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-

ers or antacids (see Drug Interactions below). Whether to administer ketoconazole with meals or during a fasted state to maximize absorption is controversial. The manufacturer recommends giving with food in human patients. Dogs or cats that develop anorexia/vomiting during therapy may benefit from administration with meals.

After absorption, ketoconazole is distributed into the bile, cerumen, saliva, urine, synovial fluid, and CSF. CSF levels are generally less than 10% of those found in the serum, but may be increased if the meninges are inflamed. High levels of the drug are found in the liver, adrenals, and pituitary gland, while more moderate levels are found in the kidneys, lungs, bladder, bone marrow, and myocardium. At usual doses (10 mg/kg), attained levels are probably inadequate in the brain, testis, and eyes to treat most infections; higher dosages are required. Ketoconazole is 84–99% bound to plasma proteins and crosses the placenta (at least in rats). The drug is found in bitch's milk.

Ketoconazole is metabolized extensively by the liver into several inactive metabolites. These metabolites are excreted primarily into the feces via the bile. About 13% of a given dose is excreted into the urine and only 2–4% of the drug is excreted unchanged in the urine. Half-life in dogs is about 1–6 hours (avg. 2.7 hours).

Contraindications/Precautions/Warnings

Ketoconazole is contraindicated in patients with known hypersensitivity to it. It should be used with caution in patients with hepatic disease or thrombocytopenia.

Adverse Effects

Gastrointestinal signs of anorexia, vomiting, and/or diarrhea are the most common adverse effects seen with ketoconazole therapy and are more prevalent in cats. Anorexia may be minimized by dividing the dose and/or giving it with meals. Appetite stimulants such as oxazepam or cyproheptadine may also be of benefit in cats.

Hepatic toxicity consisting of cholangiohepatitis and increased liver enzymes has been reported with ketoconazole, and may be either idiosyncratic in nature or a dose-related phenomenon. Cats may be more prone to developing hepatotoxicity than dogs. While liver enzymes should be monitored during therapy, an increase does not necessarily mandate dosage reduction or discontinuation unless concomitant anorexia, vomiting, diarrhea, or abdominal pain is present. Thrombocytopenia has also been reported with ketoconazole therapy, but is rarely encountered. A reversible lightening of haircoat may also occur in patients treated with ketoconazole.

Ketoconazole has a transient dose-related suppressant effect on gonadal and adrenal steroid synthesis. Doses as low as 10 mg/kg depressed serum testosterone levels in dogs within 3–4 hours after dosing, but levels returned to normal within 10 hours. Doses of 30 mg/kg/day have been demonstrated to suppress serum cortisol levels in dogs with hyperadrenocorticism (see Dosages section). Dogs undergoing high dose antifungal therapy may need additional glucocorticoid support during periods of acute stress.

Reproductive/Nursing Safety

Ketoconazole is a known teratogen and embryotoxin in rats. There have been reports of mummified fetuses and stillbirths in dogs who have been treated. Ketoconazole should not be considered absolutely contraindicated in pregnant animals, however, as it is often used in potentially life-threatening infections. The benefits of therapy should be weighed against the potential risks. Ketoconazole may cause infertility in male dogs by decreasing testosterone synthesis. Testosterone production rebounds once the drug is discontinued.

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 in 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.*)

Ketoconazole is excreted in milk; use with caution in nursing dams.

Overdosage/Acute Toxicity

No reports of acute toxicity associated with overdosage were located. The oral LD_{50} in dogs after oral administration is >500 mg/kg. Should an acute overdose occur, the manufacturer recommends employing supportive measures, including gastric lavage with sodium bicarbonate.

