Package leaflet: Information for the patient
KETALAR® 10 mg/ml, 50 mg/ml and 100 mg/ml INJECTION
Ketamine hydrochloride

Read all of this leaflet carefully before you are given 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.

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 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 safely be used in caesarean section surgery or vaginal delivery.

❖ 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:
- drink large amounts of alcohol
- have a history of drug abuse or addiction
- have a history of or have current mental health problems
- 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
• are receiving treatment for your thyroid gland
• have had any injury to your head or abnormal growth in the brain

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.
• 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 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. The medicine can affect your ability to drive as it may make you sleepy or dizzy.
• Do not drive while taking this medicine until you know how it affects you.
• It is an offence to drive if this medicine affects your ability to drive.
• However, you would not be committing an offence if:
  o The medicine has been prescribed to treat a medical or dental problem and
  o You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and
  o It was not affecting your ability to drive safely
Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

❖ Ketalar contains sodium
Ketalar 10 mg/ml Injection: Each 1 ml contains 2.6 mg 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 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 breathe.

  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 1000 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 estimated 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 or nurse. This includes any possible side effects not listed in this leaflet. You can report side effects directly via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). 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. 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
  Each 10 ml solution contains 100 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).
  100 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 three strengths. Each carton contains 1 vial.

**Marketing Authorisation Holder:**

Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom
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 Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS
Telephone 01304 616161

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The following information is intended for the healthcare professional only

SUMMARY OF PRODUCT CHARACTERISTICS

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 10mg/ml Injection: ketamine hydrochloride equivalent to 10 mg ketamine base per ml.
Excipient(s) with known effect: Each 1 ml contains 2.6 mg of sodium
Ketalar 50mg/ml Injection: ketamine hydrochloride equivalent to 50 mg ketamine base per ml.
Ketalar 100mg/ml Injection: ketamine hydrochloride equivalent to 100 mg ketamine base per ml.

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

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 Fertility, pregnancy and lactation).

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 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.

**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.

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 H₁ – 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.

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.

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
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.

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. 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:
  o The medicine has been prescribed to treat a medical or dental problem and
  o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  o It was not affecting your ability to drive safely
4.8 Undesirable effects

The following Adverse Events have been reported:

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<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency†</th>
<th>Undesirable Effects</th>
</tr>
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<tbody>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Anaphylactic reaction*</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Uncommon</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Hallucination, Abnormal dreams, Nightmare, Confusion, Agitation, Abnormal behaviour</td>
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<td></td>
<td>Uncommon</td>
<td>Anxiety</td>
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<tr>
<td></td>
<td>Rare</td>
<td>Delirium* Flashback*, Dysphoria*, Insomnia, Disorientation*</td>
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<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Nystagmus, Hypertonia, Tonic clonic movements</td>
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<td>Eye disorders</td>
<td>Common</td>
<td>Diplopia</td>
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<td></td>
<td>Not Known</td>
<td>Intraocular pressure increased</td>
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<td>Cardiac disorders</td>
<td>Common</td>
<td>Blood pressure increased, Heart rate increased</td>
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<td></td>
<td>Uncommon</td>
<td>Bradycardia, Arrhythmia</td>
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<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Hypotension</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>Respiratory rate increased</td>
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<td>Respiratory depression, Laryngospasm</td>
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<td>Rare</td>
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<td>Liver function test abnormal, Drug-induced liver injury**</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Erythema, Rash morbilliform</td>
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<td>Renal and urinary disorders</td>
<td>Rare</td>
<td>Cystitis*, Haemorrhagic cystitis*</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<td>Injection site pain, Injection site rash</td>
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</tbody>
</table>

† 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

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 thalamo-cortical 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.

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
Ketalar 10 mg/ml and 50 mg/ml: 5 years
Ketalar 100 mg/ml: 3 years

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
Do not store above 25 °C. Do not freeze. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container
Ketalar 10 mg/ml Injection: 20 ml white neutral glass vial with rubber closure and aluminium flip-off cap 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.

7. MARKETING AUTHORISATION HOLDER
Pfizer Limited, Sandwich, Kent CT13 9NJ, United Kingdom

8. MARKETING AUTHORISATION NUMBER
PL 00057/0529, PL 00057/0530, PL 00057/0531
9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
1st July 2003

10. DATE OF REVISION OF THE TEXT
02/2017

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