■ **CATTLE:**

a) Adult: 4–10 fl. oz. PO; Calves: 2–3 fl. oz PO; repeat every 2–4 hours or as indicated until condition improves. If no improvement in 48 hours additional treatment is indicated. (Label Directions; *Kao-Forte®*—Vet-A-Mix)

■ **HORSES:**

For diarrhea:

a) 2–4 quarts PO per 450 kg body weight twice daily (Robinson 1987)

b) 1 oz. per 8 kg body weight PO 3–4 times a day (Clark and Becht 1987)

c) Foals: 3–4 oz PO q6–8h (authors believe that bismuth subsalicylate is superior) (Martens and Scrutchfield 1982)

■ **SWINE:**

a) ½–2 fl. oz PO; repeat every 2–4 hours or as indicated until condition improves. If no improvement in 48 hours additional treatment is indicated. (Label Directions; *Kao-Forte®*—Vet-A-Mix)

■ **SHEEP:**

a) 3–4 oz PO q2–3h (McConnell and Hughey 1987)

■ **BIRDS:**

a) Canary or parakeet: 1 drop PO twice daily; or 1 and ½ dropperful placed in 2/3 oz. drinking water.

Medium-sized birds: 0.5 mL PO

Large birds: 1 mL PO 1 to 4 times a day (Stunkard 1984)

b) 2 mL/kg PO two to four times a day (Clubb 1986)

## Monitoring

■ Clinical efficacy

■ Fluid and electrolyte status in severe diarrhea

## Client Information

■ Shake well before using

■ If diarrhea persists, or if animal appears listless or develops a high fever, contact veterinarian

## Chemistry/Synonyms

Kaolin is a naturally occurring hydrated aluminum silicate that is powdered and refined for pharmaceutical use. Kaolin is a white/light, odorless, almost tasteless powder that is practically insoluble in water.

Pectin is a carbohydrate polymer consisting primarily of partially methoxylated polygalacturonic acids. Pectin is a course or fine, yellowish-white, almost odorless with a mucilaginous flavor. It is obtained from the inner rind of citrus fruits or from apple pomace. One gram of pectin is soluble in 20 mL of water and forms a viscous, colloidal solution.

In the United States, the two compounds generally are used together in an oral suspension formulation in most proprietary products.

Kaolin may also be known as: bolus alba, E559, weisser ton, *Childrens Diarrhoea Mixture®*, *Entrocalm®*, *Kao-Pec®*, *Kao-Pect®*, *Kao-Pront®*, *Kaogel®*; many multi-ingredient trade names are available.

## Storage/Stability/Compatibility

Kaolin/pectin should be stored in airtight containers; protect from freezing. It is physically **incompatible** when mixed with alkalis, heavy metals, salicylic acid, tannic acid, or strong alcohol.

## Dosage Forms/Regulatory Status

There are variety of kaolin/pectin products available without prescription. Several products are labeled for veterinary use; their approval status is not known. Many products that formerly contained kaolin (*e.g.*, *Kaopectate®*) no longer contain any kaolin, but use attapulgite as the adsorbent.

**VETERINARY-LABELED PRODUCTS:**

Kaolin Pectin 90 gr kaolin/2 g pectin per fluid oz. in 1 quart and 1 gallon containers. generic, (Bimeda, Durvet), *Kaolin Pectin Plus®* (AgriPharm), *Kao-Pec®* (AgriLabs), *Kao-Pect®* (Phoenix Pharmaceutical), Kaopectolin (Aspen, Butler); (OTC). Products may be labeled for use in horses, cattle, dogs and cats.

