AUSTRALIAN PRODUCT INFORMATION – KETAMINE APOTEX (KETAMINE HYDROCHLORIDE)

1 NAME OF THE MEDICINE

Ketamine hydrochloride

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Ketamine (as hydrochloride) is formulated as an acid (pH 3.5 to 5.5) solution for intravenous or intramuscular injection in concentrations containing the equivalent of 100 mg ketamine base per millilitre.

Ketamine also contains water for injections. The solution is clear and colourless to slightly yellow, essentially free from visible particulate matter.

Ketamine is freely soluble in water and methanol and is soluble in ethanol (96%).

Ketamine APOTEX 200 mg/2 mL solution for injection:

A clear and to slightly yellow solution, essentially free from visible particulate matter.
(AUST R 219040)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ketamine is recommended:

- as the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine is best suited for short procedures and it can be used with additional doses, for longer procedures;
- for the induction of anaesthesia prior to the administration of other general anaesthetic agents;
- to supplement low-potency agents, such as nitrous oxide.

4.2 DOSE AND METHOD OF ADMINISTRATION

Ketamine injection is for single use in one patient only. Discard any reside.

Pre-Operative Preparation

While vomiting has been reported following ketamine 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. Ketamine is recommended for use in the patient whose stomach is not empty only when, in the judgment of the medical practitioner, the benefits of the drug outweigh the possible risks.

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 ketamine 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 ketamine 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 ketamine 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 ketamine 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 ketamine 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 ketamine 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 ketamine 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

Ketamine 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

Ketamine 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.

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

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

Post-operative confusional states may occur during the recovery period (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Emergence Reaction**).

Because pharyngeal and laryngeal reflexes are usually active, ketamine 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 ketamine is used alone. Muscle relaxants with proper attention to respiration, may be required in both of these instances.

Resuscitative equipment should be ready for use.

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.

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

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

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

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

Use with caution in patients with seizures.

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

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

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 ketamine.

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 ketamine 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.

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. 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 hepatic impairment

In patients with significant 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.

Use in renal impairment

In patients with significant renal impairment, the elimination of ketamine could potentially be delayed.

Use in the elderly

No data available.

Paediatric use

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

No data available.

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[12].

Sympathomimetics (directly or indirectly acting) and vasopressin may enhance the sympathomimetic effects of ketamine[12].

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[6].

Concomitant use with ergometrine may lead to an increase in blood pressure and co-administration of drugs with a hypertensive effect (e.g. ergometrine) should be avoided.[11, 12]

Sustained rises in arterial pressure have been reported in patients receiving concomitant ketamine and thyroxine.[11]

Clinically significant apparent reduction in seizure threshold has been reported in patients receiving concomitant ketamine and theophylline or aminophylline.[11, 12] 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 ketamine, 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 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

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 pCO2 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.

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 fetal damage, the significance of which is considered uncertain in humans.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes.

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

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)

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 http://www.tga.gov.au/reporting-problems and contact Apotex Medical Information enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

Cardiovascular

Blood pressure and pulse rate are frequently elevated following administration of ketamine. 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 ketamine. Laryngospasm and other forms of airway obstruction have occurred during ketamine anaesthesia.

Eye

Diplopia and nystagmus have been noted following ketamine administration. Ketamine may also cause a slight elevation in intraocular pressure measurement.

Psychological (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Emergence Reaction).**

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**).

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.

Abuse Potential (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune System Disorders

Anaphylaxis has been observed.

General

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

4.9 OVERDOSE

Respiratory depression may occur with overdosage or too rapid rate of administration of ketamine, 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 ketamine (up to 10 times that usually required) have been followed by prolonged but complete recovery.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ketamine 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 ketamine has been termed 'dissociative anaesthesia' in that it appears to selectively interrupt association pathways of the brain before producing somaesthetic sensory blockade. Ketamine may selectively depress the thalamoneocortical 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

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, ketamine 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:

- debridement, painful dressings and skin grafting in burn 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;
- 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**)
- sigmoidoscopy and minor surgery of the anus and rectum and circumcision;
- extraperitoneal procedures used in gynaecology, such as dilation and curettage;
- orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations and biopsies;
- as an anaesthetic in poor-risk patients with depression of vital functions;
- in procedures where the intramuscular route of administration is preferred;
- in cardiac catheterisation procedures.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ketamine is rapidly absorbed following parenteral administration. Peak plasma levels averaged 0.75µg/ml and CSF levels were about 0.2µg/ml one hour after dosing.[1] The plasma half-life is in the range of 2 to 4 hours.[2,3,4] After IM administration (absorption half-life 2-17 minutes) it is up to 93% bioavailable.[1]

Distribution

Ketamine (as hydrochloride) is rapidly and extensively distributed throughout the body into highly perfused tissues including the brain.[3,4] 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.[6] 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 [5] (see Section 4.6 Fertility, Pregnancy and Lactation).

Metabolism[6]

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.[2,3,4] 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.[7] The renal clearance of ketamine hydrochloride is 15 ± 5 mL/min/kg.[8]

Paediatric Patients

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.[9,10]

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.'

6.2 INCOMPATIBILITIES

See section 4.5-Interactions with other medicines and other forms of interactions.

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.

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

6.5 NATURE AND CONTENTS OF CONTAINER

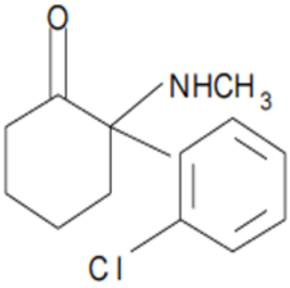
2mL ampoule pack (Type I clear glass). Available in packages of 5 ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical Name:

(2RS)-2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride

Molecular Formula

$C_{13}H_{16}CINO.HCI$.

Molecular Weight

274.2

CAS number

1867-66-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S8 – Controlled Drug

8 SPONSOR

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9 DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):

12 November 2014

10 DATE OF REVISION

18 July 2018

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information
4.4	TGA Requested SRR, as per letter TRIM ref: D18-10453988
4.5	Update in line with innovator PI
Reference	Include point 12

Reference:

1 Clements JA, Nimmo WS, Grant IS. Bioavailability, pharmacokinetics and analgesic activity of ketamine in humans. J Pharm Sci 1982; 71: 539-41.

2 Clements JA, Nimmo WS. Pharmacokinetics and analgesic effects of ketamine in man. Br J Anaesth 1981; 53: 27-30.

3 Grant IS, et al. Pharmacokinetics and analgesic affects of IM and oral ketamine. Br. J Anaesth 1981; 53: 805-9.

4 Wieber J, Gryler RD, Hengstmann JH, Dengler HJ. Pharmacokinetics of ketamine in man. Anaesthesist 1975; 24: 260-6.

5 Little B, Chang T, Chaucet L, et al. A study of ketamine as an obstetrical anesthetic. Am J Obstet Gynecol 1972; 113: 247-58.

6 Therapeutic Drugs. Edited by Sir Colin Dollery, 1991, Vol 2: K7-13.

7 United States Pharmacopeia Dispensing Information, 1998, 18th Edition, pg 1775-7.

8 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.

9 Nimmo WS, et al. Pharmacokinetics of ketamine in children. Br J Anaesth 1982; 14: 144P.

10 Grant IS, et al. Ketamine disposition in adults and children Br J Anaesth 1983, 55: 1107-11.

11 Martindale The Complete Drug Reference, MICROMEDEX® Healthcare series Vol. 105 IncCopyright 2000 Pharmaceutical Press.

12 12 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.