

AUG 3 1998

Stamp Date: _____

FREEDOM OF INFORMATION SUMMARY
ORIGINAL NEW ANIMAL DRUG APPLICATION

ANADA 200-055

VetaketTM (ketamine hydrochloride solution, USP)
For use in cats for restraint or as the sole anesthetic agent for
diagnostic or minor, brief, surgical procedures that do not
require skeletal muscle relaxation. It may be used in subhuman
primates for restraint.

Sponsored by:

Lloyd Incorporated
604 W. Thomas Avenue
P.O. Box A
Shenandoah, Iowa 51601

ANADA 200-055

FOIS 1

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

ANADA: 200-055

Sponsor: Lloyd Incorporated
604 W. Thomas Avenue
P.O. Box A
Shenandoah, Iowa 51601
Drug Labeler Code: 061690

Generic Name: ketamine hydrochloride solution, USP

Trade Name: VetaKet™

Dosage Form: Injectable solution

How Supplied: 10 mL vials

How Dispensed: Rx

Amount of Active
Ingredients: 100 mg ketamine hydrochloride per mL

Route of
Administration: Intramuscular injection

Species: Cats and subhuman primates

Labeled Dosage:

Cats: A dose of 11 mg/kg (5 mg/lb) is recommended to produce restraint. Dosages from 22 to 33 mg/kg (10 to 15 mg/lb) produce anesthesia that is suitable for diagnostic or minor surgical procedures that do not require skeletal muscle relaxation.

Subhuman Primates: The dose varies from 3 to 15 mg/kg, depending on the species. See the labeling for the exact dose by species. Additional doses for other subhuman primate species are listed on the label under the CLINICAL STUDIES heading.

Indications for Use:

VetaKet™ may be used in cats for restraint or as the sole anesthetic agent for diagnostic or minor, brief, surgical procedures that do not require skeletal muscle relaxation. It may be used in subhuman primates for restraint.

Pioneer Product/

Listed Product: Vetalar® (NADA 045-290, Fort Dodge Laboratories)

2. TARGET ANIMAL SAFETY and DRUG EFFECTIVENESS

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act, (53 FR 50460, December 15, 1988, First GADPTRA Policy Letter) an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety data, drug effectiveness data, and human food safety data (other than tissue residue data) are not required for approval of an ANADA. An ANADA relies on bioequivalence with the pioneer product to demonstrate target animal safety, drug effectiveness, and human safety.

Ordinarily, the ANADA sponsor shows that the generic product is bioequivalent to the pioneer. If bioequivalence is demonstrated through a clinical end-point study, then a tissue residue study to establish the withdrawal time for the generic product is also required. For certain dosage forms, the agency will grant a waiver from conducting an *in vivo* bioequivalence study (Fifth GADPTRA Policy Letter: 55 FR 24645, June 18, 1990; Bioequivalence Guidance: 61 FR 26182 - 26186, May 24, 1996).

Based upon the formulation characteristics of the generic product, Lloyd Incorporated was granted a waiver from conducting an *in vivo* bioequivalence study for VetaKet™. The generic and pioneer products contain the same active and inactive ingredients and are injectable solutions.

3. HUMAN SAFETY:

Human Safety Relative to Food Consumption:

None required as VetaKet™ Liquid is intended for use only in cats and subhuman primates. The labeling includes the statement, "For Intramuscular use in Cats and Subhuman Primates Only".

Human Safety Relative to Possession, Handling, and Administration:

Labeling contains adequate caution/warning statements.

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug and Cosmetic Act satisfies the requirements of section 512(n) of the Act and demonstrates that VetaketTM (ketamine hydrochloride injection, USP), when used under the proposed conditions of use, is safe and effective for the labeled indications.

Attachments:

1. Generic Labeling:

Vial Label
Package Insert

2. Pioneer Labeling

Vial Label
Carton
Package Insert

For Intramuscular Use
Dosage: See package insert.
For Use in cats and sub-human primates only.
Color of solution may vary from 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.

