Fresenius Kabi USA, LLC

Three Corporate Drive
Lake Zurich, Illinois 60047
T 847-550-2300
T 888-391-6300

August 30, 2019

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act (FDC Act), and in accordance with 21 CFR 314.93, 21 CFR 10.20, and 10.30 requesting the Commissioner of the Food and Drug Administration to determine that the drug product, Ketamine Hydrochloride Injection 100 mg/10 mL and 50 mg/5 mL (10 mg/mL) is suitable for submission as an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that Ketamine Hydrochloride Injection, 100 mg/10 mL (10 mg/mL) and 50 mg/5 mL (10 mg/mL) is suitable for submission as an ANDA. The listed reference drug product (RLD), upon which this petition is based, is KETALAR® (Ketamine Hydrochloride) Injection, 200 mg/20 mL (10 mg/mL), 500 mg/10 mL (50 mg/mL) and 500 mg/5 mL (100 mg/mL), NDA #016812, currently held by Par Sterile Product. Therefore, this petition seeks a change in strength (from 200 mg/20 mL to 100 mg/10 mL and 50 mg/5 mL) from the listed drug. Notably the proposed change only represents a change in total drug volume and hence total content, while the concentration (10 mg/mL) is consistent with the approved listed drug product.

B. Statement of Grounds

Under Section 505(j)(2)(C) of the FDA Act, a petition may be filed with the Agency seeking permission to file an ANDA for a proposed drug product that differs from the RLD in "strength" (21 U.S.C § 355(j)(2)(C)).

The RLD, KETALAR (Ketamine Hydrochloride) Injection by Par Sterile Products is an injection product containing 200 mg/20 mL (10 mg/ mL) as well as 500 mg/10 mL (50 mg/mL) and 500 mg/5 mL (100 mg/mL). The FDA approved NDA #016812 prior to January 1, 1982 (February 19, 1970). Information on KETALAR as listed in FDA's Approved Drug Product with Therapeutic Equivalence Evaluations (Orange Book) is provided as (**Attachment 1**).

The active ingredient in the proposed product is the same as that of the RLD and hence as required by 21 CFR 314.93(d)(1) and (2), is of the same pharmacological and therapeutic class and can be expected to have the same therapeutic effect as the RLD when administered to patients for the conditions of use in the RLD's Prescribing Information (**Attachment 2**).

The proposed product is the same concentration (10 mg/mL) as a presentation currently approved by FDA for the RLD (200 mg/20 ml) and thus, this petitioner seeks a change in strength (total drug volume and content) to 100 mg/10 mL and 50 mg/5 mL.

The proposed changes in strength represent dosages clearly provided for in the approved labelling for KETALAR and contains information pertaining to 10 mg Ketamine base per milliliter. Changes in the labeling would be limited to describing the proposed new presentations. The product uses, indications, warnings and precautions will remain the same as that of the RLD. The current approved labeling for the RLD is included in **Attachment 2**. Draft labeling with the proposed presentation, is included in **Attachment 3**.

According to the Dosage and Administration section in the currently approved Prescribing Information (PI) of RLD KETALAR, the initial dose of Ketamine administered intravenously for induction of anesthesia may range from 1 mg/kg to 4.5 mg/kg. The average dose required to produce five to ten minutes of surgical anesthesia is 2 mg/kg.

Moreover, as per the literature, most commonly used dose of Ketamine for induction of anesthesia is in the range of 1-2 mg/kg. ***(Galizia JP 1987, Gales A 2018, Swaroop VP 2015, Dobson MB 1978, Knox JWD 1970)***

As per the RLD PI, the maintenance dose should be adjusted according to the patient's anesthetic needs. Increments of one-half to the full induction dose may be repeated as needed for maintenance of anesthesia. Adult patients induced with Ketamine augmented with intravenous diazepam may be maintained on Ketamine given by slow micro drip infusion technique at a dose of 0.1 to 0.5 mg/minute. Furthermore, as per literature, maintenance of anesthesia can be done through

intermittent dosage administration or continuous intravenous infusion. When given as intermittent bolus, increments of one-half to the full induction dose over 60 seconds is administered intravenously and repeated as needed. **(*Gales A 2018, PDR-Ketamine Hydrochloride)***

