Bioniche Pharma Labeling

Ketamine Label

Main Panel

NDC 62082-108-10
10 mL Sterile Vial
KETAMINE HYDROCHLORIDE INJ., USP
100 mg/mL
Rx Only
Bioniche Pharma (Canada) Ltd.

Side Panel

Each mL contains Ketamine Hydrochloride equivalent to 100 mg of ketamine with a pH range of 3.5-5.5. Also contains not more than 0.1 mg/mL of benzethonium chloride added as a preservative.

Color of solution may vary form colorless to very slightly yellowish and may darken upon prolonged exposure to light. This darkening does not affect potency. Do not use if precipitate appears.

Keep this and all drugs out of the reach of children.

Usual dosage, see package insert.

For slow intraveneous use (with proper dilution) or intramuscular use.

Store at room temperature 15°C-30°C (59°F-86°F). Protect from light.

Manufactured for: Bioniche Pharma (Canada) Ltd.
London, ON Canada N6M 1A3
Manufactured by: Bioniche Pharma, Galway Co., Inverin, Ireland
Lot:
Exp:

Ketamine Carton
Front Panel

10 x 10 mL Sterile Vials NDC 62086-108-10

KETAMINE HYDROCHLORIDE INJECTION, USP

100 mg/mL

Rx Only

BIONICHE PHARMA (CANADA) LTD.

Back Panel

Each mL contains Ketamine Hydrochloride equivalent to 100 mg of ketamine with a pH range of 3.5-5.5. Also contains not more than 0.1 mg/mL of benzethonium chloride added as a preservative.

Color of solution may vary form colorless to very slightly yellowish and may darken upon prolonged exposure to light. This darkening does not affect potency. Do not use if precipitate appears.

Keep this and all drugs out of the reach of children.

Usual dosage, see package insert.

For slow intraveneous use (with proper dilution) or intramuscular use.

Store at room temperature 15°C-30°C (59°F-86°F). Protect from light.

Manufactured for: Bioniche Pharma (Canada) Ltd.
London, ON Canada
N6M 1A3

Manufactured by: Bioniche Pharma
Galway Co.
Inverin Ireland

Top Panel

10 x 10 mL Sterile Vials NDC 62086-108-10

KETAMINE HYDROCHLORIDE INJECTION, USP

100 mg/mL

Rx Only

Side Panel

10 x 10 mL Sterile Vials NDC 62086-108-10

KETAMINE HYDROCHLORIDE INJECTION, USP

100 mg/mL

LOT:
EXP:

Side Panel

UPC CODE

KETAMINE HYDROCHLORIDE INJECTION, USP

SPECIAL NOTE
EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PERCENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTAIONS VARY IN SEVERITY BETWEEN PLEASANT DREAM-LIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY IS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETAMINE HYDROCHLORIDE INJECTION, USP.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA 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 AND THE INCIDENCE IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

THE INCIDENCE OF PSYCHOLOGICAL MANIFESTATIONS DURING EMERGENCE, PARTICULARLY DREAM-LIKE OBSERVATIONS AND EMERGENCE DELIRIUM, MAY BE REDUCED BY USING LOWER RECOMMENDED DOSAGES OF KETAMINE HYDROCHLORIDE INJECTION, USP IN CONJUNCTION WITH INTRAVENOUS DIAZEPAM DURING INDUCTION AND MAINTENANCE OF ANESTHESIA. (See DOSAGE AND ADMINISTRATION Section.) ALSO, THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS.

IN ORDER TO TERMINATE A SEVERE EMERGENCE REACTION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA SHORT-ACTING BARBITURATE MAY BE REQUIRED.

WHEN KETAMINE HYDROCHLORIDE INJECTION, USP IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

DESCRIPTION
Ketamine Hydrochloride Injection, USP is a nonbarbiturate anesthetic chemically designated *dl* 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acid (pH 3.5-5.5) sterile solution for intravenous or intramuscular injection concentrations containing the equivalent of either 50, or 100 mg ketamine base

per milliliter and contains not more than 0.1 mg/mL (benzethonium chloride) added as a preservative.

