# AUSTRALIAN PRODUCT INFORMATION – KETALAR® (ketamine hydrochloride)

## 1. NAME OF THE MEDICINE

Ketamine hydrochloride

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of KETALAR contains 100 mg ketamine base (ketamine hydrochloride 115.3 mg/mL).

For the full list of excipients, see section **6.1 List of excipients**.

## 3. PHARMACEUTICAL FORM

KETALAR is a clear, colourless solution for intravenous or intramuscular injection.

It is formulated as an acid (pH 3.5 to 5.5) solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

KETALAR is recommended:

1. as the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. KETALAR is best suited for short procedures and it can be used with additional doses, for longer procedures;

2. for the induction of anaesthesia prior to the administration of other general anaesthetic agents;

3. to supplement low-potency agents, such as nitrous oxide.

### 4.2 Dose and method of administration

**Pre-Operative Preparation**

1. While vomiting has been reported following KETALAR administration, airway protection is usually afforded because of active laryngeal-pharyngeal reflexes. However, because these reflexes may also be diminished by supplementary anaesthetics or muscle relaxants, the possibility of aspiration must be considered. KETALAR is recommended for use in the patient whose stomach is not empty only when, in the judgement of the medical practitioner, the benefits of the drug outweigh the possible risks.

2. Atropine, hyoscine or other 'drying' agents should be given at an appropriate interval prior to induction.

**Dosage**

As with other general anaesthetic agents, the individual response to KETALAR is somewhat varied depending on the dose, route of administration and age of patient, so that the dosage recommended cannot be absolutely determined in a fixed manner. The drug should be titrated against the patient's requirements.

**Onset and Duration**

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration. The onset of action of KETALAR is rapid; an intravenous dose of 2 mg/kg of body weight usually produces surgical anaesthesia within 30 seconds after injection, with the anaesthetic effect usually lasting 5 to 10 minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anaesthesia without producing significant cumulative effect.

From experience, intramuscular doses (primarily in children, in a range of 9 to 13 mg/kg) usually produce surgical anaesthesia within 3 to 4 minutes following administration, with the anaesthetic effect usually lasting 12 to 25 minutes.

**Induction**

**Intravenous route:** the initial dose of KETALAR administered intravenously may range from 1 mg/kg to 4.5 mg/kg. The average amount required to produce 5 to 10 minutes of surgical anaesthesia has been 2 mg/kg.

**NOTE**

The 100 mg/mL concentration of KETALAR **should not** be injected intravenously without appropriate dilution. It is recommended the drug be diluted with an equal volume of either sterile water for injection, normal saline or, 5% glucose in water. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours.

**Rate of administration:** it is recommended that KETALAR be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

**Intramuscular route:** the initial dose of KETALAR administered intramuscularly ranges from 6.5 to 13 mg/kg. A dose of 10 mg/kg will usually produce 12 to 25 minutes of surgical anaesthesia.

If the ketamine dose is augmented with diazepam, the two drugs must be given separately. Do **not** mix ketamine and diazepam in the same syringe or infusion flask.

**Dosage in Hepatic Insufficiency:** Dose reductions should be considered in patients with cirrhosis or other types of liver impairment (see section **4.4 Special warnings and precautions for use**).

**Maintenance of Anaesthesia**

Increments of one half to the full induction dose may be repeated, as needed, for maintenance of anaesthesia. However it should be noted that involuntary and tonic-clonic movements of extremities might occur during the course of anaesthesia. These movements do not imply a level of attenuated anaesthesia and are not indicative of the need for additional doses of the anaesthetic. It should be recognised that the greater the total dose of KETALAR administered, the longer will be the time to complete recovery.

This product is for one dose in one patient only. Discard any remaining contents.

## 4.3 Contraindications

KETALAR is contraindicated in patients with any condition in which a significant elevation of blood pressure would be hazardous such as: severe cardiovascular disease, heart failure, severe or poorly controlled hypertension, recent myocardial infarction, history of stroke, cerebral trauma, intracerebral mass or haemorrhage. Ketamine is also contraindicated in those who have shown hypersensitivity to the drug or its components.

