


Package leaflet: Information for the patient



KETALAR™ 10mg/ml, 50mg/ml

SOLUTION FOR INJECTION / INFUSION

Ketamine hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- If you have been given Ketalar in an emergency you will not have had a chance to read this leaflet. Your doctor or anaesthetist will have considered the important safety information in this leaflet, but your urgent need for treatment may have been more important than some of the usual precautions.
- If you are discharged on the same day as the operation, you should be accompanied by another adult.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.4.

What is in this leaflet

1. What Ketalar Injection is and what it is used for
2. What you need to know before you are given Ketalar Injection
3. How Ketalar Injection is given
4. Possible side effects
5. How to store Ketalar Injection
6. Contents of the pack and other information

1. What Ketalar Injection is and what it is used for

- This medicine contains ketamine hydrochloride which belongs to a group of medicines called anaesthetic agents, which are used to put you to sleep during an operation. Ketalar may be used in both routine and emergency surgery.
- Ketalar is used in adults, the elderly and children.
- Ketalar can be given alone or in combination with other anaesthetic agents.

2. What you need to know before you are given Ketalar Injection

Do not take Ketalar:

- if you are allergic (hypersensitivity) to ketamine hydrochloride or any of the other ingredients of this medicine (listed in section 6).
- if you are suffering from any condition in which an increase in blood pressure may be harmful to you or have suffered in the past from a medical condition which may have been caused/made worse by an increase in blood pressure.
- if you have been pregnant and during your pregnancy you have suffered from a condition called eclampsia or pre-eclampsia which causes an increase in your blood pressure.
- if you have recently suffered a stroke or serious head or brain injury.
- if you have severe heart disease.
- if you are pregnant, trying to become pregnant or breast-feeding. However, Ketalar may be used in caesarean section surgery and vaginal delivery.
- if you have a history of or have current mental health problems.

Warnings and precautions

Talk to your doctor or nurse if any of the following apply to you, to help them decide if Ketalar is suitable for you. If you:

- regularly drink alcohol or have recently drank a large amount of alcohol.
- have a history of drug abuse or addiction.
- have a chest infection or problems breathing.
- have problems with your liver.

- have increased pressure in the eye (glaucoma).
- have an inherited disease that affects the blood (porphyria).
- have ever had seizures (i.e. fits).
- have mental health problems (e.g. schizophrenia, hallucinations or psychosis).
- are receiving treatment for your thyroid gland.
- have had any injury to your head or abnormal growth on the brain.
- suffer from dehydration or have recently lost a lot of blood.
- suffer from heart failure or have had a heart attack or have any other form of heart problem.
- have mild to moderate increase in high blood pressure.
- have an irregular heartbeat.

If before your operation the pressure in your spinal cord is raised, your anaesthetist will pay special attention to this during the operation.

Other medicines and Ketalar

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Ketalar is usually given together with other medicines during surgery.

- When used for an operation on the chest or abdominal organs, Ketalar is usually combined with a pain-killer. This is not because you would be conscious of any pain but to stop any reflexes which might be triggered.
- Tell your doctor if you are taking barbiturates (e.g. thiopental) and narcotics (morphine-like drugs) since use with Ketalar may slow your recovery from anaesthesia. Otherwise, Ketalar may be used with all other general and local anaesthetics.

Ketalar must be used with particular care on anyone who is a chronic alcoholic, who is intoxicated (drunk) or who has a history of drug abuse or dependence.

The use of Ketalar with other central nervous system (CNS), blocking drugs (e.g. atracurium, tubocurarine, ethanol, phenothiazines) may stop the transmission of nerves to the muscles. This may also slow down your rate of breathing.

If before your operation the pressure inside your spinal cord is raised, your anaesthetist will pay special attention to this during the operation.

Ketalar should be given with care to patients taking thyroid hormones, as they have a high risk of developing high blood pressure.

Using Ketalar with anti-hypertensive agents also increases the risk of developing low blood pressure and changes in the heart's rhythm.

Using Ketalar with theophylline may cause unpredicted seizures.