Chemical Drawing will go here.

CLINICAL PHARMACOLOGY

Ketamine Hydrochloride Injection, USP is a rapid-acting general anesthetic producing an anesthetic state characterized 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 unimpaired pharyngeal and laryngeal reflexes. (See WARNINGS AND PRECAUTIONS Sections.)

The biotransformation of Ketamine Hydrochloride Injection, USP includes N-dealkylation (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).

Following intravenous administration, the ketamine concentration has an initial slope (alpha phase) lasting about 45 minutes with a half-life of 10 to 15 minutes. This first phase corresponds clinically to the anesthetic effect of the drug. The anesthetic action is terminated by a combination of redistribution from the CNS to slower equilibrating peripheral tissues and by hepatic biotransformation to metabolite I. This metabolite is about 1/3 as active as ketamine in reducing halothane requirements (MAC) of the rat. The later half-life of ketamine (beta phase) is 2.5 hours.

The anesthetic state produced by Ketamine Hydrochloride Injection, USP has been termed "dissociative anesthesia" in that it appears to selectively interrupt association pathways of the brain before producing somatesthetic sensory blockade. It may selectively depress the thalamoneocortical system before significantly obtunding the more ancient cerebral centers 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 preanesthetic values within 15 minutes after injection. In the majority of cases, the systolic and diastolic blood pressure peaks from 10% to 50% above preanesthetic levels shortly after induction of anesthesia, but the elevation can be higher or longer in individual cases (see CONTRAINDICATIONS Section.)

Ketamine has a wide margin of safety; several instances of unintentional administration of overdoses of Ketamine Hydrochloride Injection, USP (up to ten times that usually required) have been followed by prolonged but complete recovery.

Ketamine Hydrochloride Injection, USP 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 Hydrochloride Injection, USP was administered as the sole agent, as induction for other general agents, or to supplement low-potency agents.

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 pneumonencephalograms, ventriculograms, myelograms, and lumbar punctures. See also Precaution concerning increased intracranial pressure.
3. diagnostic and operative procedures of the eye, ear, nose and mouth, including dental extractions.
4. diagnostic and operative procedures of the pharnyx, larynx, or bronchial tree. NOTE: Muscle relaxants, with proper attention to respiration, may be required (see PRECAUTIONS Section).
5. sigmoidoscopy and minor surgery of the anus and rectum, and circumcision.
6. extraperitoneal procedures used in gynecology such as dilation and curettage.
7. orthopedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies.
8. as an anesthetic in poor-risk patients with depression of vital functions.
9. in procedures where the intramuscular route of administration is preferred.
10. in cardiac catheterization procedures

In these studies, the anesthesia was rated either "excellent" or "good" by the anesthesiologist and the surgeon at 90% and 93%, respectively; rated "fair" at 6% and 4% respectively; and rated "poor" at 4% and 3% respectively. In a second method of evaluation, the anesthesia was rated "adequate" in at least 90% and "inadequate" in 10% or less of the procedures.

INDICATIONS AND USAGE
Ketamine Hydrochloride Injection, USP is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine Hydrochloride Injection, USP is best suited for short procedures but it can be used, with additional doses, for longer procedures.

Ketamine Hydrochloride Injection, USP is indicated for the induction of anesthesia prior to the administration of other general anesthetic agents.

Ketamine Hydrochloride Injection, USP is indicated to supplement low-potency agents, such as nitrous oxide.
Specific areas of application are described in the CLINICAL PHARMACOLOGY Section.

CONTRAINDICATIONS
Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and in those who have shown hypersensitivity to the drug.

WARNINGS

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
Postoperative confusional states may occur during the recovery period. (See Special Note.)

