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

is warranted. If renal effects are also expected, fluid diuresis is warranted.

Drug Interactions

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

- **AMINOGLYCOSIDES** (**gentamicin, amikacin,** etc.): Increased risk for nephrotoxicity
- **ANTICOAGULANTS** (**heparin, LMWH, warfarin**): Increased risk for bleeding possible
- **ASPIRIN**: When aspirin is used concurrently with ketoprofen, plasma levels of ketoprofen could decrease and an increased likelihood of GI adverse effects (blood loss) could occur. Concomitant administration of aspirin with ketoprofen cannot be recommended.
- **BISPHOSPHONATES** (**alendronate,** etc.): May increase risk for GI ulceration
- **CORTICOSTEROIDS**: Concomitant administration with NSAIDs may significantly increase the risks for GI adverse effects
- **CYCLOSPORINE**: May increase risk for nephrotoxicity
- **FLUCONAZOLE**: May increase NSAID levels
- **FUROSEMIDE**: Ketoprofen may reduce the saluretic and diuretic effects of furosemide
- **HIGHLY PROTEIN BOUND DRUGS** (*e.g.,* **phenytoin, valproic acid, oral anticoagulants,** other **antiinflammatory agents, salicylates, sulfonamides,** and the **sulfonylurea antidiabetic agents**): Because ketoprofen is highly bound to plasma proteins (99%), it potentially could displace other highly bound drugs; increased serum levels and duration of actions may occur. Although these interactions are usually of little concern clinically, use together with caution.
- **METHOTREXATE**: Serious toxicity has occurred when NSAIDs have been used concomitantly with methotrexate; use together with extreme caution.
- **PROBENECID**: May cause a significant increase in serum levels and half-life of ketoprofen

Laboratory Considerations

Ketoprofen may cause:

- Falsely elevated **blood glucose** values when using the glucose oxidase and peroxidase method using ABTS as a chromogen;
- Falsely elevated **serum bilirubin** values when using DMSO as a reagent;
- Falsely elevated **serum iron** concentrations using the Ramsey method, or falsely decreased serum iron concentrations when using bathophenanthroline disulfonate as a reagent

Doses

- **DOGS:**

  As an antiinflammatory/analgesic:

  a) 2 mg/kg IV one time (Hardie 2000)

  b) For osteoarthritis unresponsive to aspirin: 0.5–1 mg/kg PO twice daily with food; decrease the dose by 50% when giving to geriatric patients (Trepanier 1999)

  c) For post-operative pain control: 1–2 mg/kg IV, IM once daily for 2–3 days duration (Tranquilli 2003)

  d) For post-operative pain control: 1–2 mg/kg IV, SC once daily for 3 days duration after surgery; or 1 mg/kg PO once daily for 5 days, after surgery (Hansen 2003b)

  e) For acute indications: 2 mg/kg SC, IM, IV once daily for up to 3 consecutive day. If preferred after one injection treatment may be followed on the next day with tablets at 1 mg/kg PO per day and continued on successive days for up to 4 days (*i.e.,* up to 5 days in total). For chronic pain: 0.25 mg/kg PO once daily for up to 30 days. (Label Information *Ketofen 1%*; *Ketofen® Tablets*—Merial U.K.)

- **CATS:**

  As an antiinflammatory/analgesic:

  a) 2 mg/kg IV one time (Hardie 2000)

  b) For mild to moderate pain: 1–2 mg/kg SC, IM initially, then 0.5–1 mg PO, SC once daily; not recommended to treat more than 5 days (Nieves 2002)

  c) For post-operative pain control: 1–2 mg/kg IV, SC once daily for 3 days duration after surgery; or 1 mg/kg PO once daily for 3 days, after surgery (Hansen 2003b)

  d) 2 mg/kg SC once daily for up to 3 consecutive days. If preferred after one injection treatment may be followed on the next day with tablets at 1 mg/kg and continued on successive days for up to 4 days (*i.e.,* up to 5 days in total). (Label Information *Ketofen 1%*; *Ketofen® Tablets*—Merial U.K.)

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

  a) Rabbits: For chronic pain/antiinflammatory: 1 mg/kg IM q12–24h (Ivey and Morrisey 2000)

  b) Rats: 5 mg/kg SC (Adamcak and Otten 2000)

- **HORSES:** (**Note:** ARCI UCGFS Class 4 Drug)

  a) For labeled indications: 2.2 mg/kg (1 mL/100 lbs) IV once daily for up to 5 days (Package insert; *Ketofen®*)

  b) As an adjunctive treatment for laminitis: 2.2 mg/kg IV once daily (Brumbaugh, Lopez et al. 1999)

- **CATTLE:**

  a) 3 mg/kg IV or deep IM once daily for up to 3 days; withdrawal times (U.K.) are meat: 4 days; milk: 0 days (Label information *Comforion Vet®*—Merial U.K.)

  b) 3.3 mg/kg; duration of effect 24 hours; appropriate withdrawal times: 24 hour for milk; 7 days for meat. (Walz 2006b)

- **SWINE:**

  a) 3 mg/kg IM once daily for up to 3 days; withdrawal times (U.K.) for meat: 4 days (Label information *Comforion Vet®*—Merial U.K.)

- **BIRDS:**

  a) As an antiinflammatory analgesic 2 mg/kg IM q8–24 hours (Clyde and Paul-Murphy 2000)

Monitoring

- Efficacy
- Adverse Effects (occasional liver or renal function tests are recommended with long-term therapy)

Chemistry/Synonyms

A propionic acid derivative nonsteroidal antiinflammatory agent (NSAID), ketoprofen occurs as an off-white to white, fine to granular powder. It is practically insoluble in water, but freely soluble in alcohol at 20°C. Ketoprofen has a pK_a of 5.9 in a 3:1 methanol:water solution. Ketoprofen has both an S enantiomer and R enantiomer. The commercial product contains a racemic mixture of both. The S (+) enantiomer has greater antiinflammatory potency than the R (-) form.