Drug Interactions

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

- **ALCOHOL:** Ethanol may interact with ketoconazole and produce a disulfiram-like reaction (vomiting)
- **ANTACIDS:** May reduce oral absorption of ketoconazole; administer ketoconazole at least 1 hour before or 2 hours after
- **ANTIDEPRESSANTS, TRICYCLIC** (**amitriptyline, clomipramine**): Ketoconazole may reduce metabolism and increase adverse effects
- **BENZODIAZEPINES** (**midazolam, triazolam**): Ketoconazole may increase levels
- **BUSPIRONE:** Plasma concentrations may be elevated
- **BUSULFAN:** Ketoconazole may increase levels
- **CALCIUM-CHANNEL BLOCKING AGENTS** (**amlodipine, verapamil**): Ketoconazole may increase levels
- **CISAPRIDE:** Ketoconazole may increase cisapride levels and possibility for toxicity; use together contraindicated in humans
- **CORTICOSTEROIDS:** Ketoconazole may inhibit the metabolism of corticosteroids; potential for increased adverse effects
- **CYCLOPHOSPHAMIDE:** Ketoconazole may inhibit the metabolism of cyclophosphamide and its metabolites; potential for increased toxicity
- **CYCLOSPORINE:** Increased cyclosporine levels
- **DIGOXIN:** Ketoconazole may increase digoxin levels
- **FENTANYL/ALFENTANIL:** Ketoconazole may increase fentanyl or alfentanil levels
- **H2-BLOCKERS** (**ranitidine, famotidine**, etc.): Increased gastric pH may reduce ketoconazole absorption
- **HEPATOTOXIC DRUGS, OTHER:** Because ketoconazole can cause hepatotoxicity, it should be used cautiously with other hepatotoxic agents
- **ISONIAZID:** May affect ketoconazole levels and concomitant use not recommended in humans
- **IVERMECTIN:** Ketoconazole may increase risk for neurotoxicity
- **MACROLIDE ANTIBIOTICS** (**erythromycin, clarithromycin**): May increase ketoconazole concentrations
- **MITOTANE:** Mitotane and ketoconazole are not recommended for use together to treat hyperadrenocorticism as the adrenolytic effects of mitotane may be inhibited by ketoconazole's inhibition of cytochrome P450 enzymes
- **PHENYTOIN:** May decrease ketoconazole levels
- **PROTON-PUMP INHIBITORS** (**omeprazole**, etc.): Increased gastric pH may reduce ketoconazole absorption

- **QUINIDINE:** Ketoconazole may increase quinidine levels
- **RIFAMPIN:** May decrease ketoconazole levels; ketoconazole may increase rifampin levels
- **SUCRALFATE:** May reduce absorption of ketoconazole
- **SULFONYLUREA ANTIDIABETIC AGENTS** (*e.g.,* **glipizide, glyburide**): Ketoconazole may increase levels; hypoglycemia possible
- **THEOPHYLLINE:** Ketoconazole may decrease serum theophylline concentrations in some patients; theophylline levels should be monitored
- **VINCRISTINE/VINBLASTINE:** Ketoconazole may inhibit vinca alkaloid metabolism and increase levels
- **WARFARIN:** Ketoconazole may cause increased prothrombin times in patients receiving warfarin or other coumarin anticoagulants

Doses

Note: Clinical antifungal effects may require 10–14 days of therapy

- **DOGS:**

For coccidioidomycosis:

a) For the systemic form of the disease: 5–10 mg/kg PO twice daily; For the CNS form: 15–20 mg/kg PO twice daily. Treatment should persist for a minimum of 3–6 months. Animals with bony lesions or relapses after discontinuing therapy, give lifelong therapy at 5 mg/kg PO every other day. (Macy 1988)

b) 10–30 mg/kg PO divided twice a day, most animals need to be treated for 6–12 months (Taboada 2000)

For blastomycosis:

a) 10 mg/kg PO twice daily (15–20 mg/kg PO twice daily if CNS involvement) for at least 3 months with amphotericin B: initially at 0.25–0.5 mg/kg every other day IV. If tolerated, increase dose to 1 mg/kg until 4–5 mg/kg total dose is administered. See amphotericin B monograph for more information. (Macy 1988)

b) Ketoconazole 20 mg/kg/day PO once daily or divided twice daily; 40 mg/kg divided twice daily for ocular or CNS involvement (for at least 2–3 months or until remission then start maintenance) with amphotericin B 0.15–0.5 mg/kg IV 3 times a week. When a total dose of amphotericin B reaches 4–6 mg/kg, start maintenance dosage of amphotericin B at 0.15–0.25 mg/kg IV once a month or use ketoconazole at 10 mg/kg PO either once daily, divided twice daily or ketoconazole at 2.5–5 mg/kg PO once daily. If CNS/ocular involvement, use ketoconazole at 20–40 mg/kg PO divided twice daily (Greene, O'Neal, and Barsanti 1984)