0796

10 mL

VetaKet™

KETAMINE HCl
INJECTION, USP

Equivalent to
100 mg per mL Ketamine

Caution: Federal law restricts
this drug to use by or on the order
of a licensed veterinarian.

ANADA # 200-065. Approved by FDA.

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

Not more than 0.1 mg/mL
benzalkonium chloride
added as a preservative.

Manufactured for:

LLOYD

Laboratories
A division of LLOYD Inc.
Shenandoah, Iowa 51601
List No. 4571

Lot
Exp:

DOSAGE:

Cats: A dose of 11 mg/kg (5 mg/lb) is recommended to produce restraint. Dosages from 22 to 33 mg/kg (10 to 15 mg/lb) produce anesthesia that is suitable for diagnostic or minor surgical procedures that do not require skeletal muscle relaxation.

Subhuman primates: The recommended restraint dosages of ketamine hydrochloride for the following species are: *Cercocebus torquatus* (white-collared mangabey), *Papio cynocephalus* (yellow baboon), *Pan troglodytes verus* (chimpanzee), *Papio anubis* (olive baboon), *Pongo pygmaeus* (orangutan), *Macaca nemestrina* (pig-tailed macaque) 5 to 7.5 mg/kg; *Presbytis entellus* (entellus langur) 3 to 5 mg/kg; *Gorilla gorilla gorilla* (gorilla) 7 to 10 mg/kg; *Aotus trivirgatus* (night monkey) 10 to 12 mg/kg; *Macaca mulatta* (rhesus monkey) 5 to 10 mg/kg; *Cebus capucinus* (white-throated capuchin) 13 to 15 mg/kg; and *Macaca fascicularis* (crab-eating macaque), *Macaca radiata* (bonnet macaque), and *Saimiri sciureus* (squirrel monkey) 12 to 15 mg/kg.

A single intramuscular injection produces restraint suitable for TB testing, radiography, physical examination, or blood collection.

HOW SUPPLIED: VetaKet (ketamine hydrochloride injection, USP) is supplied as the hydrochloride in concentrations equivalent to ketamine base.

Each 10 mL vial contains 100 mg/mL.
NDC 11789-487-10 — 10 mL — vial

CLINICAL STUDIES: Ketamine hydrochloride has been clinically studied in subhuman primates in addition to those species listed under Dosage and Administration. Dosages for restraint in these additional species, based on limited clinical data, are: *Cercopithecus aethiops* (grivet), *Papio papio* (guinea baboon) 10 to 12 mg/kg; *Erythrocebus patas patas* (patas monkey) 3 to 5 mg/kg; *Hylobates lar* (white-handed gibbon) 5 to 10 mg/kg; *Lemur catta* (ringtailed lemur) 7.5 to 10 mg/kg; *Macaca fuscata* (Japanese macaque) 5 mg/kg; *Macaca speciosa* (stumptailed macaque) and *Miopithecus talapoin* (mangrove monkey) 5 to 7.5 mg/kg; and *Symphalangus syndactylus* (siamangs) 5 to 7 mg/kg.

Taxonomy from "A Handbook of Living Primates" by Napier and Napier, Academic Press, New York, NY.

Manufactured for



Laboratories

A division of LLOYD Inc.
Shenandoah, Iowa 51601 U.S.A.
By Taylor Pharmaceuticals, Decatur, IL 62525

0698

ANADA # 200-055, Approved by FDA

VetaKet®

Ketamine Hydrochloride Injection, USP

For Intramuscular Use in Cats and
Subhuman Primates Only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Ketamine hydrochloride is a rapid-acting, nonnarcotic, nonbarbiturate agent for anesthetic use in cats and for restraint in subhuman primates. It is chemically designated *dl* 2-(o-chlorophenyl) - 2 - (methylamino) cyclohexanone hydrochloride and is supplied as a slightly acid (pH 3.0 to 5.0) solution for intramuscular injection in a concentration containing the equivalent of 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL benzethonium chloride as a preservative.