Listed below are the examples of calculated total doses that will typically be administrated to patients for the induction (doses of 1-2 mg/kg) and maintenance of anesthesia (doses of 0.5-2 mg/kg) :

Table 1 Amount of Ketamine Hydrochloride to be administered for Induction of Anesthesia

Patient weight	**Initial Ketamine Hydrochloride Dose mg (mL)** (with induction dose of 1-2 mg/kg)
50 kg	50-100 mg (5-10 mL)
60 kg	60-120 mg (6-12 mL)
70 kg	70-140 mg (7-14 mL)
80 kg	80-160 mg (8-16 mL)
90 kg	90-180 mg (9-18 mL)
100 kg	100-200 mg (10-20 mL)

Table 2 Amount of Ketamine Hydrochloride to be administered for Maintenance of Anesthesia

Patient weight	**Ketamine Hydrochloride Dose mg(mL)** (with maintenance dose of 0.5-2 mg/kg)
50 kg	25-100 mg (2.5-10 mL)
60 kg	30-120 mg (3-12 mL)
70 kg	35-140 mg (3.5-14 mL)
80 kg	40-160 mg (4-16 mL)
90 kg	45-180 mg (4.5-18 mL)
100 kg	50-200 mg (5-20 mL)

The proposed presentation provides the fill volume which closely matches the commonly used dosage range of Ketamine Hydrochloride for induction and maintenance of anesthesia.

The proposed presentations can be used to administer the initial dose for induction and maintenance of anesthesia. Moreover, in the instances, when doses higher than that contained in approved presentations is required, the proposed presentations can be used to supplement the dosing from the currently approved presentations. For e.g. if dose of 4.5 mg/kg is required for a 50 kg patient, total dose will be 225 mg and this dose can be administered by using approved presentation of 200 mg/20 ml and proposed presentation of 50mg/5ml. If a similar dose is used in patient of 100 kg weight, the total dose of 450 mg can be administered by using approved presentation (200 mg/20 ml) in addition to the proposed presentation of 50 mg/5 ml. Availability of these proposed presentations can thus also result in significantly less wastage of drug compared to the approved presentations. Listed below in Table 3 are examples of less wastage of drug that would occur with the proposed presentations for different dosing ranges that would be administered.

Table 3 Comparison of wastage of drug with proposed and currently approved presentations

Patient weight	Dose of Ketamine Hydrochloride (0.5-2 mg/kg) Dose in mg(mL)	Wastage with proposed presentations (50mg/5 mL and 100 mg/10 mL)	Wastage with approved presentation (200 mg/20 mL)
50 kg	25-100 mg (2.5-10 mL)	0-2.5 mL	10-17.5 mL
60 kg	30-120 mg (3-12 mL)	2-3 mL	8-17 mL
70 kg	35-140 mg (3.5-14 mL)	1-1.5 mL	6-16.5 mL
80 kg	40-160 mg (4-16 mL)	1-4 mL	4-16 mL
100 kg	50-200 mg (5-20 mL)	0 mL	0-15 mL

As per the Controlled Substances Act, Ketamine is categorized under Schedule III due to the intermediate level of misuse potential ***(Gabay M 2013).*** There has been apparent increase in the illicit use of Ketamine in recent years as a drug of abuse ***(Higgins SS et al 2016)***, the proposed presentations will lead to the reduction in drug product wastage with subsequent decrease in the risk of abuse/misuse.