For histoplasmosis:

a) 10 mg/kg PO once a day or twice a day for at least 3 months. Treat at least 30 days after complete resolution of clinical disease. If patient relapses, retreat as above then put on maintenance 5 mg/kg PO every other day indefinitely. For acute cases: use with amphotericin B (see blastomycosis recommendation by same author above) (Macy 1988)

b) Ketoconazole 10–20 mg/day PO once daily or divided twice daily (for at least 2–3 months or until remission then start maintenance) with amphotericin B at 0.15–0.5 mg/kg IV 3 times a week. When a total dose of amphotericin B reaches 2–4 mg/kg start maintenance dosage of amphotericin B at 0.15–0.25 mg/kg IV once a month or use ketoconazole at 10 mg/kg PO either once daily, divided twice daily or at 2.5–5 mg/kg PO once daily (Greene, O'Neal, and Barsanti 1984)

For aspergillosis:

a) 20 mg/kg PO for at least 6 weeks; may require long-term/maintenance therapy (Macy 1988)

b) For nasal aspergillosis: 10 mg/kg PO once daily (q24h) or 5 mg/kg PO q12h. Treatment requires many weeks and should continue for 1 month beyond last detection of infection. Itraconazole somewhat more effective. (Greene, Hartmannn et al. 2006)

For cryptococcosis:

a) Amphotericin B 0.15–0.4 mg/kg IV 3 times a week with flucytosine 150–175 mg/kg PO divided three to four times a day. When a total dose of amphotericin B reaches 4–6 mg/kg start maintenance dosage of amphotericin B at 0.15–0.25 mg/kg IV once a month with flucytosine at dosage above or with ketoconazole at 10 mg/kg PO once daily or divided twice daily (Greene, O'Neal, and Barsanti 1984)

For fungal myocarditis:

a) 10 mg/kg PO three times daily (Ogburn 1988)

For Candidiasis:

a) 10 mg/kg PO once daily (q24h) or 5 mg/kg PO q12h. Treatment requires many weeks and should continue for 1 month beyond last detection of infection. Itraconazole somewhat more effective. (Greene, Hartmannn et al. 2006)

For Sporotrichosis:

a) 15 mg/kg PO q12h. Treatment requires many weeks and should continue for 1 month beyond last detection of infection. (Greene, Hartmannn et al. 2006)

For Malassezia dermatitis:

a) 5–10 mg/kg PO twice a day for 30 days. Often used with therapeutic shampoos containing selenium disulfide, miconazole, ketoconazole or chlorhexidine. Underlying conditions must be identified and remedied or condition will recur. (Noxon 1997)

b) 5–10 mg/kg PO daily for 10 days, then every other day for an additional 10 days. This regimen resolves the majority of cases, but some may need higher dosages. (Muse 2000)

c) Initial dose is 5 mg/kg twice daily for 21–30 days, may increase to 10 mg/kg PO twice daily if poor response. Absorption is enhanced when administered with food and is ideal in an acid environment. (McDonald 1999)

d) 2.5–10 mg/kg PO once daily (q24h) for 7–14 days; once a good response is seen taper to every other day (q48h) and continue until a complete remission occurs. In the rare case when ketoconazole is ineffective or intolerance or toxicity is seen, itraconazole or fluconazole can be used. (Rosenkrantz 2006a)

