NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Ketamine 100 mg per 100 ml IV Infusion.

Ketamine 100 mg per 10 ml IV Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 ml of Ketamine 100 mg per 100 ml contains ketamine hydrochloride equivalent to 100 mg ketamine base.

Each 10 ml of Ketamine 100 mg per 10 ml contains ketamine hydrochloride equivalent to 100 mg ketamine base.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A clear, colourless isotonic solution for injection or infusion.

It contains no preservative. It is formulated as an acid (pH 3.5 to 5.5) solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ketamine is recommended:

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

Dose

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 to maintain anaesthesia without producing significant cumulative effect.

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

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.

Paediatric population
Currently available data are described in section 5.2 but no recommendation on a dosage can be made.

Method of Administration

Intravenous infusion or intravenous injection.

It is recommended that ketamine infusion be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

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

1. 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.
2. Barbiturates and ketamine, 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 ketamine.

4. Post-operative confusional states may occur during the recovery period (see also Emergence Reaction).
5. 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.
6. Resuscitative equipment should be ready for use.
7. Rapid administration may result in respiratory depression or apnoea and enhanced pressor response.
8. In surgical procedures involving visceral pain pathways, ketamine 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 ketamine. 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 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. 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.

Paediatric population

Paediatric neurotoxicity:

Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans.

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also section 4.6).

Interference with serological testing

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

4.5 Interaction with other medicines and other forms of interaction

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.

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.

Co-administration of drugs with a hypertensive effect (e.g. ergometrine) should be avoided.

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

Clinically apparent reduction in seizure threshold has been reported in patients receiving concomitant ketamine and theophylline. 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 also section 4.4).

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 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

Pregnancy
Category B3

Risk summary statement:

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Preclinical data

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

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.

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.

Breast-feeding
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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable effects

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.

Neurological
In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements, sometimes resembling seizures (see also section 4.2).

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 also section 4.2). Hypersalivation has also been observed.

Abuse Potential
See section 4.4.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other general anaesthetics, ATC code: N01AX03

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 also section 4.4).

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.

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. The plasma half-life is in the range of 2 to 4 hours. After IM administration (absorption half-life 2-17 minutes) it is up to 93 % bioavailable.

Distribution
Ketamine (as hydrochloride) is rapidly and extensively distributed throughout the body into highly perfused tissues including the brain. 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. 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 (see also section 4.6).

Biotransformation
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.

Elimination
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. 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. The renal clearance of ketamine hydrochloride is 15 ± 5 mL/min/kg.

Paediatric Patients
Plasma half-life, clearance and volume of distribution (relative to body weight) are not significantly different between adults and children.

Clinical Studies
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:

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 also section 4.4)
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 cardiac catheterisation procedures.

5.3 Preclinical safety data

Animal toxicology and/or pharmacology

Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

NEW ZEALAND DATA SHEET

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities

Ketamine 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

Ketamine 100 mg per 100 ml IV Infusion bags have a shelf life of 12 months from the date of manufacture.

Ketamine 100 mg per 10 ml IV Injection syringes have a shelf life of 12 months from the date of manufacture.

6.4 Special precautions for storage

Ketamine 100 mg per 100 ml IV Infusion bags are to be stored at 15 – 25 °C.

Ketamine 100 mg per 10 ml IV Injection syringes are to be stored at 15 – 25 °C.

Do not use if the solution is coloured and/or contains particulate matter.

6.5 Nature and contents of container

Ketamine 100 mg per 100 ml IV Infusion is available in flexible 100 ml propylene bags.

Ketamine 100 mg per 10 ml IV Injection is available in 10 ml polypropylene syringes.

6.6 Special precautions for disposal

For single use only. Discard any unused product.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

See also section 4.2.

7. MEDICINE SCHEDULE

Controlled Drug C4

8. SPONSOR

Biomed Limited
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NEW ZEALAND DATA SHEET

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9. DATE OF FIRST APPROVAL

5 May 2011

10. DATE OF REVISION OF THE TEXT

15 May 2017

Summary table of changes:

Section changed	Summary of new information
1, 2, 6	To remove references to Ketamine 2 mg/ml 50 ml and 4 mg/ml 50 ml syringes
4.4, 4.6, 5.3	Warning added regarding risk of neurotoxicity and adverse effects on brain development in children
6.3	Update shelf-life for Ketamine 10 mg/ml 10 ml syringes from 6 months to 12 months
All	Format update