In view of above justification, the proposed presentations provide the benefit to be used for initial dosing for induction and maintenance of anaesthesia in patients with body weight on lower side and as add on to the approved presentations to administer higher doses. The use in these scenarios will lead to decrease in wastage and will help in controlling/minimizing misuse potential. With the continuing rise in controlled substance abuse and related overdose deaths, these proposed presentations will be the step towards risk mitigation strategies to curb the epidemic of controlled substance abuse and misuse.

As stated above, there are no proposed changes in labeling with the exception of the obvious changes in strength sought in this petition. Draft labeling for the proposed product is included in Attachment 3, and the RLD's approved labeling is provided in Attachment 2.

Therefore, the petitioner's request to the Commissioner for a change in strength (total drug content) from 200 mg/20 mL to 100 mg/10 mL and 50 mg/5 mL, with the concentration (10 mg/mL) remaining the same can be adequately evaluated in an ANDA without data from investigations to establish safety and effectiveness of the proposed change.

C. Inapplicability of the Pediatric Research Equity Act ("PREA")

PREA, which is codified at FD&C Act§ 505B, does not apply to a new strength, such as the one proposed in this petition. As such, PREA should not serve as an impediment to the Agency's granting of this petition.

D. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31 and an environmental assessment is not required.

E. Economic Impact

The petitioner does not believe that this is applicable in this case but will agree to provide such an analysis if requested by the Agency.

F. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Digitally signed by Aparna Dagar
DN: c=US, st=Illinois, l=Lake Zurich, o=Fresenius Netcare, ou=IT, cn=Aparna Dagar, email=Aparna.Dagar@fresenius-kabi.com
Reason: I attest to the accuracy and integrity of this document
Date: 2019.08.30 15:16:41 -05'00'

Aparna Dagar Ph.D., RAC
Director, Regulatory Affairs
Fresenius Kabi USA, LLC

Attachments:
1. RLD product information from the current edition of the electronic Approved Drug Products with Therapeutic Equivalence Evaluations
2. Labeling for KETALAR Injection
3. Draft Insert Labeling Proposed for Ketamine Hydrochloride Injection.
4. References
   - *i. Dobson MB 1978.*
   - *ii. Gabay M 2013*
   - *iii. Gales A 2018,*
   - *iv. Galizia JP 1987.*
   - *v. Higgins SS 2016*
   - *vi. Knox JWD 1970.*
   - *vii. PDR-Ketamine Hydrochloride*
   - *viii. Swaroop VP 2015*

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 016812

Expand all

KETALAR (KETAMINE HYDROCHLORIDE)
EQ 10MG BASE/ML — Marketing Status: Prescription

Active Ingredient: KETAMINE HYDROCHLORIDE
Proprietary Name: KETALAR
Dosage Form; Route of Administration: INJECTABLE; INJECTION
Strength: EQ 10MG BASE/ML
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code: AP
Application Number: N016812
Product Number: 001
Approval Date: Approved Prior to Jan 1, 1982
Applicant Holder Full Name: PAR STERILE PRODUCTS LLC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=016812&Appl_type=N)

KETALAR (KETAMINE HYDROCHLORIDE)
EQ 50MG BASE/ML Marketing Status: Prescription

KETALAR (KETAMINE HYDROCHLORIDE)
EQ 100MG BASE/ML Marketing Status: Prescription

RLD PRESCRIBING INFORMATION

KETALAR (ketamine hydrochloride) injection

CIII

For intravenous and intramuscular use

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PERCENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS 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 KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE 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.

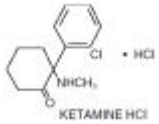
THE INCIDENCE OF PSYCHOLOGICAL MANIFESTATIONS DURING EMERGENCE, PARTICULARLY DREAM-LIKE OBSERVATIONS AND EMERGENCE DELIRIUM, MAY BE REDUCED BY USING LOWER RECOMMENDED DOSAGES OF KETALAR IN CONJUNCTION WITH INTRAVENOUS DIAZEPAM DURING INDUCTION AND MAINTENANCE OF ANESTHESIA. (See **DOSAGE AND ADMINISTRATION** 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 KETALAR 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

KETALAR is a nonbarbiturate general 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 in concentrations containing the equivalent of either 10, 50 or 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL Phemerol® (benzethonium chloride) added as a preservative. The 10 mg/mL solution has been made isotonic with sodium chloride.



