SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Esketamine 5 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Esketamine ***5 mg/ml***

1 ml of solution contains 5 mg of esketamine (corresponding to 5.77 mg of esketamine hydrochloride).

Each 5 ml ampoule contains 25 mg of esketamine (corresponding to 28.85 mg of esketamine hydrochloride).

Excipient with known effect:
Each 2 ml ampoule contains 2.36 mg of sodium.

Each 5 ml ampoule contains 15.75 mg of sodium.

Each 10 ml ampoule contains 11.8 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless solution free from visible particles.

pH of solution is 3.0 - 5.0.

Osmolality is 270 - 310 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Induction and maintenance of general anaesthesia, as the only anaesthetic or in combination with another anaesthetic.
- Anaesthesia and pain relief (analgesia) in emergency medicine.
- Supplementation of regional or local anaesthesia.

4.2 Posology and method of administration

Posology

Only for hospital use or prehospital emergency care. Esketamine can only be administered by or under the supervision of a specialist of anaesthesiology. The equipment for maintenance of vital functions should be available.

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

Although esketamine has only a minor effect on the protective reflexes of the pharynx and the airways, the possibility of aspiration of fluid or solid materials cannot be completely excluded. High doses or too rapid intravenous administration can cause respiratory depression.

Increased salivation may be associated with the use of esketamine and can be prevented by giving the patient atropine or another anticholinergic.

Adults

For induction of general anaesthesia, 0.5 to 1 mg/kg of esketamine is given intravenously or 2 to 4 mg/kg intramuscularly.

For maintenance of general anaesthesia, half the initial dose is injected as needed, generally every 10 to 15 minutes.

Esketamine can also be administered as a continuous infusion at a dose of 0.5 to 3 mg/kg/h.

Dose reduction is required in patients with multiple injuries and in patients with a poor general condition. For example, the dose in patients in shock should be reduced; as a guideline about half the normal dose should be administered.

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 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.

As with other general anaesthetic agents, the individual response to esketamine is somewhat varied depending on the dose, route of administration, age of patient, and concomitant use of other agents, so that dosage recommendation cannot be absolutely fixed. The dose should be titrated against the patient’s requirements.

Hepatic impairment

When insufficient liver function has been described, a dose reduction should be considered in patients diagnosed with cirrhosis or other liver impairment (see section 4.4).

Paediatric population

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

Note:

In paediatric surgery, as well as in emergency medicine, esketamine is mostly used on its own; in case of other indications a combination with hypnotics is recommended.

Method of administration

Esketamine is given as a slow intravenous or intramuscular injection. If needed, injection can be repeated or the preparation can be administered as an infusion.

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

4.3 Contraindications

Patients to whom elevation of blood pressure or intracranial pressure forms a serious risk.

As sole anaesthetic agent in patients with manifest ischemic cardiac disorders.

Eclampsia and pre-eclampsia.

In combination with xanthine derivatives and ergometrine.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Please see section 4.5 Interaction with other medicinal products and other forms of interaction.

4.4 Special warnings and precautions for use

Esketamine should be used with precaution in the following situations:

- hypovolemia, dehydration or heart disease especially coronary artery disease (e.g. congestive heart failure, myocardial ischemia and myocardial infarction), because of the substantial increase in myocardial oxygen consumption
- decompensated cardiac failure and untreated hypertension
- unstable angina pectoris or myocardial infarction in the last 6 months
- mild to moderate hypertension and tachyarrhythmias
- elevated intracranial pressure and damages or diseases of the central nervous system, as elevation of cerebrospinal pressure has been described in connection with ketamine anaesthesia
- pulmonary or upper respiratory infection (esketamine sensitises the gag reflex, potentially causing laryngospasm)
- in patients with increased intraocular pressure (e.g. glaucoma), penetrating eye injury, and in connection with eye examination or eye surgery in which intraocular pressure should not increase

- acute intermittent porphyria (because of the possibility of triggering a porphyric reaction)
- patients under chronic or acute influence of alcohol
- patients who have or have had severe psychiatric disturbances
- insufficiently treated hyperthyroidism
- situations which require relaxed uterus myometrium (e.g. threatening uterus rupture, prolapsed umbilical cord)

Esketamine is metabolized in the liver and hepatic clearance is required for termination of 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 (see section 4.2).

In case of high dosage and rapid intravenous injection respiratory depression might occur.