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

PRECAUTIONS

General

Ketamine Hydrochloride Injection, USP should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

Because pharyngeal and laryngeal reflexes are usually active, Ketamine Hydrochloride Injection, USP 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 Hydrochloride Injection, USP 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 incidence of emergence reactions may be reduced if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

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

In surgical procedures involving visceral pain pathways, Ketamine Hydrochloride Injection, USP 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 hydrochloride. Use with extreme caution in patients with preanesthetic cerebrospinal fluid pressure.

Information for Patients

As appropriate, especially in cases where early discharge is possible, the duration of Ketamine Hydrochloride Injection, USP and other drugs employed during the conduct of anesthesia should be considered. The patients should be cautioned that driving an automobile, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours of more (depending upon the dosage of Ketamine

Hydrochloride Injection, USP and consideration of other drugs employed) after anesthesia.

Drug Interactions
Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketamine Hydrochloride Injection, USP.

Ketamine Hydrochloride Injection, USP is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

Usage in Pregnancy
Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended (see ANIMAL PHARMACOLOGY AND TOXICOLOGY, Reproduction).

Pediatric Use
See DOSAGE AND ADMINISTRATION

ADVERSE REACTIONS
Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketamine Hydrochloride Injection, USP alone. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketamine Hydrochloride Injection, USP. Laryngospasms and other forms of airway obstruction have occurred during Ketamine Hydrochloride Injection, USP anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketamine Hydrochloride Injection, USP administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note.)

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see DOSAGE AND ADMINISTRATION Section).

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 DOSAGE AND ADMINISTRATION Section.)

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

DRUG ABUSE AND DEPENDENCE
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.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Note: Barbiturates and Ketamine Hydrochloride Injection, USP, being chemically incompatible because of precipitate formulation *should not* BE INJECTED FROM THE SAME SYRINGE.

If the Ketamine Hydrochloride Injection, USP dose is augmented with diazepam, the two drugs must be given separately. Do not mix Ketamine Hydrochloride Injection, USP and diazepam in syringe or infusion flask. For additional information on the use of diazepam, refer to the WARNINGS and DOSAGE AND ADMINISTRATION Sections of the diazepam insert.

Preoperative Preparations

1. While vomiting has been reported following Ketamine Hydrochloride Injection, USP administration, some airway protection may be afforded because of active laryngeal-pharyngeal reflexes. However, since aspiration may occur with Ketamine Hydrochloride Injection, USP and since protective reflexes may also be diminished by supplementary anesthetics and muscle relaxants, the possibility of aspiration must be considered. Ketamine Hydrochloride Injection, USP is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.
2. Atropine, scopolamine, or another drying agent should be given at an appropriate interval prior to induction.

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 Hydrochloride Injection, USP is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in pediatric patients, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within 3 to 4 minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Dosage:
As with other general anesthetic agents, the individual response to Ketamine Hydrochloride Injection, USP is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Induction:
Intravenous Route: The initial dose of Ketamine Hydrochloride Injection, USP administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

Alternatively, in adult patients an induction dose of 1 mg to 2 mg/kg intravenous ketamine at a rate of 0.5 mg/kg/min may be used for induction of anesthesia. In addition, diazepam in 2 mg to 5 mg doses, administered in a separate syringe over 60 seconds, may be used. In most cases, 15 mg of intravenous diazepam *or less* will suffice. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this induction dosage program.

Note: The 100 mg/mL concentration of Ketamine Hydrochloride Injection, USP *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketamine Hydrochloride Injection, USP 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 Hydrochloride Injection, USP administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:
The maintenance dose should be adjusted according to the patient's anesthetic needs and whether an additional anesthetic agent is employed.

Increments of one-half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketamine Hydrochloride Injection, USP administered, the longer will be the time to complete recovery.

Adult patients induced with Ketamine Hydrochloride Injection, USP augmented with intravenous diazepam may be maintained on Ketamine Hydrochloride Injection, USP given by slow microdrip infusion technique at a dose of 0.1 to 0.5 mg/minute, augmented with diazepam 2 to 5 mg administered intravenously as needed. In many cases 20 mg *or*

less of intravenous diazepam total for combined induction and maintenance will suffice. However, slightly more diazepam may be required depending on the nature and duration of the operation, physical status of the patient, and other factors. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this maintenance dosage program.