KETAMINE HCl

CLINICAL PHARMACOLOGY

KETALAR 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. The mechanism of action is primarily due to antagonism of N-methyl-D-aspartate (NMDA receptors) in the central nervous system.

A patent airway is maintained partly by virtue of unimpaired pharyngeal and laryngeal reflexes. (See **WARNINGS** and **PRECAUTIONS** Sections).

The biotransformation of KETALAR 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 KETALAR 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 KETALAR (up to ten times that usually required) have been followed by prolonged but complete recovery.

KETALAR has been studied in over 12,000 operative and diagnostic procedures, involving over 10,000 patients from 105 separate studies. During the course of these studies KETALAR was administered as the sole agent, as induction for other general 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 pharynx, 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 dilatation 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

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

KETALAR is indicated for the induction of anesthesia prior to the administration of other general anesthetic agents.

KETALAR 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 KETALAR, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Pediatric Neurotoxicity

Published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data, 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. (See **PRECAUTIONS/Pregnancy**).

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

Anesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

PRECAUTIONS

General

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

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, KETALAR 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 elevated cerebrospinal fluid pressure.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ketamine.

Mutagenesis

In a published report, ketamine was clastogenic in the in vitro chromosomal aberration assay.

Impairment of Fertility

Adequate studies to evaluate the impact of ketamine on male or female fertility have not been conducted. Male and female rats were treated with 10 mg/kg ketamine IV (0.8 times the average human induction dose of 2 mg/kg IV based on body surface area) on Days 11, 10, and 9 prior to mating. No impact on fertility was noted; however, this study design does not adequately characterize the impact of a drug on fertility endpoints.

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KETALAR in pregnant women. In animal reproduction studies in rats developmental delays (hypoplasia of skeletal tissues) were noted at 0.3 times

the human intramuscular dose of 10 mg/kg. In rabbits, developmental delays and increased fetal resorptions were noted at 0.6 times the human dose. Published studies in pregnant primates demonstrate that the administration of anesthetic and sedation drugs 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.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
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**).

Data
Animal Data

Pregnant rats were treated intramuscularly with 20 mg/kg ketamine (0.3 times the human dose of 10 mg/kg IM based on body surface area) on either Gestation Days 6 to 10 or Gestation Days 11 to 15. Ketamine treatment produced an increased incidence of hypoplastic skull, phalanges, and sternebrae in the pups.

Pregnant rabbits were treated intramuscularly with 20 mg/kg ketamine (0.6 times the human dose of 10 mg/kg IM based on body surface area) on either Gestation Days 6 to 10 or Gestation Days 11 to 15. An increase in resorptions and skeletal hypoplasia of the fetuses were noted. Additional pregnant rabbits were treated intramuscularly with a single dose 60 mg/kg (1.9 times the human dose of 10 mg/kg IM based on body surface area) on Gestation Day 6 only. Skeletal hypoplasia was reported in the fetuses.

In a study where pregnant rats were treated intramuscularly with 20 mg/kg ketamine (0.3 times the human dose of 10 mg/kg IM based on body surface area) from Gestation Day 18 to 21. There was a slight increase in incidence of delayed parturition by one day in treated dams of this group. No adverse effects on the litters or pups were noted; however, learning and memory assessments were not completed.

Three pregnant beagle dogs were treated intramuscularly with 25 mg/kg ketamine (1.3 times the human dose of 10 mg/kg IM based on body surface area) 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.

In a published study in primates, administration of an anesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the fetus. 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. 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. (See **WARNINGS/Pediatric Neurotoxicity, Pediatric Use**, and **ANIMAL TOXICOLOGY AND PHARMACOLOGY**).