ACTION: Ketamine hydrochloride is a rapid-acting agent whose pharmacological action is characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, mild cardiac stimulation and respiratory depression. Skeletal muscle tone is variable and may be normal, enhanced or diminished. The anesthetic state produced does not fit into the conventional classification of stages of anesthesia, but instead ketamine hydrochloride produces a state of unconsciousness which has been termed "dissociative" anesthesia in that it appears to selectively interrupt association pathways to the brain before producing somesthetic sensory blockade.

In contrast to other anesthetics, protective reflexes, such as coughing and swallowing, are maintained under ketamine hydrochloride anesthesia. The degree of muscle tone is dependent upon level of dose; therefore, variations in body temperature may occur. At low dosage levels there may be an increase in muscle tone and a concomitant slight increase in body temperature. However, at high dosage levels there is some diminution in muscle tone and a resultant decrease in body temperature, to the point where supplemental heat may be advisable.

In cats, there is usually some transient cardiovascular stimulation, increased cardiac output with slight increase in mean systolic pressure with little or no change in total peripheral resistance. At higher doses respiratory rate is usually decreased.

The assurance of a patent airway is greatly enhanced by virtue of maintained pharyngeal-

laryngeal reflexes. Although some salivation is occasionally noted, the persistence of the swallowing reflex aids in minimizing the hazards associated with ptyalism. Salivation may be effectively controlled with atropine sulfate in dosages of 0.04 mg/kg (0.02 mg/lb) in cats and 0.01 to 0.05 mg/kg (0.005 to 0.025 mg/lb) in subhuman primates.

Other reflexes, e.g., corneal, pedal, etc., are maintained during ketamine hydrochloride anesthesia, and should not be used as criteria for judging depth of anesthesia. The eyes normally remain open with the pupils dilated. It is suggested that a bland ophthalmic ointment be applied to the cornea if anesthesia is to be prolonged.

Following administration of recommended doses, cats become ataxic in about 5 minutes with anesthesia usually lasting from 30 to 45 minutes at higher doses. At the lower doses, complete recovery usually occurs in 4 to 5 hours but with higher doses recovery time is more prolonged and may be as long as 24 hours.

In studies involving 14 species of subhuman primates represented by at least 10 anesthetic episodes for each species, the median time to restraint ranged from 1.5 [*Aotus trivirgatus* (night monkey) and *Cebus capucinus* (white-throated capuchin)] to 5.3 minutes [*Macaca nemestrina* (pig-tailed macaque)]. The median duration of restraint ranged between 20 and 55 minutes in all but five of the species studied. Total time from injection to end of restraint ranged from 43 [*Saimiri sciureus* (squirrel monkey)] to 183 minutes [*Macaca nemestrina* (pig-tailed macaque)] after injection. Recovery is generally smooth and uneventful. The duration is dose related.

By single intramuscular injection, ketamine hydrochloride usually has a wide margin of safety in cats and subhuman primates. In cats, cases of prolonged recovery and death have been reported.

INDICATIONS: VetaKet (ketamine hydrochloride injection, USP) may be used in cats for restraint or as the sole anesthetic agent for diagnostic or minor, brief, surgical procedures that do not require skeletal muscle relaxation. It may be used in subhuman primates for restraint.

CONTRAINDICATIONS: Ketamine hydrochloride is contraindicated in cats and subhuman primates suffering from renal or hepatic insufficiency.

Ketamine hydrochloride is detoxified by the liver and excreted by the kidneys; therefore, any preexistent hepatic or renal pathology or impairment of function can be expected to result in prolonged anesthesia; related fatalities have been reported.

PRECAUTIONS: In cats, doses in excess of 50 mg/kg during any single procedure should not

be used. The maximum recommended dose in subhuman primates is 40 mg/kg.

To reduce the incidence of emergence reactions, animals should not be stimulated by sound or handling during the recovery period. However, this does not preclude the monitoring of vital signs.

Apnea, respiratory arrest, cardiac arrest, and death have occasionally been reported with ketamine used alone, and more frequently when used in conjunction with sedatives or other anesthetics. Close monitoring of patients is strongly advised during induction, maintenance, and recovery from anesthesia.