For treatment of hyperadrenocorticism:

a) 5 mg/kg PO twice a day for 7 days. If no problems with appetite or icterus, increase dose to 10 mg/kg PO twice a day. Repeat ACTH response test in 14 days (animal stays on drug). If not satisfactorily controlled, increase to 15 mg/kg twice a day. Goal is pre- and post-ACTH plasma cortisol levels of less than 5 mcg/kg. (Feldman 2000)

b) Begin with a dose of 5 mg/kg q12h for 5–7 days and if there are no side effects (usually GI-related), increase dose to 10 mg/kg q12h for 10–14 days and perform ACTH stimulation test. Plasma cortisol levels should be between 0.7–1.8 mcg/dl if ketoconazole is to be effective. Over 25% of cases do not respond to ketoconazole and many cases that do respond, require doses of between 15–20 mg/kg q12h. Because of unpredictable efficacy, high occurrence of adverse effects, twice daily dosing, and expense, ketoconazole usage for PDH has been limited. (Church 2004)

c) For palliative treatment of canine Cushing's syndrome: 15 mg/kg PO q12h (Lorenz and Melendez 2002b)

To reduce the dosage requirements of cyclosporine:

a) Ketoconazole at 5–10 mg/kg PO per day can be administered concurrently with cyclosporine; in these patients the cyclosporine dose can be reduced (approximately half) or possibly tapered sooner than in patients not receiving the combination. Addition of ketoconazole is particularly useful in allergic patients with concurrent Malassezia dermatitis or otitis. (Hnilica 2006)

b) To treat perianal fistula: ketoconazole 7.5 mg/kg PO twice daily; cyclosporine 0.5–0.75 mg PO twice daily. (O'Neill, Edwards et al. 2001)

c) For atopic dermatitis: Cyclosporine at 5–7 mg/kg/day or less. Ideally should be given on an empty stomach, but if causes GI upset administration with food may help. In large dogs, administration of cyclosporine at 2.5 mg/kg/day with ketoconazole (5 mg/kg/day) may give good results and reduce expenses. (White 2007)

d) As an alternative immunosuppressive agent for refractory IMHA, especially those that are non-regenerative: Cyclosporine at 5–10 mg/kg PO divided twice daily to achieve plasma trough levels of >200 ng/mL (**Note:** reference states >200 mg/mL, but it is believed this is a typo). Large breed dogs can be dosed concurrently with ketoconazole (10 mg/kg/day) to allow reduction of cyclosporine dose. (Macintire 2006d)

■ **CATS:**

Note: Use of ketoconazole in cats is somewhat controversial and some clinicians recommend that it not be used in this species because of its toxic potential. Consider using itraconazole in its place.

a) For coccidioidomycosis: 10–30 mg/kg PO divided twice a day, most animals need to be treated for 6–12 months (Taboada 2000)

b) For coccidioidomycosis: 50 mg per cat PO once daily; or 25–75 mg per cat q12–48h. Treatment requires many months (9–12 on average) and should continue for 1 month beyond last detection of infection. (Greene, Hartmannn et al. 2006)

c) For blastomycosis: 10 mg/kg q12h PO (for at least 60 days) with amphotericin B: 0.25 mg/kg in 30 mL D_5W IV over 15 minutes q48h. Continue amphotericin B therapy until a cumulative dose of 4 mg/kg is given or until BUN >50 mg/dl. If renal toxicity does not develop, may increase dose to 0.5 mg/kg of amphotericin B. (Legendre 1989)

d) For cryptococcosis: 10 mg/kg twice daily. Very useful for this condition in cats, but at this dosage can produce anorexia and debility. (Legendre 1995)

e) For aspergillosis: 10 mg/kg PO q12h (Legendre 1989)

f) For dermatophytosis: Usually reserved for when griseofulvin ineffective or not tolerated. 10 mg/kg PO once daily with an acidic meal. Prolonged course of therapy required. Begin taking cultures after 4 weeks of treatment. Continue therapy for 2 weeks beyond clinical cure and when 2–3 negative cultures are obtained at weekly intervals. (Frank 2000)

g) For Sporotrichosis: 5–10 mg/kg PO q12–24h. Treatment requires many weeks (2–4 months on average) and should continue for 1 month beyond last detection of infection. (Greene, Hartmannn et al. 2006)