Ketalar with food and drink

It is normal not to eat or drink for at least six hours before an operation; therefore Ketalar is usually given when your stomach is empty. If in an emergency, this is not possible, Ketalar may still be used.

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 for advice before being given this medicine.

Driving and using machines

Caution should be taken when driving or operating machines following treatment with Ketalar. You should not drive or operate machines in the first 24 hours after your operation.

Ketalar contains sodium

The 10mg/ml vials contain 52.8mg of sodium. Patients on a sodium controlled diet should take this into consideration.

3. How Ketalar Injection is given

- Except in an emergency, Ketalar should only be used in hospitals by experienced anaesthetists with resuscitation equipment available.
- Before your operation you will usually be given a medicine such as atropine or hyoscine to dry up your secretions (body fluids like saliva and tears) and another medicine called a benzodiazepine. The benzodiazepine will help you to relax and help to prevent a side effect known as "emergence reaction".



The following information is intended for healthcare professional only
SUMMARY OF PRODUCT CHARACTERISTICS



Ketalar 10mg/ml & 50mg/ml

Solution for Injection/Infusion

Ketamine hydrochloride

1. NAME OF THE MEDICINAL PRODUCT

Ketalar 10mg/ml Solution for Injection/Infusion
Ketalar 50mg/ml Solution for Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ketalar 10mg/ml Solution for Injection/Infusion
Ketamine Hydrochloride equivalent to 10 mg ketamine base per ml.
A 20ml solution contains ketamine hydrochloride equivalent to 200mg ketamine base.
Excipients with known effect: Each 1 ml contains 2.6mg of sodium.

Ketalar 50mg/ml Solution for Injection/Infusion
Ketamine Hydrochloride equivalent to 50mg ketamine base per ml.
A10ml solution contains ketamine hydrochloride equivalent to 500mg ketamine base.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion
A clear, colourless aqueous solution for injection or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. As an anaesthetic agent for short diagnostic and surgical procedures which do not require skeletal muscle relaxation.
2. For the induction of anaesthesia prior to the administration of other general anaesthetic agents.
3. To supplement other anaesthetic agents.
4. When airway control is difficult.

Specific areas of application or types of procedures:

1. When the intramuscular route of administration is more convenient.
2. Debridement, painful dressings, and skin grafting in burned patients, as well as other superficial surgical procedures.
3. For certain neurological, radiodiagnostic and therapeutic procedures in children to abolish movement.
4. When airway control is difficult.

Note: Ketamine should be used only with caution in surgical procedures involving pharynx, larynx or trachea as it increases salivary and tracheo-bronchial secretions and does not reliably suppress pharyngeal or laryngeal reflexes.

4.2 Posology and method of administration

For intravenous infusion, intravenous injection or intramuscular injection.

Note: All doses are given in terms of ketamine base
Adults, elderly (over 65 years) and children
For surgery in elderly patients ketamine has been shown to be suitable either alone or supplemented with other anaesthetic agents.

Preoperative preparations

1. Ketalar has been safely used alone when the stomach was not empty. However, since it may also cause vomiting and since the need for supplemental agents and muscle relaxants cannot be predicted, when preparing for elective surgery it is advisable that nothing be given by mouth for at least six hours prior to anaesthesia.
2. Ketamine increases salivation. Premedication with an anticholinergic agent (e.g. atropine, hyoscine, glycopyrrolate) or another drying agent should be given at an appropriate interval prior to induction to reduce ketamine-induced hypersalivation (see section 4.8).

3. Midazolam, diazepam, lorazepam, or flunitrazepam used as a premedicant or as an adjunct to ketamine, have been effective in reducing the incidence of emergence reactions.

Onset and duration

As with other general anaesthetic agents, the individual response to Ketalar 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.