Dilution: To prepare a dilute solution containing 1 mg of ketamine per mL, aseptically transfer 10 mL (50 mg per mL Sterile Vial) or 5 mL (100 mg per mL Sterile Vial) to 500 mL of 5% Dextrose Injection, USP or Sodium Chloride (0.9%) Injection, USP (Normal Saline) and mix well. The resultant solution will contain 1 mg ketamine per mL.

The fluid requirements of the patient and duration of anesthesia must be considered when selecting the appropriate dilution of Ketamine Hydrochloride Injection, USP. If fluid restriction is required, Ketamine Hydrochloride Injection, USP can be added to a 250 mL infusion as described above to provide a Ketamine Hydrochloride Injection, USP concentration of 2 mg/mL.

Supplementary Agents
Ketamine Hydrochloride Injection, USP is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

The regimen of a reduced dose of Ketamine Hydrochloride Injection, USP supplemented with diazepam can be used to produce balanced anesthesia by combination with other agents such as nitrous oxide and oxygen.

HOW SUPPLIED

Ketamine Hydrochloride Injection, USP is supplied as the hydrochloride in concentrations equivalent to ketamine base.

NDC 62086-001-10 Each 10 mL vial contains 50 mg/mL. Supplied in cartons of 10.
NDC 62086-108-10 Each 10 mL vial contains 100 mg/mL. Supplied in cartons of 10.

Store between 15°-30°C (59°-86°F).

Protect from light.

Caution – Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Toxicity: The acute toxicity of Ketamine Hydrochloride Injection, USP has been studied in several species. In mature mice and rats, the intraperitoneal LD_{50} values are approximately 100 times the average human intravenous dose and approximately 20 times the average human intramuscular dose. A slightly higher acute toxicity observed in neonatal rats was not sufficiently elevated to suggest an increased hazard when used in pediatric patients. Daily intravenous injections in rats of five times the average human intravenous dose and intramuscular injections in dogs at four times the average human intramuscular dose demonstrated excellent tolerance for as long as 6 weeks. Similarly, twice weekly anesthetic sessions of one, three, or six hours' duration in monkeys over a four – to – six week period were well tolerated.

Interaction with Other Drugs Commonly Used for Preanesthetic medication: Large doses (three or more times the equivalent effective human dose) of morphine, meperidine, and atropine increased the depth and prolonged the duration of anesthesia produced by a standard anesthetizing dose of Ketamine Hydrochloride Injection, USP in Rhesus monkeys. The prolonged duration was not of sufficient magnitude to contraindicate the use of these drugs for preanesthetic medication in human clinical trials.

Blood Pressure: Blood pressure responses to Ketamine Hydrochloride Injection, USP vary with the laboratory species and experimental conditions. Blood pressure is increased in normotensive and renal hypertensive rats with and without adrenalectomy and under pentobarbital anesthesia.

Intravenous Ketamine Hydrochloride Injection, USP produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect the dog mimics the cardiovascular effect observed in man. The pressor response to Ketamine Hydrochloride Injection, USP injected into intact, unanesthetized dogs is accompanied by a tachycardia, rise in cardiac output and a fall in total peripheral resistance. It causes a fall in perfusion pressure following a large dose injected into an artificially perfused vascular bed (dog hindquarters), and it has little or no potentiating effect upon vasoconstriction responses of epinephrine or norepinephrine. The pressor response to Ketamine Hydrochloride Injection, USP is reduced or blocked by chlorpromazine (central depressant and peripheral *a*-adrenergic blockade), by β-adenergic blockade, and by ganglionic blockade. The tachycardia and increase in myocardial contractile force seen in tact animals does not appear in isolated hearts (Langendorff) at a concentration of 0.1 mg of Ketamine Hydrochloride Injection, USP or in Starling dog heart-lung preparations at a Ketamine Hydrochloride Injection, USP concentration of 50 mg/kg of HLP. These observations support they hypothesis that the hypertension produced by Ketamine Hydrochloride Injection, USP is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output. The dog myocardium is not sensitized to epinephrine and Ketamine Hydrochloride Injection, USP appears to have a weak antiarrythmic activity.