■ **RABBITS/RODENTS/SMALL MAMMALS:**

a) Rabbits: 10–40 mg/kg per day PO for 14 days (Ivey and Morrisey 2000)

b) Hamsters, Gerbils, Mice, Rats, Guinea pigs, Chinchillas: For systemic mycoses/candidiasis: 10–40 mg/kg per day PO for 14 days (Adamcak and Otten 2000)

■ **BIRDS:**

For susceptible fungal infections:

a) For severe refractory candidiasis in Psittacines: 5–10 mg/kg as a gavage twice daily for 14 days. For local effect in crop dissolve ¼ tablet (50 mg) in 0.2 mL of 1 N hydrochloric acid and add 0.8 mL of water. Solution turns pale pink when dissolved. Add mixture to food for gavage.

To add to water for most species: 200 mg/L for 7–14 days. As drug is not water soluble at neutral pH, dissolve in acid prior to adding to water (see above).

To add to feed for most species: 10–20 mg/kg for 7–14 days. Add to favorite food or add to mash. (Clubb 1986)

b) 20–30 mg/kg PO twice daily (based on the kinetics determined in a single trial of Moluccan Cockatoos) (Flammer 2003a)

c) Ratites: 5–10 mg/kg PO once daily (Jenson 1998)

■ **REPTILES:**

a) For susceptible infections: For most species: 15–30 mg/kg PO once daily for 2–4 weeks (Gauvin 1993)

b) For fungal shell diseases in turtles/tortoises: 25 mg/kg PO once a day for 2–4 weeks (Rosskopf 1986)

Monitoring

■ Liver enzymes with chronic therapy (at least every 2 months; some clinicians say monthly)
■ CBC with platelets
■ Efficacy and other adverse effects

Client Information

■ If animal develops gastrointestinal signs divide dose and administer with meals.
■ Long-term therapy with adequate dosing compliance is usually necessary for successful results
■ Clients must be committed for both the financial and dosing burdens associated with therapy.

Chemistry/Synonyms

An imidazole antifungal agent, ketoconazole occurs as a white to slightly beige powder with pK_as of 2.9 and 6.5. It is practically insoluble in water.

Ketoconazole may also be known as ketoconazolum, and R-41400; many trade names are available.

Storage/Stability

Ketoconazole tablets should be stored at room temperature in well-closed containers.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Ketoconazole Tablets: 200 mg (scored); *Nizoral*® (Janssen); generic; (Rx)

Topical forms are also available.

KETOPROFEN

(kee-toe-***proe***-fen) Ketofen®

NON-STEROIDAL ANTIINFLAMMATORY AGENT

Prescriber Highlights

- Nonsteroidal antiinflammatory agent used in horses, cats (short-term) & dogs
- Contraindications: Hypersensitivity to ketoprofen
- Cautions: GI ulceration or bleeding, hypoproteinemia, breeding animals (especially late in pregnancy), significant renal or hepatic impairment; may mask the signs of infection (inflammation, hyperpyrexia)
- Adverse Effects: Horses: Potentially, gastric mucosal damage & GI ulceration, renal crest necrosis, & mild hepatitis may occur. Dogs: Vomiting, anorexia, & GI ulcers
- Do not administer intra-arterially & avoid SC injections
- Drug-drug; drug-lab interactions

Uses/Indications

Ketoprofen is labeled for use in horses for the alleviation of inflammation and pain associated with musculoskeletal disorders. Like flunixin (and other NSAIDs), ketoprofen potentially has many other uses in a variety of species and conditions. There are approved dosage forms for dogs and cats in Europe and Canada. Some consider ketoprofen to be the NSAID of choice for use short-term for analgesia in cats.

Pharmacology/Actions

Ketoprofen exhibits actions similar to that of other nonsteroidal antiinflammatory agents in that it possesses antipyretic, analgesic and antiinflammatory activity. Its purported mechanism of action is the inhibition of cyclooxygenase catalysis of arachidonic acid to prostaglandin precursors (endoperoxides), thereby inhibiting the synthesis of prostaglandins in tissues. Ketoprofen purportedly has inhibitory activity on lipoxygenase, whereas flunixin reportedly does not at therapeutic doses. *In vitro* studies have not confirmed lipoxygenase activity in studied species.