Kaolin Pectin 90 gr kaolin/4 g pectin per fl oz. in 1 gallon containers. Kaolin Pectin Suspension (Vedco); (OTC)

**HUMAN-LABELED PRODUCTS:**

Kaolin, Pectin Antidiarrheal Suspension: 90 g kaolin, 2 g pectin/30 mL in 180 mL and 360 mL, pt and UD 30 mL; Kaopectolin (various); generic; (OTC)

# KETAMINE HCL

**(*kee*-ta-meen) Ketaset®, Ketaflo®, Vetalar®**

**DISSOCIATIVE GENERAL ANESTHETIC; NMDA-RECEPTOR ANTAGONIST**

## Prescriber Highlights

- **Dissociative general anesthetic; also inhibits NMDA-receptors so may be adjunctively useful to control pain**
- **Contraindications: Prior hypersensitivity reactions; animals to be used for human consumption, alone for general anesthesia, increased CSF pressure/head trauma**
- **Relative contraindications: Significant blood loss, malignant hyperthermia, increased intra-ocular pressure or open globe injuries; procedures involving the pharynx, larynx, or trachea**
- **Caution: Significant hypertension, heart failure, & arterial aneurysms, hepatic or renal insufficiency, seizure disorders**
- **Adverse Effects: Hypertension, hypersalivation, respiratory depression, hyperthermia, emesis, vocalization, erratic & prolonged recovery, dyspnea, spastic jerking movements, seizures, muscular tremors, hypertonicity, opisthotonos, & cardiac arrest; pain after IM injection may occur**
- **Cats' eyes remain open after ketamine; protect**
- **Minimize exposure to handling or loud noises during the recovery period, but monitor adequately**
- **Drug interactions**

## Uses/Indications

Ketamine has been approved for use in humans, sub-human primates, and cats, although it has been used in many other species (see Dosage section). The approved indications for cats include, "for restraint, or as the sole anesthetic agent for diagnostic, or minor, brief, surgical procedures that do not require skeletal muscle relaxation… and in subhuman primates for restraint." (Package Insert; *Ketaset®*—Bristol).

Ketamine can inhibit NMDA receptors in the CNS and can decrease "wind-up" effect. There is increasing interest in using it to prevent exaggerated pain associated with surgery or chronic pain states in animals.

### Pharmacology/Actions

Ketamine is a rapid acting general anesthetic that has significant analgesic activity and a lack of cardiopulmonary depressant effects. It is thought to induce both anesthesia and amnesia by functionally disrupting the CNS through over stimulating the CNS or inducing a cataleptic state. Ketamine inhibits GABA, and may block serotonin, norepinephrine, and dopamine in the CNS. The thalamoneocortical system is depressed while the limbic system is activated. It induces anesthetic stages I and II, but not stage III. In cats, it causes a slight hypothermic effect as body temperatures decrease on average by 1.6°C after therapeutic doses.

Effects on muscle tone are described as being variable, but ketamine generally either causes no changes in muscle tone or increased tone. Ketamine does not abrogate the pinnal and pedal reflexes, nor the photic, corneal, laryngeal or pharyngeal reflexes.

Ketamine's effects on the cardiovascular system include increased cardiac output, heart rate, mean aortic pressure, pulmonary artery pressure, and central venous pressure. Its effects on total peripheral resistance are described as being variable. Cardiovascular effects are secondary to increased sympathetic tone; ketamine has negative inotropic effects if the sympathetic system is blocked.

Ketamine does not cause significant respiratory depression at usual doses, but at higher doses it can cause respiratory rates to decrease. In humans with asthma, ketamine causes decreased airway resistance.

### Pharmacokinetics

After IM injection in the cat, peak levels occur in approximately 10 minutes. Ketamine is distributed into all body tissues rapidly, with highest levels found in the brain, liver, lung, and fat. Plasma protein binding is approximately 50% in the horse, 53% in the dogs, and 37–53% in the cat.

The drug is metabolized in the liver principally by demethylation and hydroxylation and these metabolites, along with unchanged ketamine, are eliminated in the urine. Ketamine will induce hepatic microsomal enzymes, but there appears to be little clinical significance associated with this effect. The elimination half-life in the cat, calf, and horse is approximately 1 hour, in humans it is 2–3 hours. Like the thiobarbiturates, the redistribution of ketamine out of the CNS is more of a factor in determining duration of anesthesia than is the elimination half-life.