Because of rapid induction following intravenous injection, the patient should be in a supported position during administration. An intravenous dose of 1 – 2 mg/kg of bodyweight usually produces surgical anaesthesia within 30 seconds – 1 minute after injection and the anaesthetic effect usually lasts 5 to 10 minutes. An intramuscular dose of 10mg/kg of bodyweight usually produces surgical anaesthesia within 3 to 4 minutes following injection and the anaesthetic effect usually lasts 12 to 25 minutes. Return to consciousness is gradual.

A. Ketalar as the sole anaesthetic agent

Intravenous Infusion

The use of Ketalar by continuous infusion enables the dose to be titrated more closely, thereby reducing the amount of drug administered compared with intermittent administration. This results in a shorter recovery time and better stability of vital signs.

A solution containing 1mg/ml of ketamine in dextrose 5% or sodium chloride 0.9% is suitable for administration by infusion.

If fluid restriction is required, ketamine can be added to 250ml infusion fluid to provide a ketamine concentration of 2mg/ml. Ketamine vials in the 10mg/ml concentration are not recommended for dilution.

Induction

An infusion corresponding to 0.5– 2 mg/kg as total induction dose.

Maintenance of anaesthesia

Anaesthesia may be maintained using a microdrip infusion of 10 - 40 microgram/kg/min (approximately 1 - 3mg/min).

The rate of infusion will depend on the patient's reaction and response to anaesthesia. The dosage required may be reduced when a long acting neuromuscular blocking agent is used.

Intermittent Injection

Induction

Intravenous Route

The initial dose of Ketalar administered intravenously may range from 1mg/kg to 4.5 mg/kg. The average amount required to produce 5 to 10 minutes of surgical anaesthesia has been 2.0 mg/kg. It is recommended that intravenous administration be accomplished slowly (over a period of 60 – 120 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Dosage in Obstetrics

In obstetrics, for vaginal delivery or in caesarean section, intravenous doses ranging from 0.2 to 1.0 mg/kg are recommended (see section 4.6 Fertility, pregnancy and lactation). However, data are lacking for maintenance infusion of ketamine in the parturient population and dosing recommendations cannot be made.

Intramuscular Route

The initial dose of Ketalar administered intramuscularly may range from 6.5 mg/kg to 13 mg/kg, usually 10 mg/kg. A low initial intramuscular dose of 4 mg/kg has been used in diagnostic manoeuvres and procedures not involving intensely painful stimuli. A dose of 10 mg/kg will usually produce 12 to 25 minutes of surgical anaesthesia.

Hepatic Insufficiency

Dose reductions should be considered in patients with cirrhosis or other types of liver impairment (see section 4.4).

Dosage in Obstetrics

Data are lacking for intramuscular injection in the parturient population, and dosing recommendations cannot be made. Available pharmacokinetic data are presented in section 5.2.

Maintenance of anaesthesia

Lightening of anaesthesia may be indicated by nystagmus, movements in response to stimulation, and vocalization. Anaesthesia is maintained by the administration of additional doses of Ketalar by either the intravenous or intramuscular route. However, data are lacking regarding the maintenance dosage of ketamine in the parturient population and dosing recommendations cannot be made.



Each additional dose is from 1½ to the full induction dose recommended above for the route selected for maintenance, regardless of the route used for induction.

The larger the total amount of Ketalar administered, the longer will be the time to complete recovery.

Purposeless and tonic-clonic movements of extremities may occur during the course of anaesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anaesthetic.

B. Ketalar as induction agent prior to the use of other general anaesthetics

Induction is accomplished by a full intravenous or intramuscular dose of Ketalar as defined above. If Ketalar has been administered intravenously and the principal anaesthetic is slow-acting, a second dose of Ketalar may be required 5 to 8 minutes following the initial dose. If Ketalar has been administered intramuscularly and the principal anaesthetic is rapid-acting, administration of the principal anaesthetic may be delayed up to 15 minutes following the injection of Ketalar.

C. Ketalar as supplement to anaesthetic agents

Ketalar is clinically compatible with the commonly used general and local anaesthetic agents when an adequate respiratory exchange is maintained. The dose of Ketalar for use in conjunction with other anaesthetic agents is usually in the same range as the dosage stated above; however, the use of another anaesthetic agent may allow a reduction in the dose of Ketalar.