Information for Patients

Risk of Drowsiness
As appropriate, especially in cases where early discharge is possible, the duration of KETALAR 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 or more (depending upon the dosage of KETALAR and consideration of other drugs employed) after anesthesia.

Effect of anesthetic and sedation drugs on early brain development
Studies conducted in young animals and children suggest repeated or prolonged use of general anesthetic or sedation drugs in children younger than 3 years may have negative effects on their developing brains. Discuss with parents and caregivers the benefits, risks, and timing and duration of surgery or procedures requiring anesthetic and sedation drugs (See **WARNINGS/Pediatric Neurotoxicity**).

Drug Interactions
Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with KETALAR. KETALAR is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

Geriatric Use
Clinical studies of ketamine hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 16 have not been established.

Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as KETALAR, that either block NMDA receptors or potentiate the activity of GABA 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 of gestation 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 ketamine that produced a light surgical plane of anesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer of isoflurane increased neuronal cell loss. Data from isoflurane-treated rodents and ketamine-treated primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in pregnant women, neonates, and young children who require procedures with the potential risks suggested by the nonclinical data. (See **WARNINGS/ Pediatric Neurotoxicity**, **Pregnancy**).

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of KETALAR 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 KETALAR. Laryngospasms and other forms of airway obstruction have occurred during KETALAR anesthesia.

Eye: Diplopia and nystagmus have been noted following KETALAR administration. It also may cause a slight elevation in intraocular pressure measurement.

Genitourinary: In individuals with history of chronic ketamine use or abuse, lower urinary tract and bladder symptoms including dysuria, increased urinary frequency, urgency, urge incontinence, and hematuria have been reported (see DOSAGE AND ADMINISTRATION Section). In addition, diagnostic studies performed to assess the cause of these symptoms have reported cystitis (including cystitis non-infective, cystitis interstitial, cystitis ulcerative, cystitis erosive and cystitis hemorrhagic) as well as hydronephrosis and reduced bladder capacity.

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.

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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 anxiety, dysphoria, disorientation, insomnia, flashbacks, hallucinations, and psychotic episodes.

Ketamine dependence and tolerance are possible following prolonged administration. A withdrawal syndrome with psychotic features has been described following discontinuation of long-term ketamine use. Therefore, ketamine should be prescribed and administered with caution.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

If the KETALAR dose is augmented with diazepam, the two drugs must be given separately. Do not mix KETALAR 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 KETALAR administration, some airway protection may be afforded because of active laryngeal-pharyngeal reflexes. However, since aspiration may

occur with KETALAR and since protective reflexes may also be diminished by supplementary anesthetics and muscle relaxants, the possibility of aspiration must be considered. KETALAR 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 KETALAR is rapid; an intravenous dose of 2 mg/kg 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, in a range of 9 to 13 mg/kg 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 KETALAR 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.

In individuals with a history of chronic ketamine use for off-label indications, there have been case reports of genitourinary pain that may be related to the ketamine treatment, not the underlying condition (see **Adverse Reactions** Section). Consider cessation of ketamine if genitourinary pain continues in the setting of other genitourinary symptoms.

Induction:

Intravenous Route: The initial dose of KETALAR administered intravenously may range from 1 mg/kg to 4.5 mg/kg . The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg.

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 KETALAR 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 KETALAR be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of KETALAR administered intramuscularly may range from 6.5 to 13 mg/kg. A dose of 10 mg/kg 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 KETALAR administered, the longer will be the time to complete recovery.

Adult patients induced with KETALAR augmented with intravenous diazepam may be maintained on KETALAR 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 from a 50 mg per mL vial or 5 mL from a 100 mg per mL 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 of ketamine per mL.

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

KETALAR 10 mg/mL vials are not recommended for dilution.

Supplementary Agents:

KETALAR 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 KETALAR supplemented with diazepam can be used to produce balanced anesthesia by combination with other agents such as nitrous oxide and oxygen.