By increasing the dose, the duration of anesthesia will increase, but not the intensity.

### Contraindications/Precautions/Warnings

Ketamine is contraindicated in patients who have exhibited prior hypersensitivity reactions to it and animals to be used for human consumption. Use in patients with significant hypertension, heart failure, and arterial aneurysms could be hazardous. The manufacturer warns against its use in patients with hepatic or renal insufficiency but in humans with renal insufficiency, the duration of action is not prolonged. Because ketamine does not provide good muscle relaxation, it is contraindicated when used alone for major surgery.

Ketamine can cause increases in CSF pressure and it should not be used in cases with elevated pressures or when head trauma has occurred. Because of its supposed epileptogenic potential, it should generally not be used (unless very cautiously) in animals with preexisting seizure disorders. As myelography can induce seizures, ketamine should be used cautiously in animals undergoing this procedure.

Ketamine is considered to be relatively contraindicated when increased intra-ocular pressure or open globe injuries exist, and for procedures involving the pharynx, larynx, or trachea. Animals that have lost significant amounts of blood, may require significantly reduced ketamine dosages.

While ketamine has been used safely in humans with malignant hyperthermia, its use in animals susceptible to this condition is controversial. Hyperthyroid human patients (and those receiving exogenous thyroid replacement) may be susceptible to developing severe hypertension and tachycardia when given ketamine. The veterinary significance of this potential problem is unknown.

Cats' eyes remain open after receiving ketamine, and should be protected from injury plus an ophthalmic lubricant (*e.g.*, *Lacri-Lube®*) should be applied to prevent excessive drying of the cornea.

To minimize the incidences of emergence reactions, it is recommended to minimize exposure to handling or loud noises during the recovery period. The monitoring of vital signs should still be performed during the recovery phase, however.

Because ketamine can increase blood pressure, careful control of post-surgical hemorrhage (*e.g.*, declawing) should be managed. It is not essential to withhold food or water prior to surgery, but in elective procedures, it is recommended to withhold food for 6 hours prior to surgery.

### Adverse Effects

In approved species the following adverse reactions are listed by the manufacturer: "respiratory depression . . . following high doses, emesis, vocalization, erratic and prolonged recovery, dyspnea, spastic jerking movements, convulsions, muscular tremors, hypertonicity, opisthotonos and cardiac arrest. In the cat, myoclonic jerking and/or tonic/clonic convulsions can be controlled by ultrashort-acting barbiturates or acepromazine. These latter drugs must be given intravenously, cautiously, and slowly, to effect (approximately 1/6 to ¼ the normal dose may be required)." (Package Insert; *Ketaset®*—Fort Dodge)

Seizures have been reported to occur in up to 20% of cats that receive ketamine at therapeutic dosages. Diazepam is suggested if treatment is necessary. It has been reported to rarely cause a variety of other CNS effects (mild CNS effects to blindness and death). Ketamine has been documented to cause hyperthermia in cats; low doses of acepromazine (0.01–0.02 mg/kg IV) may alleviate. Anecdotal reports of ketamine causing acute, CHF in cats with mild to moderate heart disease have been reported.

Pain after IM injection may occur.

To reduce the incidence of hypersalivation and other autonomic signs, atropine or glycopyrrolate is often administered.

### Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as class: ***B*** (*Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term.*)

No specific lactation information was found.

## Overdosage/Acute Toxicity

Ketamine is considered to have a wide therapeutic index (approximately 5 times greater when compared to pentobarbital). When given too rapidly or in excessive doses, significant respiratory depression may occur. Treatment using mechanically assisted respiratory support is recommended versus the use of analeptic agents. In cats, yohimbine with 4-aminopyridine has been suggested for use as a partial antagonist.

## Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving ketamine and may be of significance in veterinary patients:

- **CHLORAMPHENICOL** (**parenteral**): May prolong the anesthetic actions of ketamine
- **CNS DEPRESSANTS**: Narcotics, barbiturates, or diazepam may prolong the recovery time after ketamine anesthesia
- **HALOTHANE**: When used with halothane, ketamine recovery rates may be prolonged and the cardiac stimulatory effects of ketamine may be inhibited; close monitoring of cardiac status is recommended when using ketamine with halothane
- **NEUROMUSCULAR BLOCKERS** (*e.g.*, **succinylcholine** and **tubocurarine**): May cause enhanced or prolonged respiratory depression
- **THYROID HORMONES**: When given concomitantly with ketamine, thyroid hormones have induced hypertension and tachycardia in humans; beta-blockers (*e.g.*, propranolol) may be of benefit in treating these effects

## Doses

**Note:** Ketamine is used in many different combinations with other agents. The following are representative, but not necessarily inclusive; it is suggested to refer to a recent veterinary anesthesia reference for more information.

- **DOGS:**

  **Note:** Ketamine/xylazine has induced cardiac arrhythmias, pulmonary edema, and respiratory depression in dogs. This combination should be used with caution.

  As an adjunct to anesthesia:

  a) Diazepam 0.5 mg/kg IV, then ketamine 10 mg/kg IV to induce general anesthesia (Booth 1988a)

  b) Midazolam 0.066–0.22 mg/kg IM or IV, then ketamine 6.6–11 mg/kg IM (Mandsager 1988)

  c) Xylazine 2.2 mg/kg IM, in 10 minutes give ketamine 11 mg/kg IM. Dogs weighing more than 22.7 kg (50 lbs.) reduce dose (per kg) of both drugs by approx. 25% (Booth 1988a)

  d) Atropine (0.044 mg/kg) IM, in 15 minutes give xylazine (1.1 mg/kg) IM, 5 minutes later give ketamine (22 mg/kg) IM (Booth 1988a)

  As an NMDA antagonist for adjunctive pain control:

  a) 0.1–1 mg/kg PO, IM or SC q4–6h for mild to moderate pain in conjunction with opioids. (Nieves 2002)

  b) For intraoperative use: If anesthesia was induced with a drug other than ketamine, give a loading dose of 0.5 mg/kg IV, then an infusion of 10–20 mcg/kg/minute. A CRI of 2–10 mcg/kg/minute can be used post-op. (Hellyer 2006)

- **CATS:**

  Most clinicians recommend giving atropine or glycopyrrolate before use to decrease hypersalivation.

  a) 11 mg/kg IM for restraint; 22–33 mg/kg for diagnostic or minor surgical procedures not requiring skeletal muscle relaxation (Package Insert; *Ketaset*®—Bristol)

  b) 2–4 mg/kg IV or 11–33 mg/kg IM (Davis 1985b)

  c) Restraint: 0.1 mL (10 mg) IV

  Anesthesia: 22–33 mg/kg IM or 2.2–4.4 mg/kg IV (with atropine) (Morgan 1988)

  d) Sedation, restraint: 6.6–11 mg/kg IM

  Anesthetic: 17.6–26.4 mg/kg IM

  Induction (following sedation): 4.4–11 mg/kg IV (Mandsager 1988)

  As an NMDA antagonist for adjunctive pain control:

  a) 0.1–1 mg/kg IM or SC q4–6h for mild to moderate pain in conjunction with opioids. (Nieves 2002)

  b) For intraoperative use: If anesthesia was induced with a drug other than ketamine, give a loading dose of 0.5 mg/kg IV, then an infusion of 10–20 mcg/kg/minute. A CRI of 2–10 mcg/kg/minute can be used post-op. (Hellyer 2006)

- **RABBITS/RODENTS/SMALL MAMMALS:**

  For chemical restraint:

  a) Mice: Alone: 50–100 mg/kg IM or IP, 50 mg/kg IV;

  In combination with diazepam: Ketamine 200 mg/kg with Diazepam 5 mg/kg IM or IP;

