SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Esketamine 25 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless solution.

pH 3.0 – 4.0.

Osmolality = 270 – 310 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Induction and maintenance of general anaesthesia, as the only anaesthetic or possibly in combination with hypnotics.

- Supplementation of regional or local anaesthesia.

- Anaesthesia and pain relief (analgesia) in emergency medicine.
- Pain control in artificial respiration (intubation)

4.2 Posology and method of administration

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 (see section 4.4).

The risk of psychological reactions occurring during recovery from anaesthesia can be greatly reduced by the co-administration of a benzodiazepine (see also sections 4.4 and 4.8).

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.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Esketamine must not be used:

- in the case of hypersensitivity to the active substance or to any of the excipients listed in section 6.1,

- in patients to whom elevation of blood pressure or intracranial pressure forms a serious risk,

- if hypertension is poorly adjusted or not treated (arterial hypertension - systolic / diastolic blood pressure above 180/100 mmHg at rest),

- in eclampsia and preeclampsia,

- in patients with hyperthyroidism (or insufficiently treated hyperthyroidism),

- in situations which require relaxed uterus myometrium (eg threatening uterus rupture, prolapsed umbilical cord),

- as sole anaesthetic agent in patients with manifest ischemic cardiac disorders.

- in combination with xanthine derivatives (e.g. aminophylline or theophylline) (the convulsion threshold may become lower).

- in combination with ergometrine.

4.4 Special warnings and precautions for use

Esketamine should be used with caution in the following situations:

- unstable angina pectoris or myocardial infarction in the last 6 months,
- cardiac insufficiency
- elevated intracranial pressure, except under appropriate ventilation, and in the case of central nervous system damages or diseases, since elevation of cerebrospinal pressure has been described in connection with ketamine anaesthesia,
- in patients who have or have had severe psychiatric disturbances,
- increased eye pressure (glaucoma) and perforating eye injuries as well as in connection with eye examinations or eye surgery in which intraocular pressure should not increase,
- surgery in the upper respiratory tract,
- in patients under chronic or acute influence of alcohol,
- in patients who have liver disease,
- in patients who have a history of drug abuse or addiction.

Esketamine is metabolized in the liver, and hepatic clearance is required for a termination of the clinical effects. Abnormal liver function tests associated with esketamine use have been reported, particularly with extended use (> 3 days) or drug abuse. A prolonged duration of action may occur in patients with cirrhosis or other types of liver impairment. Dose reductions should be considered in these patients.

In case of high dose and rapid intravenous injection, respiratory depression may occur.

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 (see also section 4.8).

In outpatient surgery, adequate patient monitoring must be ensured until discharge.

The patient should be accompanied home and should not consume alcohol within the next 24 hours.

Continuous monitoring of cardiac function during surgery is required in patients with hypertension or cardiac decompensation.

In surgical procedures that may involve visceral pain, muscle relaxation and supplemental analgesia (controlled ventilation and administration of nitrous oxide / oxygen) are indicated.

In patients with alcohol intoxication, care should be taken when using esketamine.

In patients with known history of severe angina pectoris, caution should be taken when using esketamine.

When using esketamine in patients in shock, the basic principles of shock therapy (volume replenishment, O_2 intake) must be observed. In the most severe patients in shock, with hardly or not measurable blood pressure, caution should be taken when using esketamine.

In diagnostic and therapeutic procedures of the upper respiratory tract, hyperreflexia and laryngospasm are possible, especially in children. In the case of interventions on the pharynx, larynx and bronchial tree, a muscle relaxation with adequate ventilation may therefore be necessary.

Long-Term Use

In patients who received racemic ketamine as long-term therapy (1 month to several years), cases of cystitis, including haemorrhagic cystitis, have been reported. Similar effects may also occur following esketamine abuse. Furthermore, hepatotoxicity has been reported in patients after extended use (> 3 days).

Drug Abuse and Dependence

Racemic ketamine has been reported being used as a drug abuse. Reports suggest that abuse of ketamine produces a variety of symptoms including, among others, flashbacks, hallucinations, dysphoria, anxiety, insomnia or disorientation. Cases of cystitis, including haemorrhagic cystitis, and cases of hepatotoxicity have also been reported after use of ketamine racemic. Similar effects therefore cannot be ruled out following esketamine use. Esketamine dependence may be developed by individuals with history of drug abuse. Therefore, esketamine should be prescribed and administered with caution only under the supervision of a doctor.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration contraindicated:

The convulsion threshold may become lower in combination with xanthine derivatives (e.g. aminophylline or theophylline). This combined administration should be avoided.