## 4.4 Special warnings and precautions for use

1. KETALAR should be used by or under the direction of medical practitioners experienced in administering general anaesthetics and in maintenance of an airway and in the control of respiratory support.

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

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

4. Post-operative confusional states may occur during the recovery period (see section **4.4 Special warnings and precautions for use - Emergence Reaction**).

5. Because pharyngeal and laryngeal reflexes are usually active, KETALAR should not be used alone in surgery or diagnostic procedures of the pharynx, larynx or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if KETALAR is used alone. Muscle relaxants with proper attention to respiration, may be required in both of these instances.

6. Resuscitative equipment should be ready for use.

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

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

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

10. An increase in cerebrospinal fluid pressure has been reported following administration of KETALAR. Use with extreme caution in patients with pre-anaesthetic elevated cerebrospinal fluid pressure.

11. In patients with significant renal or hepatic impairment, the elimination of ketamine could potentially be delayed. Dose reductions should be considered in patients with cirrhosis or other types of liver impairment.

12. Patients should be cautioned that driving an automobile, operating machinery or engaging in other hazardous activities should not be undertaken for 24 hours or more (depending on dose and other drugs employed) after anaesthesia.

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

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

15. Use with caution in patients with acute intermittent porphyria.

16. Use with caution in patients with seizures.

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

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

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

**Emergence Reaction**

Treatment-emergent adverse reactions have occurred in approximately 12% of patients. The psychological manifestations vary in severity between pleasant dream-like states, vivid imagery, hallucinations, nightmares or illusions and 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. The duration ordinarily lasts no more than a few hours; in a few cases, however, recurrences have taken place up to 24 hours post-operatively. No residual psychological effects are known to have resulted from use of KETALAR.

The incidence of these treatment-emergent adverse events is least in the young (15 years of age or less) and elderly (over 65 years of age) patient. Also they are less frequent when the drug is given intramuscularly. These reactions may be reduced if verbal, tactile and visual stimulation of the patient is minimised during the recovery period.

This does not preclude the monitoring of vital signs. In addition, the use of a small hypnotic dose of a short-acting or ultra-short-acting barbiturate may be required to terminate a severe treatment-emergent adverse reaction. The incidence of emergence reactions is reduced as experience with the drug is gained. When KETALAR is used on an out-patient basis, the

patient should not be released until recovery of anaesthesia is complete and should be accompanied by a responsible adult at discharge.

**Cardiovascular**

Because of the substantial increase in myocardial oxygen consumption, ketamine should be used with caution in patients with hypovolemia, dehydration, or cardiac disease, especially coronary artery disease (e.g., congestive heart failure, myocardial ischaemia, 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.

**Long-Term Use**

Cases of cystitis, including haemorrhagic cystitis, acute kidney injury, hydronephrosis, and ureteral disorder (see section **4.8 Adverse effects (undesirable effects)**) have been reported in patients using 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).

**Abuse Potential**

Ketamine has been reported being used as 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, acute kidney injury, hydronephrosis, ureteral disorder (see section **4.8 Adverse effects (undesirable effects)**), and hepatotoxicity have also been reported. Ketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, ketamine should be prescribed and administered with caution.

**Use in the Elderly**

No data available.

**Paediatric Use**

Plasma half-life, clearance and volume of distribution (relative to body weight) are not significantly different between adults and children, although absorption following intramuscular injection is more rapid in the latter.[1, 2]

Paediatric Neurotoxicity

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/analgesic/sedation drug administration or other factors such as the surgery or underlying illness.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined.

With inhalation or infusion of such drugs, exposure is longer than the period of inhalation or infusion. Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration.

**Effects on Laboratory Tests**

There is no information available regarding the possible effects of ketamine on clinical laboratory tests.

## 4.5 Interactions with other medicines and other forms of interactions

Halogenated hydrocarbon inhalational anaesthetics may prolong the half-life of ketamine; recovery from anaesthesia may be prolonged following concurrent use. 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.

Diazepam is known to increase the half-life of ketamine and prolongs its pharmacodynamic effects. Dose adjustments may therefore be needed[3].