  In combination with xylazine: Ketamine 100 mg/kg with Xylazine 5–15 mg/kg IM or IP (Burke 1999)

  b) Rats: Alone: 50–100 mg/kg IM or IP, 40–50 mg/kg IV;

  In combination with diazepam: Ketamine 40–60 mg/kg/Diazepam 5–10 mg/kg IP;

  In combination with xylazine: Ketamine 40–75 mg/kg with Xylazine 5–12 mg/kg IM or IP (Burke 1999)

  c) Hamsters/Gerbils: 100 mg/kg IM;

  In combination with diazepam: Ketamine 50 mg/kg with Diazepam 5 mg/kg IM;

  In combination with xylazine: Not recommended (Burke 1999)

  d) Guinea pig: Alone: 10–30 mg/kg IM;

  In combination with diazepam: Ketamine 60–100 mg/kg with Diazepam 5–8 mg/kg IM;

  In combination with xylazine: Ketamine 85 mg/kg with Xylazine 12–13 mg/kg IM (Burke 1999)

  e) Rabbits: Alone: 20–60 mg/kg IM or IV;

  In combination with diazepam: Ketamine 60–80 mg/kg with Diazepam 5–10 mg/kg IM;

  In combination with xylazine: Ketamine 10 mg/kg with Xylazine 3 mg/kg IV (Burke 1999)

  f) Rabbits: Alone: 20–50 mg/kg IM or 15–20 mg/kg IV

  In combination with diazepam for induction: Diazepam 5–10 mg/kg IM give ketamine 30 minutes after diazepam at 20–40 mg/kg IM or Diazepam 0.2–0.5 mg/kg and Ketamine 10–15 mg/kg (to effect) IV;

  In combination with diazepam for anesthesia without inhalants: Diazepam 5–10 mg/kg IM plus ketamine 60–80 mg/kg IM 30 minutes later;

  In combination with xylazine: Not recommended for pet rabbits (Ivey and Morrisey 2000)

- **FERRETS:**

  a) For injectable anesthesia: Butorphanol 0.1 mg/kg, Ketamine 5 mg/kg, medetomidine 80 mcg/kg. Combine in one syringe and give IM. May need to supplement with isoflurane (0.5–1.5%) for abdominal surgery. (Finkler 1999)

- **CATTLE:**

  a) Premedicate with atropine and xylazine, then ketamine 2 mg/kg IV bolus (Thurmon and Benson 1986)

  b) After sedation, 2.2 mg/kg IV (Mandsager 1988)

■ **HORSES:** (**Note:** ARCI UCGFS Class 2 Drug)

a) For field anesthesia: Sedate with xylazine (1 mg/kg IV; 2 mg/kg IM) given 5–10 minutes (longer for IM route) before induction of anesthesia with ketamine (2 mg/kg IV). Horse must be adequately sedated (head to the knees) before giving the ketamine (ketamine can cause muscle rigidity and seizures). If adequate sedation does not occur, either: **1**) Redose xylazine: up to half the original dose, or **2**) Add butorphanol (0.02–0.04 mg/kg IV). Butorphanol can be given with the original xylazine if you suspect that the horse will be difficult to tranquilize (*e.g.*, high-strung Thoroughbreds) or added before the ketamine. This combination will improve induction, increase analgesia and increase recumbency time by about 5–10 minutes, or **3**) Diazepam (0.03 mg/kg IV). Mix the diazepam with the ketamine. This combination will improve induction when sedation is marginal, improve muscle relaxation during anesthesia and prolong anesthesia by about 5–10 minutes, or **4**) Guaifenesin (5% solution administered IV to effect) can also be used to increase sedation and muscle relaxation. (Mathews 1999)