As aspiration cannot be completely excluded and due to the possibility of respiratory depression intubation and ventilation equipment must be available.

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

If esketamine is used in the shock patient the principles of shock therapy (volume substitution, oxygen supply) must be considered. Special caution is required in severe states of shock where blood pressure can be hardly measured or not at all.

As the need for additional anaesthetics or muscle relaxants cannot always be predicted it is recommended that the patient fasts for 4-6 hours prior to surgery to prevent aspiration. Because pharyngeal reflexes usually remains active, mechanical stimulation of the pharynx should be avoided unless muscle relaxants with proper attention are used.

Increased salivation should be prophylactically treated with atropine.

In diagnostic and therapeutic procedures of the upper respiratory tract, hyperreflexia and laryngospasms are possible, especially in children. Muscle relaxants and controlled ventilation may therefore be necessary in procedures on the pharynx, larynx and bronchi.

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

After outpatient anaesthesia the patient should be accompanied home and should not consume alcohol within the next 24 hours.

<u>Long-term use</u>

Cases of cystitis, including haemorrhagic cystitis, have been reported in patients using racemic ketamine on a long-term basis (one month to several years). Similar effects may also occur following esketamine abuse (see below). Hepatotoxicity has also been reported in patients with extended use (> 3 days).

Drug abuse and dependence

Racemic ketamine has been reported being used as a drug of abuse. Reports suggest that racemic 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. Similar effects therefore cannot be ruled out following esketamine use.

Esketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, esketamine should be prescribed and administered with caution.

The risk of psychic reaction occurring during recovery from anaesthesia (see also section 4.8) can be greatly reduced by the co-administration of a benzodiazepine.

This medicine 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 (for example aminophylline, theophylline) and these combinations should be avoided.

The product 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 and in heart rate, which should be taken into consideration in concurrent administration with esketamine.

In combination with hypnotics, benzodiazepines or antipsychotics, 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.

Diazepam is known to increase the half-life of racemic ketamine and prolongs its pharmacodynamic effects. Dose adjustments may therefore be needed also for esketamine.

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

The effect of non-depolarizing (for example pancuronium) and depolarizing (for example suxamethonium) muscle relaxants may be prolonged due to the use of esketamine.

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

Increased blood pressure has been observed in concurrent administration of esketamine and vasopressin.

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

Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of CYP3A4 substrate medications, such as esketamine. Co-administration of esketamine with drugs 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 from the use of esketamine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Use of esketamine should be restricted during pregnancy and only administered after consideration if the potential benefits for the mother outweighs the possible hazard for the child.

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

Breast-feeding

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

Fertility

There are no data on the effects of esketamine on human 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 a car.

The patient should not drive or operate machinery for at least 24 hours following esketamine anaesthesia.

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 and psychiatric (CNS) adverse effects are more common if esketamine is given as the only anaesthetic.

The adverse reactions were categorized utilizing the incidence rate as follows:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000
Not known	Cannot be estimated from the available data

Immune system disorders	
Rare	Anaphylaxis.
Psychiatric disorders	
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	
Common	Temporary tachycardia, increase in blood pressure and heart

	rate (of about 20% of the starting level is common).
Rare	Arrhythmia, bradycardia.
Vascular disorders	
Rare	Hypotension (especially in connection with circulatory shock).
Respiratory, thoracic and mediastinal disorders	
Common	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[3].
Skin and subcutaneous tissue disorders	
Uncommon	Morbilliform rash, and exanthema.
General disorders and administration site conditions	
Uncommon	Pain and erythema at the injection site.

[1] When esketamine is used as the only anaesthetic, the recovery phase may involve dose-dependent reactions in up to 30% of the patients.

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

[3] 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.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 thiopental is recommended.

No specific antidote is presently known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, other general anaesthetics, ATC code: N01A X14

Mechanism of action

Esketamine is a chiral cyclohexanone derivative with analgesic and, at increasing doses, anaesthetic effect. Esketamine produces a so-called dissociative anaesthesia. By interfering with the association pathways of the brain esketamine causes a cataleptic like state with loss of consciousness and amnesia.

Pharmacodynamic effects

The ketamine-racemate components include esketamine and (R)-ketamine. The analgesic effect is attributed primarily to the blockade of N methyl D aspartate (NMDA) receptors by esketamine. The analgesic-anaesthetic potency between the R and the S isomer is in the magnitude of approximately 1:3.