Metabolic Disposition: Ketamine Hydrochloride Injection, USP is rapidly absorbed following parenteral administration. Animal experiments indicated that Ketamine Hydrochloride Injection, USP was rapidly distributed into body tissues, with relatively high concentrations appearing in body fat, liver, lung, and brain; lower concentrations were found to occur in the heart, skeletal muscle, and blood plasma. Placental transfer of the drug was found to occur in pregnant dogs and monkeys. No significant degree of binding to serum albumin was found with Ketamine Hydrochloride Injection, USP.

Balance studies in rats, dogs, and monkeys resulted in the recovery of 85% to 95% of the dose in the urine, mainly in the form of degradation products. Small amounts of drug were also excreted in the bile and feces. Balance studies with tritium-labeled Ketamine Hydrochloride Injection, USP in human subjects (1 mg/lb given intravenously) resulted in the mean recovery of 91% of the dose in the urine and 3% in the feces. Peak plasma levels averaged about 0.75 μg/mL, and CSF levels were about 0.2 μg/mL, 1 hour after dosing.

Ketamine Hydrochloride Injection, USP undergoes N-demethylation and hydroxylation of the cyclohexanone ring, with the formation of water-soluble conjugates which are excreted in the urine. Further oxidation also occurs with the formation of a cyclohexanone derivative. The unconjugated N-demethylated metabolite was found to be less than one-sixth as potent as Ketamine Hydrochloride Injection, USP. The unconjugated demethyl cyclohexanone derivative was found to be less than one-tenth as potent as Ketamine Hydrochloride Injection, USP. Repeated doses of Ketamine Hydrochloride Injection, USP administered to animals did not produce any detectable increase in microsomal enzyme activity.

Reproduction: Male and female rats, when given five times the average human intravenous dose of Ketamine Hydrochloride Injection, USP for three consecutive days about one week before mating, had a reproductive performance equivalent to that of saline-injected controls. When given to pregnant rats and rabbits intramuscularly at twice the average human intramuscular dose during the respective periods of organogenesis, the litter characteristics were equivalent to those of saline-injected controls. A small group of rabbits was given a single large dose (six times the average human dose) of Ketamine Hydrochloride Injection, USP on Day 6 of pregnancy to simulate the effect of an excessive clinical dose around the period of nidation. The outcome of pregnancy was equivalent in control and treated groups.

To determine the effect of Ketamine Hydrochloride Injection, USP on the perinatal and postnatal period, pregnant rats were given twice the average human intramuscular dose during Days 18 to 21 of pregnancy. Litter characteristics at birth and through the weaning period were equivalent to those of the control animals. There was a slight increase in incidence of delayed parturition by one day in treated dams of this group. Three groups each of mated beagle bitches were given 2.5 times the average human intramuscular dose twice weekly for the three weeks of the first, second, and third trimesters of pregnancy, respectively, without the development of adverse effects in the pups.