b) Initially give xylazine 1.1 mg/kg IV and wait for full sedative effect (4–8 minutes); then give ketamine 2.2–2.75 mg/kg IV only (the higher dose may be necessary for ponies, young "high-strung" Arabians, Hackneys, and Thoroughbreds) as a bolus. Do not administer to an "excited" horse. If surgery time requires additional anesthesia, ⅓–½ of the original xylazine/ketamine doses may be given IV. For procedures where better muscle relaxation is required, use guaifenesin-thiobarbiturate. Do not disturb horse until fully recovered. (Thurmon and Benson 1987)

c) For foals and ponies: Add 500 mg ketamine and 250 mg xylazine to 500 mL of 5% guaifenesin solution. For induction, give 1.1 mL/kg IV rapidly. Anesthesia may be maintained by constant IV infusion of 2–3 mL/kg/hr. Lower doses for foals, higher doses for ponies. (Thurmon and Benson 1987)

d) For induction of surgical colic patients: Use guaifenesin to effect, than 1.6–2.2 mg/kg ketamine (Mandsager 1988)

e) 200 mg bolus (in a 454 kg horse) intra-operatively to reduce movement with light general anesthesia (Mandsager 1988)

■ **SWINE:**

a) Give atropine, then ketamine at 11 mg/kg IM. To prolong anesthesia and increase analgesia give additional ketamine 2–4 mg/kg IV. Local anesthetics injected at the surgical site (*e.g.*, 2% lidocaine) may enhance analgesia. (Thurmon and Benson 1986)

b) Ketamine (22 mg/kg) combined with acepromazine (1.1 mg/kg) IM (Swindle 1985)

c) 4.4 mg/kg IM or IV after sedation (Mandsager 1988)

■ **SHEEP:**

a) Premedicate with atropine (0.22 mg/kg) and acepromazine (0.55 mg/kg; then ketamine 22 mg/kg IM. To extend anesthetic time, may give ketamine intermittently IV at 2–4 mg/kg. (Thurmon and Benson 1986)

b) 2 mg/kg IV for induction, then 4 mL/minute constant infusion of ketamine in a concentration of 2 mg/mL in $D_5W$ (Thurmon and Benson 1986)

■ **GOATS:**

a) Give atropine 0.4 mg/kg, followed by xylazine 0.22 mg/kg IM 20–25 minutes later. Approximately 10 minutes after xylazine give ketamine 11 mg/kg IM. To extend anesthesia give ketamine 2–4 mg/kg IV (shorter extension) or 6 mg/kg (longer extension). (Thurmon and Benson 1986)

■ **REPTILES:**

a) Medium to small land Tortoises: Medetomidine 100–150 mcg/kg with ketamine 5–10 mg/kg IV or IM;

Freshwater Turtles: Medetomidine 150–300 mcg/kg with ketamine 10–20 mg/kg IV or IM;

Giant Land Tortoises: 200 kg Aldabra tortoise: Medetomidine 40 mcg/kg with ketamine 4 mg/kg IV or IM

Smaller Aldabra tortoises: Medetomidine 40–80 mcg/kg with ketamine 4–8 mg/kg IV or IM. Wait 30–40 minutes for peak effect;

Iguanas: Medetomidine 100–150 mcg/kg with ketamine 5–10 mg/kg IV or IM;

Reversal of all dosages with atipamezole is 4–5 times the medetomidine dose (Heard 1999)

b) 20–60 mg/kg IM (McConnell and Hughey 1987)

■ **SUB-HUMAN PRIMATES:**

a) Doses vary with regard to individual species; refer to package insert for *Ketaset®*.

■ **BIRDS:**

a) Birds weighing:

<100 grams (canaries, finches, budgies): 0.1–0.2 mg/gm IM;

250–500 grams (parrots, pigeons): 0.05–0.1 mg/gm IM;

500 grams–3 kg (chickens, owls, hawks): 0.02–0.1 mg/gm IM;

>3 kg (ducks, geese, swans): 0.02–0.05 mg/gm IM (Booth 1988a)

b) In combination with xylazine: Ketamine 10–30 mg/kg IM; Xylazine 2–6 mg/kg IM; birds less than 250 g require a higher dosage (per kg) than birds weighing greater than 250 g. Xylazine is not recommended to be used in debilitated birds because of its cardiodepressant effects.