Esketamine should not be used in combination with ergometrine.

Concomitant administration with precaution:

Sympathomimetics (directly or indirectly acting), thyroid hormones, and vasopressin may lead to an increase in blood pressure (arterial hypertension) and in heart rate acceleration (tachycardia), which should be taken into consideration in concurrent administration with esketamine.

In combination with hypnotics, especially benzodiazepines or neuroleptics, there is a reduction in adverse effects, but also a prolongation of the duration of effect of esketamine.

Barbiturates and opiates given concurrently with esketamine may prolong the recovery phase.

The anaesthetic effect of halogenated hydrocarbons (e.g. isoflurane, desflurane, sevoflurane) is potentiated by administration of esketamine, so lower doses of halogenated hydrocarbons may be needed.

The effect of certain muscle relaxants (depolarizing or non-depolarizing muscle relaxants, e.g. suxamethonium, pancuronium) may be prolonged due to the combined use of esketamine.

Diazepam is known to increase the half-life of racemic ketamine and prolongs its pharmacodynamic effect. Therefore, dose adjustments may also be needed for esketamine.

The risk of cardiac arrhythmia after administration of adrenaline may increase in concurrent administration of esketamine and halogenated hydrocarbons.

Medicinal products that inhibit CYP3A4 activity generally decrease hepatic clearance, resulting in increased plasma concentration of CYP3A4 substrates medicinal products, such as esketamine. Co-administration of esketamine with medicinal products that inhibit the enzyme CYP3A4 enzyme may require a decrease in esketamine dosage to achieve the desired clinical outcome.

Medicinal products that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of CYP3A4 substrate medicinal products, such as esketamine. Co-administration of esketamine with medicinal products that induce CYP3A4 enzyme may require an increase in esketamine dosage to achieve the desired clinical outcome.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data on the use of esketamine in pregnant women. The informative value of the present animal reproduction studies is insufficient, but the available data do not indicate any adverse effects on pregnancy, embryofetal development, parturition or postnatal development. The potential risk for humans is unknown. Esketamine must not be used during pregnancy unless, after careful consideration, the benefit for the mother is judged to outweigh the possible hazard for the child.

Esketamine crosses the placental barrier and may cause respiratory depression in neonates if used during delivery.

Breast-feeding

Esketamine passes into breast milk, but an effect on the child seems unlikely when using therapeutic doses.

Fertility

There are no clinical data on the effects of esketamine on fertility.

4.7 Effects on ability to drive and use machines

Treatment with Esketamine may result in reduced reaction ability. This should be taken into consideration in connection with situations requiring special alertness, e.g. when driving. The patient is not allowed to drive, operate machinery or operate dangerous activities for at least 24 hours following esketamine administration.

- The patient should go home only if accompanied.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you

- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse effects are usually dependent on the dose and speed of injection and are spontaneously reversible.

Nervous system (CNS) and psychiatric adverse effects are more common if esketamine is administered as the only anaesthetic. The risk of psychic reaction occurring during recovery from anaesthesia can be greatly reduced by the co-administration of a benzodiazepine.

The adverse reaction terms were categorized utilising the incidence rate as follows:

Very common (≥ 1/10)

Common (≥ 1/100, < 1/10)

Uncommon (≥ 1/1,000, < 1/100)

Rare (≥ 1/10,000, < 1/1,000)

Very rare (< 1/10,000)

Not known (frequency cannot be estimated from the available data)

Immune system disorder	
Rare	Anaphylaxis
Very rare	Hypersensitivity reactions (anaphylactoid reactions). In patients with shock, there may also be a further reduction in blood pressure.
Psychiatric disorders	
Very common	Recovery reactions[1]. These include vivid dreams, including nightmares, dizziness and motor restlessness[2]
Not known	Hallucinations, dysphoria, anxiety and disorientation
Nervous system disorders	
Uncommon	Tonic and clonic movements, which can resemble convulsions (as a result of increased muscle tonus), and nystagmus