Sympathomimetics (directly or indirectly acting) and vasopressin may enhance the sympathomimetic effects of ketamine[3].

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

Benzodiazepines may prolong the half-life of ketamine; recovery from anaesthesia may be prolonged following concurrent use.[4]

Concomitant use with ergometrine may lead to an increase in blood pressure and Co-administration of drugs with a hypertensive effect should be avoided.[3,5]

Sustained rises in arterial pressure have been reported in patients receiving concomitant ketamine and thyroxine.[5]

Clinically significant reduction in seizure threshold may be observed in patients receiving concomitant ketamine and theophylline or aminophylline.[3,5] Unpredictable extensor-type seizures have been reported with concurrent administration of these agents.

There is no information available on the interactions between ketamine and antihypertensive agents. However, given the marked increase in arterial pressure following administration of ketamine, cardiac function should be monitored (see section **4.4 Special warnings and precautions for use**).

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

Ketamine is clinically compatible with the commonly used general and local anaesthetic agents when an adequate respiratory exchange is maintained.

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

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.

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

## 4.6 Fertility, pregnancy and lactation

**Effects on fertility**

No data available.

**Use in pregnancy - Category B3**

Limited studies in animals have not shown that ketamine causes birth defects; however, it crosses the placenta. Histological changes in the heart (degeneration and oedema of cardiac muscle), liver (diffuse haemopoietic cell infiltration, parenchymal cell degeneration) and kidneys (proximal convoluted tubule degeneration) were observed in foetuses following administration of ketamine to pregnant rats during the period of organogenesis at doses similar to the maximum human dose, on a body surface area basis; a NOEL for these effects was not established. Ketamine administration to pregnant monkeys near term was associated with increased blood $pCO_2$ and a dose-dependent respiratory depression in neonates, at a dose about one sixteenth the maximum human dose on a body surface area basis.

With the exception of administration during surgery for abdominal delivery or vaginal delivery, no controlled clinical studies in pregnancy have been conducted. The safe use of ketamine in pregnancy has not been established, and such use is not recommended.

Nonclinical research has shown that administration of anaesthetic and sedation drugs that block NMDA receptors, including ketamine, and/or potentiate GABA activity, can increase neuronal cell death in the brain and result in long-term deficits in cognition and behaviour of juvenile animals when administered at either high doses, or for prolonged periods, or both during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. The relevance of these nonclinical findings to human use is unknown.

Australian categorisation definition of Category B3:

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Refer to section **4.4 Special warnings and precautions for use - Paediatric Neurotoxicity**

**Use in lactation**

Ketamine is likely to be excreted in breast milk and therefore breastfeeding should be discontinued when ketamine is in use.

## 4.7 Effects on ability to drive and use machines

This medicine can temporarily impair cognitive function, which can affect a patient's ability to drive safely. Patients should be cautioned that driving an automobile, operating machinery or engaging in other hazardous activities should not be undertaken for 24 hours or more (depending on dose and other drugs employed) after anaesthesia.

## 4.8 Adverse effects (undesirable effects)

**Cardiovascular**

Blood pressure and pulse rate are frequently elevated following administration of KETALAR. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

**Respiration**

Although respiration is frequently stimulated, severe depression of respiration or apnoea* may occur following rapid intravenous administration of high doses of KETALAR. Laryngospasm and other forms of airway obstruction* have occurred during KETALAR anaesthesia.

**Eye**

Diplopia have been noted following KETALAR administration. KETALAR may also cause a slight elevation in intraocular pressure measurement.

**Psychological**

Agitation, disorientation, insomnia. See also section **4.4 Special warnings and precautions for use - Emergence Reaction & Abuse Potential**.

**Neurological**

In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements, sometimes resembling seizures (see section **4.2 Dose and method of**

**administration**). Hypertonia and nystagmus have been noted following KETALAR administration.

**Gastrointestinal**

Anorexia, nausea and vomiting have been observed. However this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see section **4.2 Dose and method of administration**). Hypersalivation* has also been observed.