Management of patients in recovery

Following the procedure the patient should be observed but left undisturbed. This does not preclude the monitoring of vital signs. If, during the recovery, the patient shows any indication of emergence delirium, consideration may be given to the use of diazepam (5 to 10 mg I.V. in an adult). A hypnotic dose of a thiobarbiturate (50 to 100 mg I.V.) may be used to terminate severe emergence reactions. If any one of these agents is employed, the patient may experience a longer recovery period.

4.3 Contraindications

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

Ketalar is contraindicated in persons in whom an elevation of blood pressure would constitute a serious hazard (see section 4.8). Ketalar should not be used in patients with eclampsia or pre-eclampsia, severe coronary or myocardial disease, C.V.A. or cerebral trauma. Known history of psychiatric problems.

4.4 Special warnings and precautions for use

To be used only in hospitals by or under the supervision of experienced medically qualified anaesthetists except under emergency conditions.

As with any general anaesthetic agent, resuscitative equipment should be available and ready for use.

Use of this agent should always be preceded by appropriate doses of atropine, hyoscine or another drying agent.

Ketalar is chemically incompatible with barbiturates and diazepam. Therefore, these should not be mixed in the same syringe or infusion fluid.

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

Emergence delirium phenomena may occur during the recovery period. The incidence of these reactions may be reduced if verbal and tactile stimulation of the patient is minimised during the recovery period. This does not preclude the monitoring of vital signs.

The psychological manifestations vary in severity between pleasant dream-like states, vivid imagery, hallucinations, nightmares and emergence delirium (often consisting of dissociative or floating sensations). In some cases these states have been accompanied by confusion, excitement, and irrational behaviour which a few patients recall as an unpleasant experience (see section 4.8).

Because pharyngeal and laryngeal reflexes usually remain active, mechanical stimulation of the pharynx should be avoided unless muscle relaxants, with proper attention to respiration, are used.

The high plasma concentration following intravenous administration has been shown to depress respiration and the pharyngolaryngeal reflexes for a brief period. Slow injection of the dilute solution is required to minimize these effects. Aspiration of contrast medium has been reported during Ketalar anaesthesia under experimental conditions (Taylor, P. A and Towey, R.M. Brit. Med. J. 1971, 2: 688) and, although in clinical practice aspiration is seldom a problem, the possibility should be borne in mind.

Due to substantial increase in myocardial oxygen consumption, Ketalar should be used with caution in patients with hypovolaemia, dehydration, or cardiac disease, especially coronary artery disease (e.g. congestive heart failure, myocardial ischemia and myocardial infarction). In addition ketamine should be used with caution in patients with mild-to-moderate hypertension and tachyarrhythmias.

Ketalar should be used with caution in patients with pulmonary or upper respiratory infection (Ketalar sensitizes the gag reflex, potentially causing laryngospasm).

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

Elevation of blood pressure begins shortly after the injection of Ketalar, reaches a maximum within a few minutes and usually returns to preanaesthetic values within 15 minutes after injection. The median peak rise of blood pressure in clinical studies has ranged from 20 to 25 percent of preanaesthetic values. Depending on the condition of the patient, this elevation of blood pressure may be considered a beneficial effect, or in others, an adverse reaction.

Since an increase in cerebrospinal fluid pressure has been reported during Ketalar anaesthesia, Ketalar should be used with special caution in patients with preanaesthetic elevated cerebrospinal fluid pressure.

Respiratory depression may occur with overdosage of Ketalar, in which case supportive ventilation should be employed.

Mechanical support of respiration is preferred to the administration of analeptics.

The intravenous dose should be administered over a period of 60 – 120 seconds. More rapid administration may result in transient respiratory depression or apnoea and enhanced pressor response.

In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

Ketamine is metabolized in the liver and hepatic clearance is required for termination of clinical effects. Abnormal liver function tests associated with ketamine 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.

Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

When Ketalar is used on an outpatient basis, the patient should not be released until recovery from anaesthesia is complete and then should be accompanied by a responsible adult.