HOW SUPPLIED

KETALAR is supplied as the hydrochloride in concentrations equivalent to ketamine base.

NDC 42023-113-10 — Each 20-mL multi-dose vial contains 10 mg/mL. Supplied in cartons of 10.

NDC 42023-114-10 — Each 10-mL multi-dose vial contains 50 mg/mL. Supplied in cartons of 10.

NDC 42023-115-10 — Each 5-mL multi-dose vial contains 100 mg/mL. Supplied in cartons of 10.

Store between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)

Protect from light.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Published studies in animals demonstrate that the use of anesthetic 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 anesthetic regimen that produced a light surgical plane of anesthesia 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 subtle but prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in neonates and young children who require procedures against the potential risks suggested by the nonclinical data. (See **WARNINGS**/**Pediatric Neurotoxicity**, **Use in Pregnancy**, and **Pediatric Use**).

In published studies, intraperitoneal administration of ketamine at doses greater than 40 mg/kg induced vacuolation in neuronal cells of the posterior cingulate and retrosplenial cortices in adult rats, similar to what has been reported in rodents administered other NMDA receptor antagonists. These vacuoles were demonstrated to be reversible and did not progress to degeneration or neuronal death up to doses of 80 mg/kg (1.2 times the human dose of 10 mg/kg based on body surface area). A no-effect level for neuronal vacuolation was 20 mg/kg intraperitoneal (0.3 times a human dose of 10 mg/kg on a body surface area basis). The window of vulnerability to these changes is believed to correlate with exposures in humans from the onset of puberty through adulthood. The relevance of this finding to humans is unknown.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

R07/18

PROPOSED PRESCRIBING INFORMATION

Ketamine hydrochloride Injection, Solution

CIII

For intravenous and intramuscular use

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PERCENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS 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.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE 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.

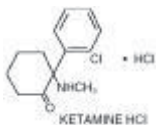
THE INCIDENCE OF PSYCHOLOGICAL MANIFESTATIONS DURING EMERGENCE, PARTICULARLY DREAM-LIKE OBSERVATIONS AND EMERGENCE DELIRIUM, MAY BE REDUCED BY USING LOWER RECOMMENDED DOSAGES OF KETAMINE IN CONJUNCTION WITH INTRAVENOUS DIAZEPAM DURING INDUCTION AND MAINTENANCE OF ANESTHESIA. (See **DOSAGE AND ADMINISTRATION** 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 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 is a nonbarbiturate general 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 in concentrations containing the equivalent of either 10, 50 or 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL Phemerol® (benzethonium chloride) added as a preservative. The 10 mg/mL solution has been made isotonic with sodium chloride.



CLINICAL PHARMACOLOGY

Ketamine 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. The mechanism of action is primarily due to antagonism of N-methyl-D-aspartate (NMDA receptors) in the central nervous system.

A patent airway is maintained partly by virtue of unimpaired pharyngeal and laryngeal reflexes. (See **WARNINGS** and **PRECAUTIONS** Sections).

The biotransformation of Ketamine 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 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 (up to ten times that usually required) have been followed by prolonged but complete recovery.

Ketamine 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 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 pharynx, 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 dilatation 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 70% and 83%, 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 is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine Hydrochloride is best suited for short procedures but it can be used, with additional doses, for longer procedures.

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

Ketamine Hydrochloride is indicated to supplement low-potency agents, such as nitrous oxide.

Specific areas of application are described in the **CLINICAL PHARMACOLOGY** Section.

CONTRAINDICATIONS

Ketamine 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, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Pediatric Neurotoxicity

Published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data, 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. (See **PRECAUTIONS/Pregnancy**).

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

Anesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

PRECAUTIONS

General

Ketamine 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 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 *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 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 preanesthetic elevated cerebrospinal fluid pressure.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ketamine.