**Immune System Disorders**

Anaphylaxis* has been observed.

**Hepatobiliary Disorders**

Drug-induced liver injury* has been reported, especially in extended period use (>3 days) or drug abuse. Abnormal liver function test* was also identified.

**Renal and Urinary Disorders**

Acute kidney injury*, hydronephrosis*, ureteral disorder* (including ureteral polyp, ureteritis, ureteric stenosis, and ureteric obstruction), haemorrhagic cystitis*, and cystitis* have been reported during long-term use (1 month to several years) and especially in the setting of ketamine abuse.

**General**

Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

*ADR identified during post-marketing use.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

## 4.9 Overdose

Respiratory depression may occur with overdosage or too rapid rate of administration of KETALAR, in which case, supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Ketamine 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

### Mechanism of action

KETALAR is a rapid-acting, general anaesthetic producing an anaesthetic state characterised by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally, a transient and minimal respiratory depression.

A patent airway is maintained, partly by virtue of relatively unimpaired pharyngeal and laryngeal reflexes (see section **4.4 Special warnings and precautions for use**).

The anaesthetic state produced by KETALAR has been termed 'dissociative anaesthesia' in that it appears to selectively interrupt association pathways of the brain before producing somaesthetic sensory blockade. KETALAR may selectively depress the thalamo-neocortical system before significantly obtunding the more ancient cerebral centres and pathways (reticular-activating and limbic systems).

Elevation of blood pressure begins shortly after injection, reaches a maximum within a few minutes and usually returns to pre-anaesthetic values within 15 minutes after injection. The median peak rise has ranged from 20 to 25% of pre-anaesthetic values.

### Clinical trials

KETALAR ketamine (as hydrochloride) has been studied in over 12,000 operative and diagnostic procedures involving over 10,000 patients from 105 separate studies. During the course of these studies, KETALAR was administered as the sole agent, as induction for other general anaesthetic agents, or to supplement low potency agents. In these studies, the anaesthesia was rated either “excellent” or “good” by the anaesthetist and the surgeon at 90% and 93% respectively. In a second method of evaluation, the anaesthesia was rated “adequate” in at least 90% and “inadequate” in 10% or less of procedures. Specific areas of application have included the following:

1. debridement, painful dressings and skin grafting in burn patients as well as other superficial surgical procedures;

2. neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms and lumbar punctures;

3. diagnostic and operative procedures of the eye, ear, nose and mouth including dental extractions;

4. diagnostic and operative procedures of the pharynx, larynx or bronchial tree;

   Note: muscle relaxants with proper attention to respiration, may be required (see section **4.4 Special warnings and precautions for use**).

5. sigmoidoscopy and minor surgery of the anus and rectum and circumcision;

6. extraperitoneal procedures used in gynaecology, such as dilation and curettage;

7. orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations and biopsies;

8. as an anaesthetic in poor-risk patients with depression of vital functions;

9. in procedures where the intramuscular route of administration is preferred;

10. in cardiac catheterisation procedures.

## 5.2 Pharmacokinetic properties

### Absorption

Ketamine is rapidly absorbed following parenteral administration. Peak plasma levels averaged 0.75 μg/ml and CSF levels were about 0.2 μg/ml one hour after dosing.[6] The plasma half-life is in the range of 2 to 4 hours.[7,8,9] After IM administration (absorption half-life 2-17 minutes) it is up to 93 % bioavailable.[6]

### Distribution

Ketamine (as hydrochloride) is rapidly and extensively distributed throughout the body into highly perfused tissues including the brain.[8,9] Mean volume of distribution is reported to range from approximately 1 to 3 L/kg, and the distribution half-life is approximately 7 to 11 minutes. Ketamine (as hydrochloride) is approximately 20-50% bound to plasma proteins.[4] Ketamine is likely to be excreted in breast milk, but this is unlikely to be clinically relevant. The drug crosses the placenta in induction doses but in amounts that have no adverse effects on the neonate[10] (see section **4.6 Fertility, pregnancy and lactation**).

