ETODOLAC TABLETS

(Generic of EtoGesic)

NON-STEROIDAL ANTI-INFLAMMATORY FOR ORAL USE IN DOGS ONLY

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS

Etodolac Tablets are indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

DESCRIPTION

Etodolac is a pyranocarboxylic acid, chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b] indole-1-acetic acid. The structural formula for etodolac is shown:

The empirical formula for etodolac is $C_{17}H_{21}NO_3$. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an *n*-octanol: water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

DOSAGE AND ADMINISTRATION

Always provide Client Information sheet with prescription. Carefully consider the potential benefits and risks of Etodolac and other treatment options before deciding to use Etodolac. Use the lowest effective dose for the shortest duration consistent with individual treatment response.

The recommended dose of Etodolac Tablets is 4.5 to 6.8 mg/lb body weight (10 to 15 mg/kg) administered once daily. Due to capsule sizes and scoring, dogs weighing less than 11 lb (5 kg) cannot be accurately dosed. The effective dose and duration should be based on clinical judgment of disease condition and patient tolerance of drug treatment. The initial dose level should be adjusted until a satisfactory clinical response is obtained, but should not exceed 15 mg/kg once daily.

CONTRAINDICATIONS

Etodolac Tablets are contraindicated in animals previously found to be hypersensitive to etodolac.

WARNINGS

Not for human use. Keep out of reach of children. Consult a physician in cases of accidental ingestion by humans. **Do not use in cats. For use in dogs only.**

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and

periodically during, administration of any NSAID is recommended. **Owners should be advised to observe for signs of potential drug toxicity (see Information for Dog Owners, Animal Safety, and Adverse Reactions) and be given a client information sheet about Etodolac.**

PRECAUTIONS

The safe use of Etodolac Tablets in dogs less than 12 months of age, pregnant, breeding or lactating dogs has not been established. **Owners should be advised to observe for signs of potential drug reactions.** If additional pain medication is warranted after administration of the daily dose of Etodolac, alternative analgesia should be considered. The use of another NSAID is not recommended.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from other NSAIDs. Dogs at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached and monitored. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to induce gastrointestinal ulceration and/or gastrointestinal perforation, concomitant use of Etodolac with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided.

The use of concomitantly protein-bound drugs with Etodolac has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of Etodolac has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

Treatment with Etodolac Tablets should be terminated if signs such as inappetence, emesis, fecal abnormalities, or anemia are observed. Dogs treated with non-steroidal anti-inflammatory drugs on a continuing basis, including etodolac, should be evaluated periodically to ensure that the drug is still necessary and well tolerated.

Etodolac Tablets, as with other non-steroidal anti-inflammatory drugs, may exacerbate clinical signs in dogs with pre-existing or occult gastrointestinal, hepatic or cardiovascular abnormalities, blood dyscrasias, or bleeding disorders.

ADVERSE REACTIONS

In a placebo-controlled field study with Etodolac Tablets involving 116 dogs, where treatment was administered for 8 days, the following adverse reactions were noted:

Adverse Reaction	Etodolac Tablets % of Dogs	Placebo % of Dogs
vomiting	4.3%	1.7%
regurgitation	0.9%	2.6%
lethargy	3.4%	2.6%
diarrhea/loose stool	2.6%	1.7%
hypoproteinemia	2.6%	0
urticaria	0.9%	0
behavioral change, urinating in house	0.9%	0

inappetence	0.9%	1.7%

Following completion of the field study, 92 dogs continued to receive etodolac tablets. One dog developed diarrhea following 2-1/2 weeks of treatment. Etodolac was discontinued until resolution of clinical signs was observed. When treatment was resumed, the diarrhea returned within 24 hours. One dog experienced vomiting which was attributed to treatment, and etodolac was discontinued.

Hypoproteinemia was identified in one dog following 11 months of etodolac therapy. Treatment was discontinued, and serum protein levels subsequently returned to normal.

Etodolac Tablets Post-Approval Experience:

As with other drugs in the NSAID class, adverse responses to Etodolac Tablets may occur. The adverse drug reactions listed below are based on voluntary post-approval reporting for Etodolac Tablets. The categories of adverse reaction reports are listed below in decreasing order of frequency by body system.

Gastrointestinal: Vomiting, diarrhea, inappetence, gastroenteritis, gastrointestinal bleeding, melena, gastrointestinal ulceration, hypoproteinemia, elevated pancreatic enzymes.

Hepatic: Abnormal liver function test(s), elevated hepatic enzymes, icterus, acute hepatitis.

Hematological: Anemia, hemolytic anemia, thrombocytopenia, prolonged bleeding time.

Neurological/Behavioral/Special Senses: Ataxia, paresis, aggression, sedation, hyperactivity, disorientation, hyperesthesia, seizures, vestibular signs, keratoconjunctivitis sicca.

Renal: Polydipsia, polyuria, urinary incontinence, azotemia, acute renal failure, proteinuria, hematuria.

Dermatological/Immunological: Pruritus, dermatitis, edema, alopecia, urticaria.

Cardiovascular/Respiratory: Tachycardia, dyspnea.

In rare situations, death has been reported as an outcome of some of the adverse reactions listed above.

INFORMATION FOR DOG OWNERS

Etodolac, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include decreased appetite, vomiting, diarrhea, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue Etodolac therapy and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow-up for all dogs receiving a continuing regimen of any NSAID.

CLINICAL PHARMACOLOGY

Etodolac is a non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, anti-pyretic, and analgesic activity[(1)]. The mechanism of action of etodolac, like that of other NSAIDs, is believed to be associated with inhibition of cyclooxygenase activity.