Mutagenesis

In a published report, ketamine was clastogenic in the in vitro chromosomal aberration assay.

Impairment of Fertility

Adequate studies to evaluate the impact of ketamine on male or female fertility have not been conducted. Male and female rats were treated with 10 mg/kg ketamine IV (0. times the average human induction dose of 2 mg/kg IV based on body surface area) on Days 11, 10, and prior to mating. No impact on fertility was noted; however, this study design does not adequately characterize the impact of a drug on fertility endpoints.

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of Ketamine in pregnant women. In animal reproduction studies in rats developmental delays (hypoplasia of skeletal tissues) were noted at 0.3 timesthe human intramuscular dose of 10 mg/kg. In rabbits, developmental delays and increased fetal resorptions were noted at 0.6 times the human dose. Published studies in pregnant primates demonstrate that the administration of anesthetic and sedation drugs 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.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4 and 15-20 , respectively.

Clinical Considerations

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**).

Data

Animal Data

Pregnant rats were treated intramuscularly with 20 mg/kg ketamine (0.3 times the human dose of 10 mg/kg IM based on body surface area) on either Gestation Days 6 to 10 or Gestation Days 11 to 15. Ketamine treatment produced an increased incidence of hypoplastic skull, phalanges, and sternebrae in the pups.

Pregnant rabbits were treated intramuscularly with 20 mg/kg ketamine (0.6 times the human dose of 10 mg/kg IM based on body surface area) on either Gestation Days 6 to 10 or Gestation Days 11 to 15. An increase in resorptions and skeletal hypoplasia of the fetuses were noted. Additional pregnant rabbits were treated intramuscularly with a single dose 60 mg/kg (1. times the human dose of 10 mg/kg IM based on body surface area) on Gestation Day 6 only. Skeletal hypoplasia was reported in the fetuses.

In a study where pregnant rats were treated intramuscularly with 20 mg/kg ketamine (0.3 times the human dose of 10 mg/kg IM based on body surface area) from Gestation Day 1 to 21. There was a slight increase in incidence of delayed parturition by one day in treated dams of this group. No adverse effects on the litters or pups were noted; however, learning and memory assessments were not completed.

Three pregnant beagle dogs were treated intramuscularly with 25 mg/kg ketamine (1.3 times the human dose of 10 mg/kg IM based on body surface area) 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.

In a published study in primates, administration of an anesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the fetus. 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. 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. (See **WARNINGS/Pediatric Neurotoxicity, Pediatric Use**, and **ANIMAL TOXICOLOGY AND PHARMACOLOGY**).

Information for Patients

Risk of Drowsiness

As appropriate, especially in cases where early discharge is possible, the duration of Ketamine 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 or more (depending upon the dosage of Ketamine and consideration of other drugs employed) after anesthesia.

Effect of anesthetic and sedation drugs on early brain development
Studies conducted in young animals and children suggest repeated or prolonged use of general anesthetic or sedation drugs in children younger than 3 years may have negative effects on their developing brains. Discuss with parents and caregivers the benefits, risks, and timing and duration of surgery or procedures requiring anesthetic and sedation drugs (See **WARNINGS**/**Pediatric Neurotoxicity**).

Drug Interactions
Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketamine. Ketamine is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

Geriatric Use
Clinical studies of ketamine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 16 have not been established.

Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as Ketamine, that either block NMDA receptors or potentiate the activity of GABA 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 of gestation 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 ketamine that produced a light surgical plane of anesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer of isoflurane increased neuronal cell loss. Data from isoflurane-treated rodents and ketamine-treated primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in pregnant women, neonates, and young children who require procedures with the potential risks suggested by the nonclinical data. (See **WARNINGS**/ **Pediatric Neurotoxicity**, **Pregnancy**).

ADVERSE REACTIONS

Cardiovascular—Blood pressure and pulse rate are frequently elevated following administration of Ketamine 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. Laryngospasms and other forms of airway obstruction have occurred during Ketamine anesthesia.