### Metabolism[4]

Ketamine undergoes extensive hepatic metabolism. The biotransformation includes N-dealkylation to norketamine (metabolite I), hydroxylation of the cyclohexone ring (metabolites III and IV), conjugation with glucuronic acid and dehydration of the hydroxylated metabolites to form the cyclohexene derivative (metabolite II). Norketamine (metabolite I) has about 1/6 of the potency of ketamine and is formed at concentrations in the plasma similar to those of the parent compound.

### Excretion

After intravenous bolus administration, ketamine shows a bi- or triexponential pattern of elimination. The alpha phase lasts about 45 minutes with a half-life of 10 to 15 minutes. This first phase, which represents the anaesthetic action of ketamine, is terminated by redistribution from the CNS to peripheral tissues and hepatic biotransformation to an active metabolite. The beta phase half-life is about 2.5 hours.[7,8,9] About 90% of ketamine is excreted in the urine, mostly as metabolites, with only about 2 to 4 % as the unchanged drug. Approximately 5% is recovered in the faeces.[11] The renal clearance of ketamine hydrochloride is 15 ± 5 mL/min/kg.[12]

## 5.3 Preclinical safety data

**Genotoxicity**

No data available.

**Carcinogenicity**

No data available.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Benzethonium chloride

Water for injections

## 6.2 Incompatibilities

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

## 6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 Special precautions for storage

Store below 30°C. Protect from light.

KETALAR should not be used if the solution is coloured and/or contains particulate matter.

## 6.5 Nature and contents of container

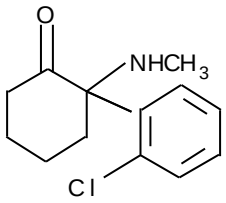
KETALAR 200 mg (base)/2 mL, 5 X 2 mL glass vials

## 6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6.7 Physicochemical properties

**Chemical structure**




Ketamine (as hydrochloride) is a non-barbiturate anaesthetic chemically designated (2*RS*)-2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. Ketamine is a racemic mixture. The molecular weight is 274.2 and the empirical formula is $C_{13}H_{16}ClNO.HCl$.

Ketamine is freely soluble in water and methyl alcohol and is soluble in alcohol.

**CAS number**

1867-66-9

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 - Controlled Drug

## 8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

## 9. DATE OF FIRST APPROVAL

14 February 2000

## 10. DATE OF REVISION

15 October 2020

® Registered trademark

**Summary Table of Changes**

| Section changed | Summary of new information |
|---|---|
| 8 | Update to Sponsor detail |

1. Nimmo WS, et al. Pharmacokinetics of ketamine in children. Br J Anaesth 1982; 14: 144P.
2. Grant IS, et al. Ketamine disposition in adults and children Br J Anaesth 1983, 55: 1107-11.
3. 2.5 Clinical Overview Updates to Section 4.5 Interaction With Other Medicinal Products and Other Forms of Interaction of the Core Data Sheet November 2016.
4. Therapeutic Drugs. Edited by Sir Colin Dollery, 1991, Vol 2: K7-13.
5. Martindale The Complete Drug Reference, MICROMEDEX ® Healthcare series Vol. 105 IncCopyright 2000 Pharmaceutical Press.
6. Clements JA, Nimmo WS, Grant IS. Bioavailability, pharmacokinetics and analgesic activity of ketamine in humans. J Pharm Sci 1982; 71: 539-41.
7. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effects of ketamine in man. Br J Anaesth 1981; 53: 27-30.
8. Grant IS, et al. Pharmacokinetics and analgesic affects of IM and oral ketamine. Br. J Anaesth 1981; 53: 805-9.
9. Wieber J, Gryler RD, Hengstmann JH, Dengler HJ. Pharmacokinetics of ketamine in man. Anaesthesist 1975; 24: 260-6.
10. Little B, Chang T, Chaucet L, et al. A study of ketamine as an obstetrical anesthetic. Am J Obstet Gynecol 1972; 113: 247-58.
11. United States Pharmacopeia Dispensing Information, 1998, 18th Edition, pg 1775-7.
12. Geisslinger G, et al. Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. Br J Anaesth 1993, 70: 666-71.