Date Prepared: March 2001

Bioniche Pharma (Canada) Ltd.
London, ON Canada
N6A 5R7

Purolator
Online Shipping

PACKAGE I.D. NO.
N° IDENT. COLIS **499 982 329 01**

SENDER (FROM) / EXPÉDITEUR (DE)

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151 Dundas ST #507

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(519) 453-0641

RECEIVER (TO) / DESTINATAIRE (À)

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Food & Drug Administration
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CONDITIONS OF CARRIAGE

1. Subject to paragraph 2 below, the contract for the carriage of goods contained in this Bill of Lading shall be deemed to include and be subject to the terms and conditions prescribed by law of the jurisdiction where the goods originate which are if Newfoundland, Saskatchewan and British Columbia, the Motor Carrier Act of each such province and the regulations thereto respectively; Nova Scotia and New Brunswick,the Motor Vehicle Act of each such province and the regulations thereto respectively: Prince Edward Island, the Highway Traffic Act; Quebec, the Transport Act and the regulations thereto, if any, and the Trucking Regulation under the Truck Transportation Act; Ontario, the Truck Transportation Act and the regulations thereto; Manitoba, The Highway Traffic Act and the regulations thereto; Alberta, the Motor Transport Act and the regulations thereto; Yukon, the Motor Transport Act; and Northwest Territories, the Motor Vehicles Act. 2. If the carriage involves an ultimate destination or stop in a country other than the country of departure, the 'Convention'(as defined below) may be applicable and the Convention governs and in most cases limits the liability of the carrier in respect of loss or damage to cargo. As used in this Bill of Lading, Convention means the Convention for the Unification of Certain Rules relating to International Carriage by Air, signed at Warsaw, Poland, 12 October, 1929 or that Convention as amended by the Hague Protocol 1955, whichever may be applicable to carriage hereunder, and 'carrier' includes Purolator Courier Ltd., its subsidiaries and branches and controlled entities and their respective employees, agents and indeperident contractors. 3. It is mutually agreed, as to each carrier of, and as to each party at any time interested in, all or any of the goods, that every service to be performed hereunder shall be subject to all conditions not prohibited by law, whether printed or written, including the Conditions of Carriage contained in this Bill of Lading and Purolator Courier Ltd.'s Online Shipping Licence which are hereby agreed to by the consignor and accepted for himself and his assigns. In tendering the shipment described herein for carriage, consignor agrees to these conditions of carriage which no agent or employee of the parties may alter and agrees that this Bill of Lading is non-negotiable and has been prepared by him or on his behalf by the carrier. 4. Having received at the point of origin on the date specified, from the consignor mentioned herein, the property herein described, in apparent good order, except as noted (contents and conditions of contents of package unknown) marked, consigned and destined as indicated herein, the carrier agrees to carry and to deliver the property herein described to the consignee at the said destination, subject to the rates and classification in effect on the date of shipment. 5. If not governed by the Convention, the amount of any loss or damage for which the carrier may be liable shall not exceed $2.00 per pound (or $4.41 per kilogram) computed on the total weight of the shipment unless a higher value is declared by consignor in specially marked Purolator Online Shipping user entry field, 'Declared Value for Insurance ($)'. 6. Where the Convention applies to the shipment, carriage hereunder is subject to the rules relating to liability established by the Convention. To the extent not in conflict with the foregoing, carriage and other services performed by the carrier are subject to the provisions set forth herein and applicable tariffs of the carrier which are made part hereof and which may be inspected at any of its offices and at airports from which it operates regular services. 7. Notwithstanding paragraph 5 above, it is further agreed as a special agreement with respect to all shipments, regardless of whether or not the Convention applies to the shipment, and notwithstanding any disclosure of the nature or value of the goods, the amount of any loss or damage, including without limitation, consequential, incidental or indirect damages including loss of earnings or profits, in any manner resulting whether or not from negligence or gross negligence, from loss of or damage to the goods and/or misdelivery, failure to deliver or delay in delivery of the goods, for which the carrier may be liable to the consignor, owner, consignee and/or any third party whether in contract, tort or otherwise, shall in no event exceed an amount equal to the carrier's maximum liability aforesaid. Notwithstanding any other condition contained herein, the carrier is not financially responsible for the consequences of a delay in delivering a shipment by any particular time or for misdelivery or a failure to deliver. All claims are subject to proof of amount of loss. 8. The carrier reserves the right to substitute alternate modes of transportation for that selected by the consignor. Any exercise by the carrier of this right shall in no way affect the carrier's maximum liability aforesaid. 