Patients should be cautioned that driving a car, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more after anaesthesia.

Ketalar should be used with caution in patients with:

- Chronic alcoholic and the acutely alcohol-intoxicated patients.
- Increased intraocular pressure (e.g. glaucoma) as the pressure may increase significantly after a single dose of ketamine.
- Neurotic traits or psychiatric illness (e.g. schizophrenia and acute psychosis).
- Acute intermittent porphyria.
- Seizures.
- Hyperthyroidism or patients receiving thyroid replacement (increased risk of hypertension and tachycardia).
- Intracranial mass lesions, a presence of head injury, globe injuries or hydrocephalus.

Long-Term Use

Cases of cystitis including haemorrhagic cystitis have been reported in patients being given ketamine on a long term basis. This adverse reaction develops in patients receiving long term ketamine treatment after a time ranging from 1 month to several years. **Ketamine is not indicated nor recommended for long term use.** Hepatotoxicity has also been reported in patients with extended use (> 3 days).

Drug Abuse and Dependence

Ketalar has been reported as being a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia, or disorientation. Cases of cystitis including haemorrhagic cystitis and cases of hepatotoxicity have also been reported. If used on a daily basis for a few weeks, dependence and tolerance may develop, particularly in individuals with a history of drug abuse and dependence. Therefore the use of Ketalar should be closely supervised and it should be prescribed and administered with caution.

Ketalar 10mg/ml injection contains 0.11 mmol (or 2.6 mg) sodium per ml, which should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

The use of barbiturates or opiate agonists concurrently with ketamine may prolong the recovery period, as may also benzodiazepines used as premedication.

Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, should not be injected from the same syringe.

Other general anaesthetics block the centrally mediated cardiovascular stimulant properties of ketamine. Significant cardiovascular depression increased risk of developing bradycardia, hypotension or decreased cardiac output have occurred with concurrent use of halothane or enflurane anaesthesia.

Ketamine may potentiate the neuromuscular blocking effects of atracurium and tubocurarine, including respiratory depression with apnea.

The use of halogenated anaesthetics concomitantly with ketamine can lengthen the elimination half life of ketamine and delay recovery from anaesthesia. Concurrent use of ketamine (especially high doses or when rapidly administered) with halogenated anaesthetics can increase the risk of developing bradycardia, hypotension or decrease cardiac output.

The use of ketamine with other central nervous system (CNS) depressants (e.g. ethanol, phenothiazines, sedating H₂- blockers or skeletal muscle relaxants) can potentiate CNS depression and/or increase the risk of developing respiratory depression. Reduced doses of ketamine may be required with concurrent administration of other anxiolytics, sedatives and hypnotics.

Ketamine has been reported to antagonize the hypnotic effect of thiopental.

Patients taking thyroid hormones have an increased risk of developing hypertension and tachycardia when given ketamine.

Concomitant use of antihypertensive agents and ketamine increases the risk of developing hypotension.

When ketamine and theophylline are given concurrently, a clinically significant reduction in the seizure threshold is observed. Unpredictable extensor-type seizures have been reported with concurrent administration of these agents.

Halothane used concomitantly slows distribution and redistribution of ketamine and inhibits its hepatic metabolism.

Concurrent use of diazepam or other benzodiazepines will increase plasma levels and reduce the clearance rate of ketamine. Concurrent use of nitrous oxide will reduce the required dose of ketamine.

The concomitant use of ketamine with gallamine will lead to tachycardia, and with pancuronium to hypertension. Neither relaxant should be used with ketamine.

Ketamine should be used cautiously in patients receiving thyroid hormone because of the increased risk of hypertension and tachycardia.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Ketamine crosses the placenta. This should be borne in mind during operative procedures in pregnancy. No controlled clinical studies in pregnancy have been conducted. The safe use in pregnancy has not been established, and such use is not recommended, with the exception of administration during surgery for abdominal delivery or vaginal delivery.