Eye disorders	
Common	Blurred vision
Uncommon	Diplopia, increased intraocular pressure
Cardiac disorders	
Very common	Increase in blood pressure and heart rate (an increase of about 20 % of the starting level is common)
Common	Temporary tachycardia
Rare	Arrhythmia, bradycardia
Vascular disorders	
Rare	Hypotension (especially in connection with circulatory shock)
Respiratory, thoracic and mediastinal disorders	
Common	Especially in patients with restricted coronary reserve, increase in vascular resistance in pulmonary circulation, and increase in mucus secretion. Increased oxygen consumption, laryngospasm, and temporary respiratory depression. (The risk of respiratory depression usually depends on the dose and the speed of the injection)
Gastrointestinal Disorders	
Common	Nausea and vomiting, increased salivation
Hepatobiliary Disorders	
Not Known	Liver function test abnormal Drug-induced liver injury*
Skin and subcutaneous tissue disorders	
Uncommon	Morbilliform rash, and exanthema
General disorders and administration site conditions	
Uncommon	Pain and erythema at the injection site
Injury, poisoning and procedural complications	
Common	Diagnostic and therapeutic interventions in the area of the upper respiratory tract (especially in children) may lead to reflex (hyperreflexia) and laryngeal spasms (laryngospasm). In the case of interventions on the pharynx, larynx and bronchial tree, a muscle relaxation with adequate ventilation may therefore be necessary. Under inadequate ventilation, there is often an increase in brain pressure, an increase in intraocular pressure, and an increase in muscle tone.

1 When esketamine is administered as the only anaesthetic, up to 30% of patients may experience dose-dependent reactions during the recovery phase.

2 The incidence of these events can be greatly reduced by the co-administration of a benzodiazepine.

* Extended period use (>3 days) or drug abuse.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme, website:

www.mhra.gov/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Above the 25-fold usual anaesthetic dose, life-threatening 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics, ATC code: N01AX14

Esketamine is a chiral cyclohexanone derivative with strong analgesic activity. At the same time it causes a so-called dissociative anaesthesia. The analgesic effect already occurs at sub-dissociative doses and persists anaesthesia.

The ketamine-racemate consists of the enantiomers esketamine ((S)-ketamine) and (R)-ketamine. The analgesic effect of Esketamine is mainly due to the blockade of N-methyl-D-aspartate (NMDA) receptors. The analgesic-anaesthetic potency between the R- and S-isomer is about 1:4. The potency of esketamine is approximately twice as high as racemic (R),(S)-ketamine in the same dose. Esketamine has a marked local anaesthetic effect on the spinal cord and on peripheral nerves.

In the EEG, the signs of attenuation of the bioelectrical cerebral cortex activity can be observed under esketamine anaesthesia, especially the frontal areas, and an activation of subcortical structures can be detected. Muscle tone is maintained or becomes increased so that the protective reflexes are generally not impaired. The convulsion threshold is not lowered. Spontaneous respiration is followed by an elevation of intracranial pressure that can be avoided by adequate pulmonary ventilation.

Due to a sympathomimetic effect, esketamine produces an increase in blood pressure and heart rate, resulting in an increase in myocardial oxygen consumption and in coronary blood flow. Esketamine hydrochloride has a negative inotropic and antiarrhythmic effect on the heart. Peripheral resistance is barely changed due to contradictory effects.

After administration of esketamine, moderate hyperventilation can be observed without substantial impairment of the blood gases. Esketamine has a relaxing effect on the bronchial musculature.

Metabolism, endocrine, kidney and intestinal function as well as the coagulation system are not influenced by esketamine.

5.2 Pharmacokinetic properties

In contrast to the pharmacodynamic differences, the pharmacokinetic properties of the enantiomers of ketamine are very similar, i.e., there are also no significant differences in the pharmacokinetics of esketamine and racemic (±) ketamine hydrochloride. Thus reference can be made to the pharmacokinetic experience with the racemic ketamine (called "ketamine" below). The pharmacokinetic of ketamine is linear.

After intravenous bolus delivery, ketamine is rapidly distributed into strongly perfused tissues (e.g. heart, lung and brain), followed by muscles and peripheral tissue, followed by adipose tissue; the peak concentrations are reached within 1 minute. There are approximately 6.5-fold higher concentrations in the brain tissue than in the plasma. Ketamine passes through the placenta. It is resorbed rapidly (half-life resorption: 2 to 17 minutes) after intramuscular administration into the deltoid muscle. After an intravenous bolus delivery of 2.5 mg/kg, the distribution phase of ketamine takes about 45 minutes at a half-life of 10 to 15 minutes, which is associated with the duration of the anaesthetic effect (about 20 minutes). After an intravenous bolus injection of 1 mg/kg esketamine, the plasma concentrations are around 2.6 µg/ml after 1 minute and 0.9 µg/ml after 5 minutes.

