heart rate.

Common side effects (may affect up to 1 in 10 patients) are:
- blurred vision;
- temporary increase in heartbeat;
- effects on breathing during anaesthesia increased oxygen consumption, laryngeal spasms (laryngospasm), and temporary respiratory depression;
- Being sick, increased salivation (drooling).

Uncommon side effects (may affect up to 1 in 100 patients) are:
- Increased body movements (for example muscle twitching), which can resemble seizures, and increased eye movements;
- double vision, increased pressure in the eye;
- skin redness (rash), and skin rash (exanthema);
- pain and/orredness at the injection site.

Rare side effects (may affect up to 1 in 1,000 patients) are:
- severe allergic reaction;
- irregular heart beat or slower heart beat;
- low blood pressure.

Very rare side effects (may affect up to 1 in 10,000 patients) are:
hypersensitivity reactions (anaphylactoid reactions).

Not known side effects (frequency can not be estimated from the available data) are:
- hallucinations, feeling of dissatisfaction, anxiety and disorientation;
- abnormal liver function test results;
- liver injury.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via het Nederlands Bijwerkingen Centrum Lareb, website: www.lareb.nl. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Esketamine IDD

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton/ampoule/vial after "Exp". The expiry date refers to the last day of that month.

Do not freeze.

The chemical and physical in-use stability of ready-to-use infusion solutions prepared with sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) infusion solution has been demonstrated over 24 hours under storage at 25°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours at 2 to 8°C, for dilution not under controlled and validated aseptic conditions.
The content is intented for single use only. Any unused residue should be discarded. Only a clear and colourless solution should be used.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Esketamine IDD contains

- The active substance is esketamine

Esketamine IDD 5 mg/ml, solution for injection/infusion

1 ml solution for injection/infusion contains 5 mg esketamine as 5.77 mg of esketamine hydrochloride.
1 ampoule of 5 ml solution for injection/infusion contains 25 mg of esketamine as 28.83 mg esketamine hydrochloride.
1 vial of 20 ml solution for injection/infusion contains 100 mg of esketamine as 115.40 mg esketamine hydrochloride.

Esketamine IDD 25 mg/ml, solution for injection/infusion

1 ml solution for injection/infusion contains 25 mg of esketamine as 28.83 mg of esketamine hydrochloride.
1 ampoule of 2 ml solution for injection/infusion contains 50 mg of esketamine as 57.66 mg of esketamine hydrochloride.
1 ampoule containing 10 ml solution for injection/infusion contains 250 mg of esketamine as 288.30 mg of esketamine hydrochloride.

1 vial of 10 ml solution for injection/infusion contains 250 mg of esketamine as 288.3 mg of esketamine hydrochloride.
1 vial of 50 ml solution for injection/infusion contains 1250 mg of esketamine as 1441.5 mg of esketamine hydrochloride.

- The other ingredients are sodium chloride, hydrochloric acid (for pH-adjustment), and water for injections.

What Esketamine IDD looks like and contents of the pack

Esketamine IDD is a clear, colourless solution for injection/infusion.

Pack sizes:

Esketamine IDD 5 mg/ml
10 ampoules each containing 5 ml of solution for injection/infusion.
1 vial containing 20 ml of solution for injection/infusion.

Esketamine IDD 25 mg/ml
10 ampoules each containing 2 ml of solution for injection/infusion.
10 ampoules each containing 10 ml of solution for injection/infusion.
1 vial containing 10 ml of solution for injection/infusion.
1 vial containing 50 ml of solution for injection/infusion.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

INTERNATIONAL DRUG DEVELOPMENT
104 boulevard Auguste Blanqui
75013 Paris
France

Manufacturer

HAUPT PHARMA LIVRON
1 rue Comte de Sinard
26250 Livron-sur-Drôme – France

This medicinal product is authorised in the Member States of the EEA under the following names:

Member States	Proposed (Invented) Names
Germany	Esketamin Sintetica 5 mg/ml Injektions-/Infusionslösung Esketamin Sintetica 25 mg/ml Injektions-/Infusionslösung
Netherlands	Esketamine IDD 5 mg/ml, oplossing voor injectie/infusie Esketamine IDD 25 mg/ml, oplossing voor injectie/infusie
Sweden	Esketamin IDD, 5 mg/ml, injektions-/infusionsvätska, lösning Esketamin IDD, 25 mg/ml, injektions-/infusionsvätska, lösning
France	ESKESIA 5 mg/ml solution injectable/pour perfusion ESKESIA 25 mg/ml solution injectable/pour perfusion
Austria	Esketamin Sintetica 5 mg/ml Injektions-/Infusionslösung Esketamin Sintetica 25 mg/ml Injektions-/Infusionslösung
Ireland	Esketamine Sintetica 5 mg/ml solution for injection/infusion Esketamine Sintetica 25 mg/ml solution for injection/infusion
UK	Esketamine Sintetica 5 mg/ml solution for injection/infusion Esketamine Sintetica 25 mg/ml solution for injection/infusion

This leaflet was last revised in 01/2023.

The following information is intended for healthcare professionals only:

Esketamine should be administered only by specialist of anaesthesiology or emergency medicine. Esketamine is for hospital use only.
As aspiration cannot be completely excluded and due to the possibility of respiratory depression, intubation and ventilation equipment must be available.

Posology

For induction of general anaesthesia 0.5 to 1 mg/kg of esketamine is given intravenously or 2 to 4 mg/kg intramuscularly, half the initial dose is re-injected as needed, generally every 10 to 15 minutes.

As an alternative to injection, esketamine can be administered as a continuous infusion at a dose of 0.5 to 3 mg esketamine/kg/h. In case of multiple injuries (polytrauma) and in patients with poor general condition a dose reduction may be necessary.

For analgesic supplementation of regional and local anaesthesia 0.125 to 0.25 mg esketamine/kg/h is administered as intravenous infusion.

For analgesia in artificial respiration (intubated intensive care patients), 0.25 mg esketamine/kg is generally used as a bolus with a subsequent continuous infusion of 0.2 to 0.5 (up to 1.5) mg esketamine/kg/h with simultaneous benzodiazepine administration.

When used as a permanent infusion for analgesia in artificial respiration, the duration of the application should not exceed 4 to 6 weeks.

For analgesia in emergency medicine 0.25 to 0.5 mg esketamine/kg is administered intramuscularly or 0.125 to 0.25 mg/kg as a slow intravenous injection.

Increased salivation should be prophylactically treated with atropine.

The risk of psychological reactions occurring during recovery from anaesthesia can be greatly reduced by the co-administration of a benzodiazepine.

Where possible, the use of esketamine should follow the ordinary guidelines regarding fasting, 4 to 6 hours before anaesthesia.

In case of hepatic impairment, a dose reduction may be required.

Paediatric population
In paediatric surgery, as well as in emergency medicine, esketamine hydrochloride is generally used as monotherapy; in case of other indications, a combination with hypnotics is recommended.

Dosage of esketamine across subgroups of paediatric patients of different ages has not been adequately studied. Based on the information available, dosage in paediatric patients is not expected to differ substantially from that in adults.

Method of administration

Esketamine is for intravenous or intramuscular use. It can be injected slowly or administered as an infusion. For infusion, either the undiluted injection solution can be used or it can be diluted beforehand.

Overdose

Above the 25-fold usual anaesthetic dose, life-treatening symptoms are expected. The clinical symptoms of overdose are convulsion, cardiac arrhythmia and respiratory arrest.
Respiratory arrest must be treated by assisted or controlled ventilation until sufficient spontaneous respiration is achieved. Convulsions should be treated with intravenous administration of diazepam. If treatment with diazepam does not result in sufficient response, administration of phenytoin or phenobarbital is recommended.
No specific antidote is presently known.

Incompatibilities

Esketamine must not be mixed with barbiturates, diazepam, 4-hydroxybutyric acid (sodium salt), theophylline, furosemide sodium or sodium bicarbonate since they are chemically incompatible and precipitation may occur.

Precautions for side effects

If high doses are administered and the injection is carried out more quickly, a respiratory standstill is to be expected, which must be bridged by means of assisted ventilation until the resetting of sufficient spontaneous breathing. The administration of hypnotics, especially benzodiazepines or neuroleptics, reduces the side effects of Esketamine IDD.