Some neonates exposed to ketamine at maternal intravenous doses \geq 1.5 mg/kg during delivery have experienced respiratory depression and low Apgar scores requiring newborn resuscitation.

Marked increases in maternal blood pressure and uterine tone have been observed at intravenous doses greater than 2 mg/kg.

Data are lacking for intramuscular injection and maintenance intravenous infusion of ketamine in the parturient population, and dosing recommendations cannot be made. Available intramuscular injection pharmacokinetic data are presented in section 5.2.

Lactation

The safe use of ketamine during lactation has not been established, and such use is not recommended.

4.7 Effects on ability to drive and use machines

Patients should be cautioned that driving a car, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more after anaesthesia.

4.8 Undesirable effects

The following Adverse Events have been reported:

MedDRA System Organ Class	Frequency†	Undesirable Effects
Immune system disorders	Rare	Anaphylactic reaction*
Metabolism and nutrition disorders	Uncommon	Anorexia

MedDRA System Organ Class	Frequency†	Undesirable Effects
Psychiatric disorders	Common	Hallucination, Abnormal dreams, Nightmare, Confusion, Agitation, Abnormal behaviour
	Uncommon	Anxiety
	Rare	Delirium* Flashback*, Dysphoria*, Insomnia, Disorientation*
Nervous system disorders	Common	Nystagmus, Hypertonia, Tonic clonic movements
Eye disorders	Common	Diplopia
	Not Known	Intraocular pressure increased
Cardiac disorders	Common	Blood pressure increased, Heart rate increased
	Uncommon	Bradycardia, Arrhythmia
Vascular disorders	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory rate increased
	Uncommon	Respiratory depression, Laryngospasm
Gastrointestinal disorders	Rare	Obstructive airway disorder*, Apnoea*
	Common	Nausea, Vomiting
	Rare	Salivary hypersecretion*
Hepatobiliary disorders	Not known	Liver function test abnormal, Drug-induced liver injury**
Skin and subcutaneous tissue disorders	Common	Erythema, Rash morbilliform
Renal and urinary disorders	Rare	Cystitis*, Haemorrhagic cystitis*
General disorders and administration site conditions	Uncommon	Injection site pain, Injection site rash

† Common (\geq 1/100 to <1/10); Uncommon (\geq 1/1,000 to <1/100); Rare (\geq 1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data)

* AE frequency estimated from post-marketing safety database

** 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Respiratory depression can result from an overdosage of ketamine hydrochloride. Supportive ventilation should be employed.

Mechanical support of respiration that will maintain adequate blood oxygen saturation and carbon dioxide elimination is preferred to administration of analeptics.

Ketalar has a wide margin of safety; several instances of unintentional administration of overdoses of Ketalar (up to 10 times that usually required) have been followed by gradual but complete recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N01 AX03

General anaesthetics, other

Ketamine is a rapidly acting general anaesthetic for intravenous or intramuscular use with a distinct pharmacological action. Ketamine hydrochloride produces dissociative anaesthesia characterised by catalepsy, amnesia, and marked analgesia which may persist into the recovery period. There is only slight diminution of pharyngeal-laryngeal reflexes and skeletal muscle tone may be normal or can be enhanced to varying degrees. Mild cardiac and respiratory stimulation and occasionally respiratory depression occur.

Mechanism of Action
Ketamine induces sedation, immobility amnesia, and marked analgesia. The anaesthetic state produced by ketamine has been termed 'dissociative anaesthesia' in that it appears to selectively interrupt association pathways of the brain before producing somesthetic sensory blockade. Numerous theories have been proposed to explain the effects of ketamine, including binding to N-methyl-D-aspartate (NMDA) receptors in the CNS, interactions with opiate receptors at central and spinal sites, and interaction with norpinephrine, serotonin and muscarinic cholinergic receptors. The activity on NMDA receptors may be responsible for the analgesic as well as the psychiatric (psychosis) effects of ketamine. Ketamine has sympathomimetic activity resulting in tachycardia, hypertension, increased myocardial and cerebral oxygen consumption, increased cerebral blood flow and increased intracranial and intraocular pressure. Ketamine is also a potent bronchodilator. Clinical effects observed following ketamine administration include increased blood pressure, increased muscle tone (may resemble cataleptia), opening of eyes (usually accompanied by nystagmus) and increased myocardial oxygen consumption.

