

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vesierra 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 of 10 ml solution for injection/infusion contains 250 mg of esketamine as 288.3 mg of esketamine hydrochloride.

Excipient with known effect: 1.2 mg sodium per ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion

Clear, colourless solution.

pH 3.0 – 5.0

Osmolality = 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.

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 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.

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

For instructions on reconstitution 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:

- decompensated cardiac failure and untreated hypertension
- unstable angina pectoris
- 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
- in connection with eye examination or eye surgery in which intraocular pressure should not increase
- 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 metabolised 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.

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.

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.

Long-Term Use

Cases of cystitis, including haemorrhagic cystitis, acute kidney injury, hydronephrosis, and ureteral disorder have been reported in patients using racemic ketamine on a long-term basis (one month to several years), especially in the setting of ketamine abuse. 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. Adverse effects have also been reported: see “Long-Term Use”. 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.

Please consider that this medicinal product contains 1.2 mg sodium per ml.

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

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 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.

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-depolarising (for example pancuronium) and depolarising (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. Coadministration 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. Coadministration 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.

Breastfeeding

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 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.

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 reaction terms were categorised utilising the incidence rate as follows:

| | |
|-------------|---|
| Very common | $\geq 1/10$ |
| Common | $\geq 1/100$ and $< 1/10$ |
| Uncommon | $\geq 1/1\ 000$ and $< 1/100$ |
| Rare | $\geq 1/10\ 000$ and $< 1/1\ 000$ |
| Very rare | $< 1/10\ 000$ |
| Not known | Cannot be estimated from the available data |

| | |
|--|---|
| Immune system disorder | |
| <i>Rare</i> | Anaphylaxis. |
| Psychiatric disorders | |
| <i>Common</i> | Recovery reactions ¹ . These include vivid dreams, including nightmares, dizziness and motor restlessness ² . |
| <i>Not known</i> | Hallucinations, dysphoria, anxiety and disorientation. |
| Nervous system disorders | |
| <i>Uncommon</i> | Tonic and clonic movements, which can resemble convulsions (as a result of increased muscle tonus), and nystagmus. |
| Eye disorders | |
| <i>Common</i> | Blurred vision. |
| <i>Uncommon</i> | Diplopia, increased intraocular pressure. |
| Cardiac disorders | |
| <i>Common</i> | Temporary tachycardia, increase in blood pressure and heart rate (of about 20 % of the starting level is common). |
| <i>Rare</i> | Arrhythmia, bradycardia. |
| Vascular disorders | |
| <i>Rare</i> | Hypotension (especially in connection with circulatory shock). |
| Respiratory, thoracic and mediastinal disorders | |
| <i>Common</i> | 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 | |
| <i>Common</i> | Nausea and vomiting, increased salivation. |
| Hepatobiliary Disorders | |
| <i>Not Known</i> | Liver function test abnormal Drug-induced liver injury ³ |
| Skin and subcutaneous tissue disorders | |
| <i>Uncommon</i> | Morbilliform rash, and exanthema. |
| General disorders and administration site | |

| | |
|-------------------|--|
| conditions | |
| <i>Uncommon</i> | Pain and erythema at the injection site. |

¹ When esketamine is used 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 at: 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: 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.

Pharmacodynamics 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 (\pm)-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 intra-muscular 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 $\mu\text{g/mL}$ at 1 minute and 0.9 $\mu\text{g/mL}$ at 5 minutes after a 1 mg/kg intravenous bolus dose of esketamine. Plasma esketamine peak concentration is about 0.14 $\mu\text{g/mL}$ at 25 minutes after a 0.5 mg/kg intramuscular dose of esketamine.

Metabolism

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

Preclinical data on esketamine with respect to genotoxicity reveal no special hazard for humans.

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.

Comparative studies with esketamine and racemic ketamine indicate a similar toxicological profile.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for injection

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.

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

6.3 Shelf life

3 years.

Stability after dilution of a 25 mg/ml ampoule:

For product diluted to a concentration of 10 mg/ml with either Dextrose 5% (glucose 50 mg/ml) or normal Saline (sodium chloride 9 mg/ml), the chemical and physical in-use stability has been demonstrated for 48 hours at 25°C.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in 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.)

Pack sizes

10 x 2 ml; 10 x (10 x 2 ml) ampoules with a red ring

1 x 10 ml; 5 x 10 ml; 5 x (5 x 10 ml) ampoules with a yellow ring

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Esketamine can be mixed with glucose 50 mg/ml and sodium chloride 9 mg/ml.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1497

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

18/06/2018

10 DATE OF REVISION OF THE TEXT

20/10/2021