ADVERSE REACTIONS: Respiratory depression may occur following administration of high doses of ketamine hydrochloride. If at any time respiration becomes excessively depressed and the animal becomes cyanotic, resuscitative measures should be instituted promptly. Adequate pulmonary ventilation using either oxygen or room air is recommended as a resuscitative measure.

Adverse reactions reported have included emesis, salivation, vocalization, erratic recovery and prolonged recovery, spastic jerking movements, convulsions, muscular tremors, hypertonicity, opisthotonos, dyspnea, and cardiac arrest. In the cat, myoclonic jerking and/or mild tonic convulsions can be controlled by ultrashort-acting barbiturates which should be given to effect. The barbiturates should be administered intravenously at a dose level of one-sixth to one-fourth the usual dose for the product being used. Acepromazine may also be used. However, recent information indicates that some phenothiazine derivatives may potentiate the toxic effects of organic phosphate compounds such as found in flea collars and certain anthelmintics. A study has indicated that ketamine hydrochloride alone does not potentiate the toxic effects of organic phosphate compounds.

DOSAGE AND ADMINISTRATION: Ketamine hydrochloride is well tolerated by cats and subhuman primates when administered by intramuscular injection.

Fasting prior to induction of anesthesia or restraint with ketamine hydrochloride is not essential; however, when preparing for elective surgery, it is advisable to withhold food for at least six hours prior to administration of ketamine hydrochloride.

Anesthesia may be of shorter duration in immature cats. Restraint in subhuman primate neonates (less than 24 hours of age) is difficult to achieve.

As with other anesthetic agents, the individual response to ketamine hydrochloride is somewhat varied depending upon the dose, general condition, and age of the subject so that dosage recommendations cannot be absolutely fixed.

Vetalar®
KETAMINE HCl INJ., USP

FORT DODGE®
Equivalent to
100 mg per mL
Ketamine
10 mL

CAUTION: Federal law restricts this drug to use
by or on the order of a licensed veterinarian.
NADA 45-290, Approved by FDA.

For Intramuscular Use
DOSAGE: See package insert.
For Use in Cats and Subhuman Primates
Only.
Store at controlled room temperature 15°-
30°C (59°-86°F). Protect from light.

Color of solution may vary from colorless to
very slightly yellowish and may darken upon
prolonged exposure to light. This darkening
does not affect potency. Do not use if precipi-
tate appears.
Not more than 0.1 mg/mL benzethonium chlo-
ride added as a preservative.

Fort Dodge Laboratories, Inc.
Fort Dodge, Iowa 50501
45518 83639

111
307011



Lot
Exp. Date



14302

Vetalar
KETAMINE HCl
INJECTION, USP

Vetalar
KETAMINE HCl
INJECTION, USP



For Intramuscular Use
Store at controlled room
temperature 15° to 30°C
(59° to 86°F). Protect
from light.
DOSAGE: See package
insert.
For use in cats and
subhuman primates only.

Fort Dodge
Laboratories, Inc.
Fort Dodge, Iowa 50501 USA

Not more than 0.1 mg/mL
benzethonium chloride
added as a preservative.
Color of solution may vary
from 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.
See bottom flap for lot
number and expiration date.

NADA 45-290, Approved by FDA

FORT DODGE® SAMPLE

Vetalar®

KETAMINE HYDROCHLORIDE INJECTION, USP

Veterinary Injection
For Intramuscular Use

DESCRIPTION

VETALAR (ketamine hydrochloride injection, USP) is a rapid-acting, nonnarcotic, non-barbiturate agent for anesthetic use in cats and for restraint in subhuman primates. It is chemically designated *d,l*-2-(*o*-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride and is supplied as a slightly acid (pH 3.0 to 5.0) solution for intramuscular injection in a concentration containing the equivalent of 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL benzethonium chloride as a preservative.

ACTION

VETALAR is a rapid-acting agent whose pharmacological action is characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, mild cardiac stimulation and respiratory depression. Skeletal muscle tone is variable and may be normal, enhanced or diminished. The anesthetic state produced does not fit into the conventional classification of stages of anesthesia, but instead VETALAR produces a state of unconsciousness which has been termed "dissociative" anesthesia in that it appears to selectively interrupt association pathways to the brain before producing somesthetic sensory blockade.