5.2 Pharmacokinetic properties

Absorption

Ketamine is rapidly absorbed following parenteral administration.

Distribution

Ketamine is rapidly distributed into perfused tissues including brain and placenta. Animal studies have shown ketamine to be highly concentrated in body fat, liver and lung. 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 ketamine peak concentrations are about 1.8 to 2.0 µg/mL at 5 minutes after an intravenous bolus injection of a 2 mg/kg dose, and about 1.7 to 2.2 µg/mL at 15 minutes after an intramuscular injection of a 6 mg/kg dose in adults and children.

In parturients receiving an intramuscular dose of 250 mg (approximately 4.2 mg/kg), placental transfer rate of ketamine from maternal artery to umbilical vein was 47% at the time of delivery (1.72 versus 0.75 µg/mL). Average delivery time for these parturients was 12 minutes from the time of ketamine injection to vaginal delivery of a newborn.

Biotransformation

Biotransformation takes place in the liver. Termination of anaesthetic is partly by redistribution from brain to other tissues and partly by metabolism. Ketamine undergoes hepatic N-demethylation (via the cytochrome P450 system) and hydroxylation of the cyclohexanone ring, with the formation of water-soluble conjugates which are excreted in the urine. 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.

Elimination

Elimination half-life is approximately 2-3 hours, and excretion renal, mostly as conjugated metabolites.

5.3 Preclinical safety data

Pre-clinical safety data does not add anything of further significance to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ketalar 10mg/ml Solution for Injection/Infusion

Sodium chloride

Benzethonium chloride

Water for injections

Ketalar 50mg/ml Solution for Injection/Infusion

Benzethonium chloride

Water for injections

6.2 Incompatibilities

Ketalar is chemically incompatible with barbiturates and diazepam because of precipitate formation. Therefore, these should not be mixed in the same syringe or infusion fluid.

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

6.3 Shelf life

Unopened: 5 years.

After opening: From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

After dilution: Use immediately after dilution.

This product should be diluted immediately after opening.
For single use only. Discard any unused product at the end of each operating session.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze.

Store in the original container.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Ketalar 10mg/ml Injection : 20 ml white neutral glass vial with rubber closure and aluminium flip-off cap containing 20ml of solution as 10 mg ketamine base per ml.

Ketalar 50mg/ml Injection: 10 ml vials containing 10 ml of solution as 50 mg ketamine base per ml.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused product at the end of each operating session.

After opening: From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. Discard unused product after dosing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

This product has been shown to be compatible with dextrose 5% and sodium chloride 0.9%. See section 4.2.

7. MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland.

9 Riverwalk, National Digital Park

Citywest Business Campus, Dublin 24, Ireland.

8. MARKETING AUTHORISATION NUMBER

Ketalar 10mg/ml Solution for Injection/Infusion PA 822/13/1

Ketalar 50mg/ml Solution for Injection/Infusion PA 822/13/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 01 April 1980

Date of latest renewal: 01 April 2010

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Ref: KE 20_2

- The dose of Ketalar depends on its use and varies from person to person. When injected directly into a vein at a dose of 2 mg for every kg of your bodyweight, Ketalar produces unconsciousness within 30 seconds and this lasts for 5 to 10 minutes. Because it works so quickly, it is important to be lying down, or supported in some other way when the drug is given. When Ketalar is injected into a muscle, at a dose of 10 mg for every kg of bodyweight, it takes longer to work (3 to 4 minutes) but lasts 12 to 25 minutes.
- Your anaesthetist will then keep you anaesthetised with either:
 - another anaesthetic
 - more Ketalar given by injection into a muscle or vein, or in a drip (infusion)
 - Ketalar together with another anaesthetic.
- When it is injected directly into a vein, Ketalar is given over at least a minute so that it does not slow your breathing too much. If breathing is slowed, it can be helped mechanically.
- While you are anaesthetised, your anaesthetist will watch over you constantly, paying particular attention to your breathing, airways, reflexes, the degree of anaesthesia and the condition of your heart.
- You should not be released from hospital until you have completely recovered from the anaesthetic. If you are discharged on the same day as the operation, you should be accompanied by another adult (see also the section on 'Driving and using machines').

