Ketalar Injection
(Ketamine Hydrochloride)

1. NAME OF MEDICINAL PRODUCT

Ketalar 10 mg/ml, 50 mg/ml, 100 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains:

Ketalar 10 mg/ml Injection:	ketamine hydrochloride equivalent to 10 mg ketamine base per ml.
Ketalar 50 mg/ml Injection:	ketamine hydrochloride equivalent to 50 mg ketamine base per ml.
Ketalar 100 mg/ml Injection:	ketamine hydrochloride equivalent to 100 mg ketamine base per ml.

Excipient with known effect:
Ketalar 10mg/ml contains 53 mg of sodium per 20 ml of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
A clear solution for injection or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ketamine is indicated in children and in adults.

Ketalar is recommended:

As an anaesthetic agent for diagnostic and surgical procedures. When used by intravenous or intramuscular injection, Ketalar is best suited for short procedures. With additional doses, or by intravenous infusion, Ketalar can be used for longer procedures. If skeletal muscle relaxation is desired, a muscle relaxant should be used and respiration should be supported.

For the induction of anaesthesia prior to the administration of other general anaesthetic agents.

To supplement other anaesthetic agents.

Specific areas of application or types of procedures:

When the intramuscular route of administration is preferred.

Debridement, painful dressings, and skin grafting in burned patients, as well as other superficial surgical procedures.

Neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms,

and lumbar punctures.

Diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions.

Note: Eye movements may persist during ophthalmological procedures.

Anaesthesia in poor-risk patients with depression of vital functions or where depression of vital functions must be avoided, if at all possible.

Orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies.

Sigmoidoscopy and minor surgery of the anus and rectum, circumcision and pilonidal sinus.

Cardiac catheterization procedures.

Caesarean section; as an induction agent in the absence of elevated blood pressure.

Anaesthesia in the asthmatic patient, either to minimise the risks of an attack of bronchospasm developing, or in the presence of bronchospasm where anaesthesia cannot be delayed.

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

Ketalar has been safely used alone when the stomach was not empty. However, 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.

Premedication with an anticholinergic agent (e.g. atropine, hyoscine or glycopyrrolate) or another drying agent should be given at an appropriate interval prior to induction to reduce ketamine-induced hypersalivation.

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 2 mg/kg of bodyweight usually produces surgical anaesthesia within 30 seconds after injection and the anaesthetic effect usually lasts 5 to 10 minutes. An intramuscular dose of 10 mg/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 1 mg/ml of ketamine in dextrose 5% or sodium chloride 0.9% is suitable for administration by infusion.

General Anaesthesia 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 - 45 microgram/kg/min (approximately 1 – 3 mg/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 1 mg/kg to 4.5 mg/kg (in terms of ketamine base). 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 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Note: the 100 mg/ml concentration of ketamine should not be injected intravenously without proper dilution. It is recommended that the drug be diluted with an equal volume of either sterile water for injection, normal saline, or 5% dextrose in water.

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).

Intramuscular Route

The initial dose of Ketalar administered intramuscularly may range from 6.5 mg/kg to 13 mg/kg (in terms of ketamine base). 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.

Dosage in 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 and maintenance infusion of ketamine in the parturient population, and recommendations cannot be made. Available data are presented in section 5.2.

Maintenance of general 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.

Each additional dose is from ½ 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.

D. 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

Ketalar is contra-indicated in persons in whom an elevation of blood pressure would constitute a serious hazard (see section 4.8). Ketamine hydrochloride is contraindicated in patients who have shown hypersensitivity to the drug or its components. Ketalar should not be used in patients with eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident or cerebral trauma.

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.

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 seconds. More rapid administration may result in transient respiratory depression or apnoea and enhanced pressor response.

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.

Although 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), in clinical practice aspiration is seldom a problem.

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

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.

Ketalar should be used with caution in patients with the following conditions:

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

Ketamine is metabolised in the liver and hepatic clearance is required for termination of clinical effects. 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. Abnormal liver function tests associated with ketamine use have been reported, particularly with extended use (>3 days) or drug abuse.

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

Use with caution in patients with globe injuries and increased intraocular pressure (e.g. glaucoma) because the pressure may increase significantly after a single dose of ketamine.

Use with caution in patients with neurotic traits or psychiatric illness (e.g. schizophrenia and acute psychosis)

Use in caution in patients with acute intermittent porphyria.