In contrast to other anesthetics, protective reflexes, such as coughing and swallowing are maintained under VETALAR anesthesia. The degree of muscle tone is dependent upon level of dose; therefore, variations in body temperature may occur. At low dosage levels there may be an increase in muscle tone and a concomitant slight increase in body temperature. However, at high dosage levels there is some diminution in muscle tone and a resultant decrease in body temperature, to the point where supplemental heat may be advisable.

In cats, there is usually some transient cardiovascular stimulation, increased cardiac output with slight increase in mean systolic pressure with little or no change in total peripheral resistance. At higher doses respiratory rate is usually decreased.

The assurance of a patent airway is greatly enhanced by virtue of maintained pharyngeal-laryngeal reflexes. Although some salivation is occasionally noted, the persistence of the swallowing reflex aids in minimizing the hazards associated with ptyalism. Salivation may be effectively controlled with atropine sulfate in dosages of 0.04 mg/kg (0.02 mg/lb) in cats and 0.01 to 0.05 mg/kg (0.005 to 0.025 mg/lb) in subhuman primates.

Other reflexes, e.g., corneal, pedal, etc., are maintained during VETALAR anesthesia, and should not be used as criteria for judging depth of anesthesia. The eyes normally remain open with the pupils dilated. It is suggested that a bland ophthalmic ointment be applied to the cornea if anesthesia is to be prolonged.

Following administration of recommended doses, cats become ataxic in about 5 minutes with anesthesia usually lasting from 30 to 45 minutes at higher doses. At the lower doses, complete recovery usually occurs in 4 to 5 hours but with higher doses recovery time is more prolonged and may be as long as 24 hours.

In studies involving 14 species of subhuman primates represented by at least 10 anesthetic episodes for each species, the median time to restraint ranged from 1.5 [*Aotus trivirgatus* (night monkey) and *Cebus capucinus* (white-throated capuchin)] to 5.3 minutes [*Macaca nemestrina* (pig-tailed macaque)]. The median duration of restraint ranged between 20 and 55 minutes in all but five of the species studied. Total time from injection to end of restraint ranged from 43 [*Saimiri sciureus* (squirrel monkey)] to 183 minutes [*Macaca nemestrina* (pig-tailed macaque)] after injection. Recovery is generally smooth and uneventful. The duration is dose related.

By single intramuscular injection, VETALAR usually has a wide margin of safety in cats and subhuman primates. In cats, cases of prolonged recovery and death have been reported.

INDICATIONS

VETALAR may be used in cats for restraint or as the sole anesthetic agent for diagnostic or minor, brief, surgical procedures that do not require skeletal muscle relaxation. It may be used in subhuman primates for restraint.

CONTRAINDICATIONS

VETALAR is contraindicated in cats and subhuman primates suffering from renal or hepatic insufficiency.

WARNINGS

FOR USE IN CATS AND SUBHUMAN PRIMATES ONLY.

VETALAR is detoxified by the liver and excreted by the kidneys; therefore, any preexistent hepatic or renal pathology or impairment of function can be expected to result in prolonged anesthesia; related fatalities have been reported.

PRECAUTIONS

In cats, doses in excess of 50 mg/kg during any single procedure should not be used. The maximum recommended dose in subhuman primates is 40 mg/kg.

To reduce the incidence of emergence reactions, animals should not be stimulated by sound or handling during the recovery period. However, this does not preclude the monitoring of vital signs.

Apnea, respiratory arrest, cardiac arrest and death have occasionally been reported with ketamine used alone, and more frequently when used in conjunction with sedatives or other anesthetics. Close monitoring of patients is strongly advised during induction, maintenance and recovery from anesthesia.

ADVERSE REACTIONS

Respiratory depression may occur following administration of high doses of VETALAR (ketamine hydrochloride injection, USP). If at any time respiration becomes excessively depressed and the animal becomes cyanotic, resuscitative measures should be instituted promptly. Adequate pulmonary ventilation using either oxygen or room air is recommended as a resuscitative measure.