The S (+) enantiomer is associated with anti-prostaglandin activity and toxicity and the R (-) form analgesia without the GI effects.

Pharmacokinetics

In species studied (rats, dog, man), ketoprofen is rapidly and nearly completely absorbed after oral administration. The presence of food or milk decreases oral absorption. Oral absorption characteristics in horses were not located. It has been reported that when comparing IV vs. IM injections in horses, the areas under the curve are relatively equivalent.

While distribution characteristics are not well described, the drug does enter synovial fluid and is highly bound to plasma proteins (99% in humans, and approximately 93% in horses). In horses, the manufacturer reports that the onset of activity is within 2 hours and peak effects 12 hours post dose.

Ketoprofen is eliminated via the kidneys both as a conjugated metabolite and unchanged drug. The elimination half-life in horses is approximately 1.5 hours.

Contraindications/Precautions/Warnings

While the manufacturer states that there are no contraindications to the drug's use (other than previous hypersensitivity to ketoprofen), it should be used only when the potential benefits outweigh the risks in cases where GI ulceration or bleeding is evident or in patients with significant renal or hepatic impairment. Ketoprofen may mask the clinical signs of infection (inflammation, hyperpyrexia). Because ketoprofen is highly protein bound, patients with hypoproteinemia may have increased levels of free drug, thereby increasing the risks for toxicity.

Adverse Effects

Because ketoprofen is a relatively new agent, its adverse effect profile in horses has not been clearly elucidated. Preliminary studies and reports indicate that ketoprofen appears relatively safe to use in horses and may have a lower incidence of adverse effects than either phenylbutazone or flunixin. Potentially, gastric mucosal damage and GI ulceration, renal crest necrosis, and mild hepatitis may occur.

Do not administer intra-arterially and avoid SC injections. While not labeled for IM use in horses, it reportedly is effective and may only cause occasional inflammation at the injection site.

In dogs or cats, ketoprofen may cause vomiting, anorexia, and GI ulcers.

Reproductive/Nursing Safety

The manufacturer cautions against ketoprofen's use in breeding animals because effects on fertility, pregnancy, or fetal health have not been established in horses. However, rat and mice studies have not demonstrated increased teratogenicity or embryotoxicity. Rabbits receiving twice the human dose exhibited increased embryotoxicity, but not teratogenicity. Because non-steroidal antiinflammatory agents inhibit prostaglandin synthesis, adversely affecting neonatal cardiovascular systems (premature closure of patent ductus), ketoprofen should not be used late in pregnancy. Studies in male rats demonstrated no changes in fertility. In humans, the FDA categorizes this drug as category ***B*** for use during the first two trimesters of pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*)

It is presently unknown whether ketoprofen enters equine milk. Ketoprofen does enter canine milk; use with caution.

Overdosage/Acute Toxicity

Horses given ketoprofen at doses up to 11 mg/kg administered IV once daily for 15 days exhibited no signs of toxicity. Severe laminitis was observed in a horse given 33 mg/kg/day (15X over labeled dosage) for 5 days. Anorexia, depression, icterus, and abdominal swelling were noted in horses given 55 mg/kg/day (25X labeled dose) for 5 days. Upon necropsy, gastritis, nephritis, and hepatitis were diagnosed in this group.

There were 24 exposures to ketoprofen reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2005–2006. In these cases 9 were dogs with 1 showing clinical signs and the remaining 15 cases were cats that showed no clinical signs. Common findings in dogs include vomiting.

Humans have survived oral ingestions of up to 5 grams. The LD_{50} in dogs after oral ingestion has been reported to be 2000 mg/kg.

This medication is a NSAID. As with any NSAID, overdosage can lead to gastrointestinal and renal effects. Decontamination with emetics and/or activated charcoal is appropriate. For doses where GI effects are expected, the use of gastrointestinal protectants