- If you are given more Ketalar than you should you may experience breathing difficulties. Your doctor or nurse may provide you with equipment to help you breath.

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

4. Possible side effects

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

Tell your doctor **immediately** if you notice pain, inflammation of the skin or rash at the injection site.

Ketalar can sometimes cause allergic symptoms ('anaphylaxis') such as breathing problems; swelling and rash. Some people have hallucinations, vivid dreams, nightmares, feel ill at ease, confused, anxious or behave irrationally while recovering from anaesthesia with Ketalar. These side effects are collectively known as an 'emergence reaction'. You will be allowed to recover from the anaesthetic in a quiet place and this helps to prevent the reaction (see Section 3 under 'How Ketalar Injection is given').

Common: may affect up to 1 in 10 people

- the following, while recovering from anaesthesia (these are collectively known as an 'emergence reaction'):
 - hallucinations (which may include flashbacks or floating sensation), vivid dreams, nightmares, feeling ill at ease, confused, anxious and irrational behaviour.
 - unusual eye movements, increased muscle tone and muscle twitches (which may resemble 'fits' or convulsions).
 - double vision.
 - increased blood pressure and increased pulse rate.
 - breathing more quickly.
 - nausea, vomiting.
 - skin inflammation/rash.

Uncommon: may affect up to 1 in 100 people

- loss of appetite.
- feeling anxious.
- slowing of heart rate, changes in heart rhythm.
- lowering of blood pressure.
- breathing more slowly, narrowing of the voice-box leading to difficulty in breathing.
- pain, inflammation of the skin or rash at the injection site.

Rare: may affect up to 1 in 1,000 people

- allergic symptoms ('anaphylaxis') such as breathing problems, swelling and rash.
- drifting in and out of consciousness (with feeling of confusion and hallucinations), flashbacks, feeling ill at ease, sleeplessness, feeling disorientated.
- affect on the reflexes which keep your airways clear, resulting in temporary inability to breathe.
- increase in salivation.
- inflammation of the bladder and/or pain when urinating ('cystitis'). The appearance of blood in the urine may also occur.

Not known: frequency cannot be estimate from the available data

- raised pressure in the eyes.
- abnormal results to liver function tests.
- drug-induced liver injury (when taken for more than 3 days).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ketalar Injection

- 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 label and carton after EXP. The expiry dates refers to the last day of that month. Your pharmacist will check this before the injection is given.
- Do not store above 25 °C. Do not freeze. Store in the original container. Keep the vial in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Ketalar contains

- The active ingredient is ketamine hydrochloride

Each 20 ml solution contains 10 mg of ketamine base per ml

Each 10 ml solution contains 50 mg of ketamine base per ml

- The other ingredients are:

10 mg/ml: sodium chloride (salt), water for injections and a preservative (benzethonium chloride).

50 mg/ml: water for injections and a preservative (benzethonium chloride).

What Ketalar looks like and contents of the pack

Ketalar is a clear solution for injection or infusion available in single glass vials and comes in two strengths. Each carton contains 1 vial.

Marketing Authorisation Holder:

Pfizer Healthcare Ireland, 9 Riverwalk, National Digital Park, Citywest Business Campus, Dublin 24, Ireland.

Manufacturer:

Hameln Pharmaceuticals GmbH, Langes Feld 13, 31789 Hameln, Germany.

Company contact address:

For further information on this medicine please contact Medical Information at Pfizer Healthcare Ireland, 9 Riverwalk, National Digital Park, Citywest Business Campus, Dublin 24, Ireland.

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