Adverse reactions reported have included emesis, salivation, vocalization, erratic recovery and prolonged recovery, spastic jerking movements, convulsions, muscular tremors, hypertonicity, opisthotonos, dyspnea and cardiac arrest. In the cat, myoclonic jerking and/or mild tonic convulsions can be controlled by ultrashort-acting barbiturates which should be given to effect. The barbiturates should be administered intravenously at a dose level of one-sixth to one-fourth the usual dose for the product being used. Acepromazine may also be used. However, recent information indicates that some phenothiazine derivatives may potentiate the toxic effects of organic phosphate compounds such as found in flea collars and certain anthelmintics. A study has indicated that ketamine hydrochloride alone does not potentiate the toxic effects of organic phosphate compounds.

ADMINISTRATION AND DOSAGE

VETALAR is well tolerated by cats and subhuman primates when administered by intramuscular injection.

Fasting prior to induction of anesthesia or restraint with VETALAR is not essential; however, when preparing for elective surgery, it is advisable to withhold food for at least six hours prior to administration of VETALAR.

Anesthesia may be of shorter duration in immature cats. Restraint in subhuman primate neonates (less than 24 hours of age) is difficult to achieve.

As with other anesthetic agents, the individual response to VETALAR is somewhat varied depending upon the dose, general condition and age of the subject so that dosage recommendations cannot be absolutely fixed.

Dosage —

Cats: A dose of 11 mg/kg (5 mg/lb) is recommended to produce restraint. Dosages from 22 to 33 mg/kg (10 to 15 mg/lb) produce anesthesia that is suitable for diagnostic or minor surgical procedures that do not require skeletal muscle relaxation.

Subhuman Primates: The recommended restraint dosages of VETALAR for the following species are: *Cercocebus torquatus* (white-collared mangabey), *Papio cynocephalus* (yellow baboon), *Pan troglodytes verus* (chimpanzee), *Papio anubis* (olive baboon), *Pongo pygmaeus* (orangutan), *Macaca nemestrina* (pig-tailed macaque) 5 to 7.5 mg/kg; *Presbytis entellus* (entellus langur) 3 to 5 mg/kg; *Gorilla gorilla gorilla* (gorilla) 7 to 10 mg/kg; *Aotus trivirgatus* (night monkey) 10 to 12 mg/kg; *Macaca mulatta* (rhesus monkey) 5 to 10 mg/kg; *Cebus capucinus* (white-throated capuchin) 13 to 15 mg/kg; and *Macaca fascicularis* (crab-eating macaque), *Macaca radiata* (bonnet macaque) and *Saimiri sciureus* (squirrel monkey) 12 to 15 mg/kg.

A single intramuscular injection produces restraint suitable for TB testing; radiography, physical examination or blood collection.

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

HOW SUPPLIED

VETALAR (ketamine hydrochloride injection, USP) is supplied as the hydrochloride in concentrations equivalent to ketamine base.

Each 10 mL vial contains 100 mg/mL.
NDC 0856-2012-01 — 10 mL — vial

CLINICAL STUDIES

VETALAR has been clinically studied in subhuman primates in addition to those species listed under Administration and Dosage. Dosages for restraint in these additional species, based on limited clinical data, are: *Cercopithecus aethiops* (grivet), *Papio papio* (guinea baboon) 10 to 12 mg/kg; *Erythrocebus patas patas* (patas monkey) 3 to 5 mg/kg; *Hylobates lar* (white-handed gibbon) 5 to 10 mg/kg; *Lemur catta* (ringtailed lemur) 7.5 to 10 mg/kg; *Macaca fuscata* (Japanese macaque) 5 mg/kg; *Macaca speciosa* (stump-tailed macaque) and *Miopithecus talapoin* (mangrove monkey) 5 to 7.5 mg/kg; and *Symphalangus syndactylus* (siamangs) 5 to 7 mg/kg.

Taxonomy from "A Handbook of Living Primates" by Napier and Napier, Academic Press, New York, N.Y.

Fort Dodge Laboratories, Inc.
Fort Dodge, Iowa 50501 USA