There are two main cyclooxygenase enzymes, COX-1 and COX-2, and a newly discovered third enzyme, COX-3, which has yet to be fully characterized[(2)]. Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiologic processes, e.g., platelet aggregation, gastric mucosal protection, and renal perfusion[(3)]. It also is constitutively expressed in the brain, spinal cord, and reproductive tract[(4)]. Cyclooxygenase-2 (COX-2) is responsible for the synthesis of inflammatory mediators, but it is also constitutively expressed in the brain, spinal cord and kidneys[(5)]. COX-2 mRNA has been identified in the dog liver, ovary, lung, cerebral cortex and gastrointestinal tract[(6)]. Cyclooxygenase-3 (COX-3) is constitutively expressed in the canine and human brain and the human heart[(7)].

In vitro experiments have shown that etodolac selectively inhibits COX-2 activity[(8)]. Inhibition of COX-1 activity is associated with adverse effects on the gastrointestinal tract, whereas inhibition of COX-2 activity is associated with reducing inflammation. The clinical relevance of these data have not been shown. Etodolac also inhibits macrophage chemotaxis *in vivo* and *in vitro*[(9)]. Because of the importance of macrophages in the inflammatory response, the anti-inflammatory effect of etodolac could be partially mediated through inhibition of the chemotactic ability of macrophages.

Pharmacokinetics in healthy beagle dogs: Etodolac is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration. The extent of etodolac absorption (AUC) is not affected by the prandial status of the animal. However, it appears that the peak concentration of the drug decreases in the presence of food. As compared to an oral solution, the relative bioavailability of the tablets when given with or without food was essentially 100%. Peak plasma concentrations are usually attained within 2 hours of administration. Though the terminal half-life increases in a nonfasted state, minimal drug accumulation (less than 30%) is expected after repeated dosing (i.e., steady-state). Pharmacokinetic parameters estimated in a crossover study (fed vs. fasted) in eighteen 5-month-old Beagle dogs are summarized in the following table:

Mean Pharmacokinetic Parameters Estimated in 18 Beagle Dogs After Oral Administration of 150 mg of Etodolac (approximately 12-17 mg/kg)

Pharmacokinetic Parameter	Capsule/Fasted	Capsule/Nonfasted
C_{max} (mcg/mL)	22.0±6.42	16.9±8.84
T_{max} (hr)	1.69±0.69	1.08±0.46
$AUC_{0-\infty}$ (mcg•hours/mL)	64.1±17.9	63.9±28.9
Terminal half-life, $t_{1/2}$ (hrs)	7.66±2.05	11.98±5.52

Pharmacokinetics of oral etodoloac in dogs with reduced kidney function: In a study involving four Beagle dogs with induced acute renal failure, there was no observed change in drug bioavailability after administration of 200 mg single oral etodolac doses. In a study evaluating an additional four Beagles, no changes in electrolyte, serum albumin/total protein and creatinine concentrations were observed after single 200 mg doses of etodolac. This was not unexpected since the kidneys in normal dogs clear very little etodolac. Most of etodolac and its metabolites are eliminated via the liver and feces. In addition, etodolac is believed to undergo enterohepatic recirculation[(10)].

EFFECTIVENESS

A placebo-controlled, double-blinded field study demonstrated the anti-inflammatory and analgesic effectiveness of Etodolac (etodolac) Tablets in various breeds of dogs. In this field study, dogs diagnosed with

osteoarthritis secondary to hip dysplasia showed objective improvement in mobility as measured by force plate parameters when given Etodolac Tablets at the label dosage for 8 days.

ANIMAL SAFETY

In target animal safety studies, Etodolac Tablets were well tolerated clinically when given at the label dosage for periods as long as one year (see Precautions).

Oral administration of etodolac at a daily dosage of 4.5 mg/lb (10 mg/kg) for twelve months or 6.8 mg/lb (15 mg/kg) for six months, resulted in some dogs showing a mild weight loss, fecal abnormalities (loose, mucoid, mucosanguineous feces or diarrhea), and hypoproteinemia. Erosions in the small intestine were observed in one of the eight dogs receiving 15 mg/kg following six months of daily dosing. In a separate pharmacokinetic study dogs were given the recommended dose level of Etodolac Tablets daily for 28 consecutive days. This repeated treatment resulted in minimal drug accumulation.

Elevated dose levels of Etodolac Tablets, i.e., ≥40 mg/kg/day (18 mg/lb/day, 2.7X the maximum daily dose), caused gastrointestinal ulceration, emesis, fecal occult blood, and weight loss. At a dose of ≥80 mg/kg/day (36 mg/lb/day, 5.3X the maximum daily dose), 6 of 8 treated dogs died or became moribund as a result of gastrointestinal ulceration. One dog died within 3 weeks of treatment initiation while the other 5 died after 3-9 months of daily treatment. Deaths were preceded by clinical signs of emesis, fecal abnormalities, decreased food intake, weight loss, and pale mucous membranes.

Renal tubular nephrosis was also found in 1 dog treated with 80 mg/kg for 12 months. Other common abnormalities observed at elevated doses included reductions in red blood cell count, hematocrit, hemoglobin, total protein and albumin concentrations; and increases in fibrinogen concentration and reticulocyte, leukocyte, and platelet counts.

In an additional study which evaluated the effects of Etodolac Tablets administered to 6 dogs at the labeled dose for approximately 9.5 weeks, the incidence of stool abnormalities (diarrhea, loose stools) was unchanged for dogs in the weeks prior to initiation of treatment with Etodolac Tablets, and during the course of this oral etodolac therapy. Five of the dogs receiving Etodolac Tablets, versus 2 of the placebo-treated dogs, exhibited excessive bleeding during an experimental surgery. No significant evidence of drug-related toxicity was noted on necropsy.

STORAGE INFORMATION

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

HOW SUPPLIED

Etodolac (etodolac) Tablets are supplied in bottles containing 100 tablets.