After an intramuscular dose of 0.5 mg/kg esketamine, the plasma esketamine peak concentration is around 0.14 µg/ml after 25 minutes.

Ketamine is 93% bioavailable after intramuscular administration. The binding to plasma protein is about 47%.

Metabolism is rapid and largely complete. Metabolic clearance is therefore high and is 1200 to 1500 ml/min. By N-demethylation, (±)-norketamine (via the cytochrome P-450 system) and a (±)-cyclohexenone derivative resulting from dehydration are obtained, which are about 1/3 to 1/10 and 1/10 to 1/100 respectively of the anaesthetic effect of ketamine. In human liver microsomes, CYP3A4 enzyme is the main enzyme responsible for the N-demethylation of ketamine to norketamine, with CYP2B6 and CYP2C9 enzymes as minor contributors.

The terminal elimination half-life for ketamine is between 79 minutes (following continuous infusion) and 186 minutes (following low-dose intravenous administration), for (±)-norketamine, 240 minutes were measured.

Ketamine and its metabolites are eliminated predominantly by the kidneys. After administration of ^{3}H-ketamine, 91 to 97% of the total radical activity was found in the urine and only 3% in the faeces in the 120 h. urine. In the 72 h. urine, only 2.3% or 1.6% of the dose is excreted as free ketamine or as free (±)-norketamine and 16% of the dose as dehydronoketamine.

In a clinical-therapeutic study (7 to 8 patients per group), plasma concentrations of the unchanged substance as well as the metabolites I (norketamine) and II (cyclohexenone derivative) were measured after intravenous administration of 2mg/kg ketamine racemate, 1 mg/kg Esketamine and 3 mg/kg of (R)-ketamine, respectively. In all cases, the plasmas mirror curves of the unchanged substance as well as the metabolites I and II were largely parallel, that is, without apparent pharmacokinetic differences. Likewise, the withdrawal profiles were comparable in all three groups.

In two more recent studies, the similarity of the pharmacokinetic profile of esketamine with that of ketamine racemate and (R)-ketamine was confirmed.

Esketamine only had the tendency to faster elimination with greater total clearance than (R)-ketamine and ketamine racemate, which promises improved controllability in clinical use.

5.3 Preclinical safety data

Acute and chronic toxicity

In studies with single and repeated intravenous administration symptoms of toxicity were due to exaggerated pharmacodynamic effects of esketamine.

Studies on animals have shown that racemic (R),(S)-ketamine can cause a NMDA antagonist-induced neuronal cell death (apoptosis) in juvenile animals when used in high doses and/or over a long period of time. S-ketamine uses the same pharmacological target structure. The relevance of these results for human use is not known.

Mutagenic and tumour-inducing potential

In vitro and *in vivo* studies on genotoxicity revealed no evidence of genotoxic potential. Long-term studies on carcinogenicity were not carried out.

Reproductive toxicity

In studies on reproductive toxicity, an increased postnatal mortality up to day 4 post-partum was found in a peri/postnatal study in rats in all dose groups, which is probably attributable to an insufficient brood care by the mother animals.

Other reproduction parameters were not affected in any dose group. Similarly, there was no influence on the parents of the F1 generation and their reproductive behaviour. There were no indications of teratogenic properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid 0.36% (pH adjustment)

Water for injections

6.2 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.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

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.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Ampoules: glass type I (Ph. Eur.)

10 ampoules with 2 ml of solution for injection/infusion.

10 ampoules with 10 ml of solution for injection/infusion.

Vials: glass vial with bromobutyl rubber stopper with aluminium seal and plastic flip-off cap

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.

6.6 Special precautions for disposal

For single use only.

Parenteral medicinal products must always be visually checked prior to administration. Only a clear and colourless solution may be used.

When diluting the solution for injection/infusion before application as an infusion:

Esketamine can be mixed with glucose 50 mg/ml (5%) or sodium chloride 9 mg/ml (0.9%).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

INTERNATIONAL DRUG DEVELOPMENT

104 boulevard Auguste Blanqui

75013 Paris

France

8 MARKETING AUTHORISATION NUMBER(S)

PL 40658/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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