In combination with diazepam: Ketamine 10–50 mg/kg IM; Diazepam 0.5–2 mg/kg IM or IV; doses can be halved for IV use

In combination with acepromazine: Ketamine 25–50 mg/kg IM; Acepromazine 0.5–1 mg/kg IM (Wheler 1993)

## Monitoring

■ Level of anesthesia/analgesia

■ Respiratory function; cardiovascular status (rate, rhythm, BP if possible)

■ Monitor eyes to prevent drying or injury;

■ Body temperature

## Client Information

■ Should only be administered by individuals familiar with its use.

## Chemistry/Synonyms

A congener of phencyclidine, ketamine HCl occurs as white, crystalline powder. It has a melting point of 258–261°C, a characteristic odor, and will precipitate as the free base at high pH. One gram is soluble in 5 mL of water, and 14 mL of alcohol. The pH of the commercially-available injections are between 3.5–5.5.

Ketamine HCl may also be known as: CI-581, CL-369, CN-52372-2, ketamini hydrochloridum, *Amtech®*, *Brevinaze®*, *Calypsol®*, *Cost®*, *Inducmina®*, *Keta®*, *Keta-Hameln®*, *Ketaject®*, *Ketalin®*, *Ketanest®*, *Ketaset®*, *Ketasthesia®*, *Keta-sthetic®*, *Ketava®*, *Ketina®*, *Ketmin®*, *Ketolar®*, *Velonarcon®*, *VetaKet®*, and *Vetalar®*.

## Storage/Stability/Compatibility

Ketamine injection should be stored between 15–30°C (59–86°C) and protected from light.

Solution may darken upon prolonged exposure to light which does not affect the drug's potency. Do not use if precipitates appear.

Ketamine may be mixed with sterile water for injection, $D_5W$, and normal saline for diluent purposes. Ketamine is physically **compatible** with xylazine in the same syringe. Do not mix ketamine with barbiturates or diazepam in the same syringe or IV bag as precipitation may occur.

### Dosage Forms/Regulatory Status

**VETERINARY-LABELED PRODUCTS:**

Ketamine HCl for Injection: 100 mg/mL in 10 mL vials; *Amtech®* *Ketamine Hydrochloride Injection*, USP (IVX), *Ketaject®* (Phoenix Pharmaceutical), *Ketaset®* (Fort Dodge), *Keta-sthetic®* (RXV), *Vetalar®* (Fort Dodge); *VetaKet®* (Lloyd), *Ketasthesia®* (Butler); (Rx, C-III). Approved for use in cats and sub-human primates.

The ARCI (Racing Commissioners International) has designated this drug as a class 2 substance. See the appendix for more information.

**HUMAN-LABELED PRODUCTS:**

Ketamine HCl Injection: 10 mg/mL in 20 mL vials; 50 mg/mL in 10 mL vials; 100 mg/mL in 5 mL vials; *Ketalar®* (Monarch); generic; (Rx, C-III)

# KETOCONAZOLE

(kee-toe-***kah***-na-zole) Nizoral®

AZOLE ANTIFUNGAL

## Prescriber Highlights

- Original imidazole oral antifungal used for systemic mycoses, including aspergillosis, cryptococcal meningitis, blastomycosis, & histoplasmosis; also used as an alternative treatment of hyperadrenocorticism in dogs.
- Contraindications: Known hypersensitivity; some believe ketoconazole is contraindicated in cats
- Caution: Hepatic disease or thrombocytopenia
- Potentially teratogenic & embryotoxic; weigh risks vs. benefits
- May cause infertility in male dogs by decreasing testosterone synthesis.
- Adverse Effects: GI (anorexia, vomiting, &/or diarrhea) most common & more prevalent in cats; hepatic toxicity, thrombocytopenia, reversible lightening of haircoat, transient dose-related suppressant effect on gonadal & adrenal steroid synthesis
- Long-term treatment may be required; relatively expensive
- Drug interactions