9. The carrier shall be exonerated from any liability in terms of published standards in the event of any delay caused by customs formalities or any other causes outlined in the applicable tariffs. 10. In the case of domestic shipments and other shipments where the Convention does not apply, no carrier is liable for loss of, damage or delay to any goods carried, under this Bill of Lading unless notice thereof setting out particulars of the origin, destination and date of shipment of the goods and the estimated amount claimed in respect of such loss, damage or delay is given in writing to the originating carrier or the delivering carrier within sixty (60) days after the delivery of the goods or, in the case of failure to make delivery, within nine (9) months from the date of shipment. The final statement of the claim must be filed within nine (9) months from the date of shipment together with a copy of the paid freight bill. 11. In the case of shipments where the Convention applies, written claims for loss or damage of or to the shipment must be received by the first carrier within fourteen (14) days from the date of receipt of the shipment; for damages or losses of any kind resulting from delay, within twenty-one (21) days from the date of receipt of the shipment; and for damages or losses of any kind due to non-delivery or misdelivery, within ninety (90) days after acceptance of the shipment for carriage, failing which no action will lie against the carrier. The right to damages of any kind against the carrier shall be extinguished unless an action is brought within two (2) years from the date of delivery of the shipment or from the date on which the shipment should have been delivered, or from the date on which the carriage stopped. 12. No claim for damage will be entertained until all transportation charges thereon have been paid. The amount of claim may not be deducted from transportation charges. 13. The consignor agrees to pay the carrier all shipping charges in the event the receiver, on a collect shipment or the third party on a third party billing shipment, refuses to pay the carrier. 14. This Bill of Lading and Purolator's Online Shipping Licence constitute the entire contract between the carrier and the consignor, and no agent, servant or representative of the carrier has authority to alter, modify or waive any provision of this contract. Upon acceptance by the carrier of the shipment herein described, the consignor agrees, regardless of whether the consignor has signed this Bill of Lading, to all the terms and conditions herein contained, and that insertion of the consignor's name in print under 'sender' on the face of this Bill of Lading shall be sufficient to constitute signature of this Bill of Lading by consignor for purposes of the Convention. 15. The consignee acknowledges that the carrier has arranged customs clearance as per consignor's instructions and that the consignee agrees to pay all outstanding charges for duties and taxes on international shipments. 16. The carrier will not be liable for the transportation of certain prohibited or 'At Shipper's Risk' items. For details contact the carrier directly. 17. Unless otherwise indicated; the consignor's name and address is the sender's name and address indicated on the face of this Bill of Lading, and the latter is the place of execution and the place of departure; the consignee's name and address is the receiver's name and address listed on the face of this Bill of Lading, and the latter is the place of destination; and the date indicated on the face of this Bill of Lading is the date of execution. 18. There are no specific stopping places which are agreed to, and the carrier reserves the right to route the shipment in any way the carrier deems appropriate. 19. The consignor warrants that each article in each shipment will be properly described on the face of this Bill of Lading and on any accompanying documentation, that it is acceptable for transport by the carrier, and that the shipment is properly marked, addressed and packed to ensure safe transportation with the carrier's ordinary care in handling. 20. Unless otherwise indicated on the face of this Bill of Lading, the consignor waives its right to determine the volume or dimension of the cargo, and to indicate same on the face of this Bill of Lading. 21. The carrier shall not be liable for damages, loss, delay, shortage, misdelivery, non-delivery, misinformation or failure to provide information in connection with the shipment described on the face of this Bill of Lading caused by events the carrier cannot control, including, but not limited to, acts of God, perils of the air, weather conditions, mechanical delays, acts of public enemies, war, strikes, civil commotion, or acts or omissions of public authorities (including customs or health officials) with actual or apparent authority. 22. Unless otherwise indicated, Purolator Courier Ltd., 5995 Avebury Road, Mississauga, Ontario, Canada, L5R 3T8, is the first carrier of this shipment.