Ketoprofen may also be known as ketoprofenum and RP-19583; many trade names are available.

Storage/Stability/Compatibility

Ketoprofen oral capsules should be stored at room temperature in tight, light resistant containers. The veterinary injection should be stored at room temperature. Compatibility studies with inject-

able ketoprofen and other compounds have apparently not been published.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Ketoprofen Injection: 100 mg/mL in 50 mL and 100 mL multi-dose vials; *Ketofen*® (Fort Dodge), generic (Phoenix Pharmaceutical), (Rx). Approved for use in horses not intended for food.

In Canada and the U.K., there are approved oral dosage forms (5, 10, 20 mg tablets) and an injectable form (10 mg/mL) for use in dogs and cats.

The ARCI (Racing Commissioners International) has designated this drug as a class 4 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Ketoprofen Capsules: 50 mg & 75 mg; generic; (Rx)

Ketoprofen Extended-Release Capsules: 100 mg, 150 mg and 200 mg; Ketoprofen (Andrx); (Rx)

KETOROLAC TROMETHAMINE

(***kee***-toe-role-ak) **Toradol®**

NON-STEROIDAL ANTIINFLAMMATORY AGENT

Prescriber Highlights

- **NSAID used primarily for short-term analgesia**
- **Contraindications: Active GI ulcers or history of hypersensitivity to the drug**
- **Relatively contraindicated: Hematologic, renal, or hepatic disease**
- **Caution: History of gastric ulcers, heart failure**
- **Adverse Effects: GI ulcers & perforation, renal effects possible with chronic use; consider co-dosing with misoprostol/sucralfate in dogs to reduce chances of ulcers**

Uses/Indications

Ketorolac is used primarily for its analgesic effects for short-term treatment of mild to moderate pain in dogs and rodents. The duration of analgesic effect in dogs is about 8–12 hours, but because of the availability of approved, safer NSAIDs for dogs, its use is questionable.

Pharmacology/Actions

Like other NSAIDs, ketorolac exhibits analgesic, antiinflammatory, and antipyretic activity probably through its inhibition of cyclooxygenase with resultant impediment of prostaglandin synthesis. Ketorolac may exhibit a more potent analgesic effect than some other NSAIDs. It inhibits both COX-1 and COX-2 receptors.

Pharmacokinetics

After oral administration, ketorolac is rapidly absorbed; in dogs peak levels occur in about 50 minutes and oral bioavailability is about 50–75%.

Ketorolac is distributed marginally through the body. It does not appear to cross the blood-brain barrier and is highly bound to plasma proteins (99%). The volume of distribution in dogs is reported to be about 0.33–0.42 L/kg (similar in humans). The drug does cross the placenta.

Ketorolac is primarily metabolized via glucuronidation and hydroxylation. Both unchanged drug and metabolites are excreted mainly in the urine. Patients with diminished renal function will have longer elimination times than normal. In normal dogs, the elimination half-life is between 4–8 hours.

Contraindications/Precautions/Warnings

Ketorolac is relatively contraindicated in patients with a history of, or preexisting, hematologic, renal or hepatic disease. It is contraindicated in patients with active GI ulcers or with a history of hypersensitivity to the drug. It should be used cautiously in patients with a history of GI ulcers, or heart failure (may cause fluid retention), and in geriatric patients. Animals suffering from inflammation secondary to concomitant infection, should receive appropriate antimicrobial therapy.

Because ketorolac has a tendency to cause gastric erosion and ulcers in dogs, long-term use (>3 days) is not recommended in this species.

Adverse Effects

Ketorolac use is limited in domestic animals because of its adverse effect profile and a lack of veterinary-labeled products. The primary issue in dogs is its GI toxicity. GI ulceration can be common if the drug is used chronically. Most clinicians who have used this medication in dogs limit treatment to less than 3 days and give misoprostol with or without sucralfate concurrently. Like other NSAIDS, platelet inhibition, renal, and hepatic toxicity are also possible with this drug.

Reproductive/Nursing Safety

Ketorolac does cross the placenta. In humans, the FDA categorizes this drug as category ***C*** for use during the *first two trimesters of 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 humans, all NSAIDs are assigned to category ***D*** for use during pregnancy during *the third trimester* or near delivery (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.*)

Most NSAIDs are excreted in milk. Ketorolac was detected in human breast milk at a maximum milk:plasma ratio of 0.037. It is unlikely to pose great risk to nursing offspring.

Overdosage/Acute Toxicity

Limited information is available. The oral LD_{50} is 200 mg/kg in mice. GI effects, including GI ulceration are likely in overdoses in small animals. Metabolic acidosis was reported in one human patient. Consider GI emptying in large overdoses; patients should be monitored for GI bleeding. Treat ulcers with sucralfate; consider giving misoprostol early.

Drug Interactions

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

- **ACE INHIBITORS**: Increased risk for nephrotoxicity
- **ALPRAZOLAM**: Hallucinations reported in some human patients taking with ketorolac
- **AMINOGLYCOSIDES** (**gentamicin, amikacin,** etc.): Increased risk for nephrotoxicity
- **ANTICOAGULANTS** (**heparin, LMWH, warfarin**): Increased risk for bleeding possible
- **ASPIRIN**: Increased likelihood of GI adverse effects (blood loss)