### Uses/Indications

Because of its comparative lack of toxicity when compared to amphotericin B, oral administration, and relatively good efficacy, ketoconazole has been used to treat several fungal infections in dogs, cats, and other small species. Ketoconazole is often employed with amphotericin B to enhance the efficacy of ketoconazole, and by reducing the dose of amphotericin B, decreasing its risk of toxicity. See the Dosage section or Pharmacology section for specifics. Newer antifungal agents (fluconazole, itraconazole) have advantages over ketoconazole, primarily less toxicity and/or enhanced efficacy; however, ketoconazole can be significantly less expensive than the newer agents. Ketoconazole is considered by some to still be the drug of choice for treating histoplasmosis in dogs.

Use of ketoconazole in cats is controversial and some say it should never be used that species.

Ketoconazole is also used clinically for the medical treatment of hyperadrenocorticism in dogs. Ketoconazole appears to be a viable option (although relatively expensive) to mitotane, particularly for palliative therapy in dogs with large, malignant, or invasive tumors where surgery is not an option. Ketoconazole is also used frequently in dogs for stabilization prior to surgery. It is a reversible inhibitor of steroidogenesis, so it is usually not a viable option for long-term treatment.

Because it interferes with the metabolism of cyclosporine, it has been used to reduce the dosage necessary for cyclosporine in dogs.

### Pharmacology/Actions

At usual doses and serum concentrations, ketoconazole is fungistatic against susceptible fungi. At higher concentrations for prolonged periods of time or against very susceptible organisms, ketoconazole may be fungicidal. It is believed that ketoconazole increases cellular membrane permeability and causes secondary metabolic effects and growth inhibition. The exact mechanism for these effects has not been determined, but may be due to ketoconazole interfering with ergosterol synthesis. The fungicidal action of ketoconazole may be due to a direct effect on cell membranes.

Ketoconazole has activity against most pathogenic fungi, including Blastomyces, Coccidioides, Cryptococcus, Histoplasma, Microsporum, and Trichophyton. Higher levels are necessary to treat most strains of Aspergillus and Sporothrix. Resistance to ketoconazole has been documented for some strains of *Candida albicans*.

Ketoconazole has *in vitro* activity against *Staphylococcus aureas* and *epidermidis*, Nocardia, enterococci, and herpes simplex virus types 1 and 2. The clinical implications of this activity are unknown.

Via inhibition of 5-lipooxygenase, ketoconazole possesses some antiinflammatory activity. The drug can suppress the immune system, probably by suppressing T-lymphocytes proliferation.

Ketoconazole also has endocrine effects as steroid synthesis is directly inhibited by blocking several P-450 enzyme systems. Measurable reductions in testosterone or cortisol synthesis can occur at dosages used for antifungal therapy, but higher dosages are generally required to reduce levels of testosterone or cortisol to be clinically useful in the treatment of prostatic carcinoma or hyperadrenocorticism. Effects on mineralocorticoids are negligible.

### Pharmacokinetics

Although it is reported that ketoconazole is well absorbed after oral administration, oral bioavailability of ketoconazole tablets in dogs is highly variable. One study (Baxter et al. 1986) in six normal dogs, found bioavailabilities ranging from 0.04–0.89 (4–89%) after 400 mg (19.5–25.2 mg/kg) was administered to fasted dogs. Peak serum concentrations occur between 1 and 4.25 hours after dosing and peak serum levels ranged from 1.1–45.6 micrograms/mL. This wide interpatient variation may have significant clinical implications from both a toxicity and efficacy standpoint, particularly since ketoconazole is often used in life-threatening infections, and assays for measuring serum levels are not readily available. Administration with food may increase absorption.

Oral absorption in horses is poor. Single doses of 30 mg/kg yielded nondetectable blood levels.

Ketoconazole absorption is enhanced in an acidic environment and should not be administered (at the same time) with $H_2$ block-