Clinical efficacy and safety

Esketamine has a marked local anaesthetic effect on the spinal cord and on peripheral nerves.

Esketamine does not cause respiratory or circulatory depression and it interferes only marginally with the protective reflexes: During esketamine anaesthesia muscle tone is maintained or becomes increased, and the protective reflexes are generally not impaired. The convulsion threshold is not lowered. Under spontaneous respiration, there is 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 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 but this has no essential effect on blood gases.

Esketamine has a bronchodilative effect which makes it a suitable option for use in asthmatic patients and during artificial ventilation of patients with status asthmaticus.

5.2 Pharmacokinetic properties

There are no or just slight differences in the pharmacokinetics of esketamine and racemic (±)-ketamine. Thus reference can be made to the pharmacokinetic experience with the racemic ketamine (called ketamine below). The pharmacokinetics of ketamine are linear.

Absorption

Ketamine is rapidly absorbed after intramuscular administration and is approximately 90% bioavailable.

Distribution

The degree of binding to plasma protein is about 50%. Lipid solubility is high.

Ketamine is rapidly distributed into highly perfused tissues (e.g. heart, lung, and brain), followed by muscle and peripheral tissues, and then fat. In humans, at an intravenous bolus dose of 2.5 mg/kg, the distribution phase of ketamine lasts about 45 minutes, with a half life of 10 to 15 minutes, which is associated with the duration of the anaesthetic effect (about 20 minutes). Plasma esketamine concentrations are about 2.6 micrograms/ml at 1 minute and 0.9 micrograms/ml at 5 minutes after a 1 mg/kg intravenous bolus dose of esketamine. Plasma esketamine peak concentration is about 0.14 micrograms/ml at 25 minutes after a 0.5 mg/kg intramuscular dose of esketamine.

Biotransformation

Ketamine is degraded in the liver via demethylation (via the cytochrome P450 system) to the significantly less potent main metabolite norketamine and other ultimately inactive metabolites. CYP3A4 enzyme is the primary enzyme responsible for ketamine N-demethylation to norketamine in human liver microsomes; with CYP2B6 and CYP2C9 enzymes as minor contributors. Metabolism is rapid and largely complete; metabolic clearance is 1200 to 1500 ml/min.

Elimination

The terminal elimination half-life for ketamine is between 79 minutes (following continuous infusion) and 186 minutes (following low-dose intravenous administration). Ketamine and its metabolites are 98% eliminated via the kidneys and 2% via faeces, with only a small amount as unchanged substance. In total, approximately 95% are eliminated during the first 24 hours.

5.3 Preclinical safety data

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

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

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.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain

that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

Esketamine is chemically incompatible with barbiturates, diazepam and doxapram because of precipitate formation. They are not to be administered with the same syringe and needle.

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

6.3 Shelf life

4 years.

Shelf life after dilution

Do not refrigerate. Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml, 5 ml or 10 ml colourless glass ampoules with one point cut. Ampoules are marked with a specific colour ring code for each strength and volume.

Ampoules are packed in polyvinylchloride film liner. Liners are packed into a cardboard box.

Pack sizes:

Esketamine ***5 mg/ml***

5 or 10 ampoules of 5 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Parenteral products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

For single use only. The medicinal product should be used immediately after opening the ampoule. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

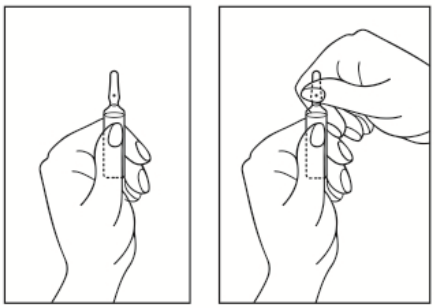
Esketamine solution for injection/infusion can be mixed with:

- sodium chloride 9 mg/ml (0.9%) solution for injection
- glucose 50 mg/ml (5%) solution for injection

After dilution to 1 mg/ml and 2 mg/ml with the above mentioned solutions Esketamine solution for injection/infusion is chemically and physically stable when in contact with PVC and EVA infusion bags, PVC and polyethylene tubing, and polypropylene and polycarbonate syringes.

Instruction of ampoule opening:

1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



7 MARKETING AUTHORISATION HOLDER

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