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

Genitourinary: In individuals with history of chronic ketamine use or abuse, lower urinary tract and bladder symptoms including dysuria, increased urinary frequency, urgency, urge incontinence, and hematuria have been reported (see DOSAGE AND ADMINISTRATION Section). In addition, diagnostic studies performed to assess the cause of these symptoms have reported cystitis (including cystitis non- infective, cystitis interstitial, cystitis ulcerative, cystitis erosive and cystitis hemorrhagic) as well as hydronephrosis and reduced bladder capacity.

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.

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. DRUG ABUSE AND DEPENDENCE

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 anxiety, dysphoria, disorientation, insomnia, flashbacks, hallucinations, and psychotic episodes.

Ketamine dependence and tolerance are possible following prolonged administration. A withdrawal syndrome with psychotic features has been described following discontinuation of long-term ketamine use. 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, 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, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

If the Ketamine dose is augmented with diazepam, the two drugs must be given separately. Do not mix Ketamine 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 administration, some airway protection may be afforded because of active laryngeal-pharyngeal reflexes. However, since aspiration may occur with Ketamine and since protective reflexes may also be diminished by supplementary anesthetics and muscle relaxants, the possibility of aspiration must be considered. Ketamine 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 is rapid; an intravenous dose of 2 mg/kg 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, in a range of to 13 mg/kg 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 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.

In individuals with a history of chronic ketamine use for off-label indications, there have been case reports of genitourinary pain that may be related to the ketamine treatment, not the underlying condition (see **Adverse Reactions** Section). Consider cessation of ketamine if genitourinary pain continues in the setting of other genitourinary symptoms.

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 five to ten minutes of surgical anesthesia has been 2 mg/kg.

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 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 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 may range from 6.5 to 13 mg/kg. A dose of 10 mg/kg 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 administered, the longer will be the time to complete recovery.

Adult patients induced with Ketamine augmented with intravenous diazepam may be maintained on Ketamine 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 from a 50 mg per mL vial or 5 mL from a 100 mg per mL 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 of ketamine per mL.

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

Ketamine 10 mg/mL vials are not recommended for dilution.

Supplementary Agents:

Ketamine 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 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 is supplied as the hydrochloride in concentration equivalent to ketamine base

Product Code	Unit of Sale	Strength (Concentration)	Fill
To be determined	NDC XXXXX-XXX-XX Unit of XX	100 mg/10 mL (10 mg/mL)	10 mL
To be determined	NDC XXXXX-XXX-XX Unit of XX	50 mg/ 5mL (10 mg/mL)	5 mL

Store between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)

Protect from light.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Published studies in animals demonstrate that the use of anesthetic 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 anesthetic regimen that produced a light surgical plane of anesthesia 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 subtle but prolonged cognitive deficits in learning and memory. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in neonates and young children who require procedures against the potential risks suggested by the nonclinical data. (See **WARNINGS**/**Pediatric Neurotoxicity**, **Use in Pregnancy**, and **Pediatric Use**).

In published studies, intraperitoneal administration of ketamine at doses greater than 40 mg/kg induced vacuolation in neuronal cells of the posterior cingulate and retrosplenial cortices in adult rats, similar to what has been reported in rodents administered other NMDA receptor antagonists. These vacuoles were demonstrated to be reversible and did not progress to degeneration or neuronal death up to doses of 0 mg/kg (1.2 times the human dose of 10 mg/kg based on body surface area). A no-effect level for neuronal vacuolation was 20 mg/kg intraperitoneal (0.3 times a human dose of 10 mg/kg on a body surface area basis). The window of vulnerability to these changes is believed to correlate with exposures in humans from the onset of puberty through adulthood. The relevance of this finding to humans is unknown.

Manufactured by

FRESENIUS KABI

Lake Zurich, IL 6004

www.fresenius-kabi.com/us

Revised 0/201