Use in caution in patients with seizures.

Use in caution in patients with hyperthyroidism or patients receiving thyroid replacement (increased risk of hypertension and tachycardia)

Use in caution in patients with pulmonary or upper respiratory infection (ketamine sensitises the gag reflex, potentially causing laryngospasm)

Use in caution in patients with intracranial mass lesions, a presence of head injury, or hydrocephalus.

Emergence Reaction

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).

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.

Cardiovascular

Because of the substantial increase in myocardial oxygen consumption, ketamine should be used in caution in patients with hypovolemia, 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.

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.

Long-Term use

Cases of cystitis, including haemorrhagic cystitis, acute kidney injury, hydronephrosis, and ureteral disorders have been reported in patients being given ketamine on a long-term basis, especially in the setting of ketamine abuse. (These adverse reactions develop 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. Adverse effects have also been reported: see “Long-Term Use”.

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.

Excipient information
Ketalar 10mg/ml Injection contains 53 mg of sodium in each vial, equivalent to 2.65% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

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

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

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 in high doses or when rapidly administered) with halogenated anaesthetics can increase the risk of developing bradycardia, hypotension or decreased cardiac output.

The use of ketamine with other central nervous system (CNS) depressants (e.g. ethanol, phenothiazines, sedating H_1 – blockers or skeletal muscle relaxants) can potentiate CNS depression and/or increase 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 antagonise the hypnotic effect of thiopental.

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

Sympathomimetics (directly or indirectly acting) and vasopressin may enhance the sympathomimetic effects of ketamine.

Concomitant use with ergometrine may lead to an increase in blood pressure.

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

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

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.

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4.6 Fertility, pregnancy and lactation

Pregnancy
Ketalar crosses the placenta. This should be borne in mind during operative obstetric procedures in pregnancy. No controlled clinical studies in pregnancy have been conducted. The 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 ≥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 infusion of ketamine in the parturient population, and recommendations cannot be made. Available data are presented in section 5.2.

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

Studies in animals have shown reproductive toxicity (see section 5.3).

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.
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

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
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
	Rare	Obstructive airway disorder*, Apnoea*
Gastrointestinal disorders	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 (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥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.

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 prolonged but complete recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N01AX03, Pharmacotherapeutic group: Other general anaesthetics.

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. Pharyngeal-laryngeal reflexes remain normal 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. It may selectively depress the thalamoneocortical system before significantly obtunding the more ancient cerebral centres and pathways (reticular-activating and limbic systems). 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 norepinephrine, serotonin and muscarinic cholinergic receptors. The activity on NMDA receptors may be responsible for the analgesic as well as 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 catatonia), opening of eyes (usually accompanied by nystagmus) and increased myocardial oxygen consumption.

5.2 Pharmacokinetic properties

Absorption
Ketamine is rapidly absorbed following intra-muscular 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 concentrations are about 1.8 to 2.0 μg/ml at 5 minutes after an intravenous bolus injection of 2 mg/kg dose, and about 1.7 to 2.2 μg/ml at 15 minutes after an intramuscular injection of 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 liver. Termination of anaesthetic is partly by redistribution from brain to other tissues and partly by metabolism. 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

Animal research has shown that ketamine can induce NMDA antagonist-induced neuronal cell death in juvenile animals (apoptosis) when administered in high doses, for prolonged periods, or both. In some cases this led to abnormalities in behaviour, learning and memory. The relevance of this finding to human use is unknown.

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

Ketalar 10 mg/ml Injection:	sodium chloride, benzethonium chloride, water for injections
Ketalar 50 mg/ml Injection:	benzethonium chloride, water for injections
Ketalar 100 mg/ml Injection:	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.

6.3 Shelf life

Please refer to outer carton for expiry date.

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

After dilution the solutions should be used immediately.

6.4 Special precautions for storage

Please refer to outer carton for storage condition.

6.5 Nature and contents of container

Ketalar 10 mg/ml Injection:	20 ml vials containing 20 ml of solution as 10 mg ketamine base per ml.
Ketalar 50 mg/ml Injection:	10 ml vials containing 10 ml of solution as 50 mg ketamine base per ml.
Ketalar 100 mg/ml Injection:	10 ml vials containing 10 ml of solution as 100 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. See

section 4.2.

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