5530G

EtoGesic®

READ BEFORE USING THIS PRODUCT

NADA 141-108, Approved by FDA

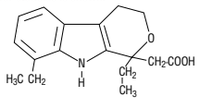
FORT DODGE®

EtoGesic®
(etodolac)
TABLETS 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.

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. Each tablet is biconvex and half-scored and contains either 150, 300 or 500 mg of etodolac.

CLINICAL PHARMACOLOGY

Etodolac is a non-narcotic, nonsteroidal 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. Two cyclooxygenase isoforms have been described in mammals[2]. The constitutive isoform, COX-1, is basally expressed by nearly all cells in mammals, including cells lining synovial spaces in all forms of arthritis, and is associated with synthesis of prostaglandins necessary for normal gastrointestinal and renal function. The inducible isoform, COX-2, which is constitutively expressed in the canine kidney, generates prostaglandins involved with inflammation. *In vitro* experiments have shown that etodolac selectively inhibits COX-2 activity[3]. 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*[4]. 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	Tablet/ Fasted	Tablet/ Nonfasted
C_{max} (µg/mL)	22.0 ± 6.42	16.9 ± 8.84
T_{max} (hr)	1.69 ± 0.69	1.08 ± 0.46
$AUC_{0-\infty}$ (µg•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 etodolac 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[5].

INDICATIONS

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

DOSAGE AND ADMINISTRATION

Always provide Client Information sheet with prescription. The recommended dose of etodolac is 10 to 15 mg/kg body weight (4.5 to 6.8 mg/lb) administered once daily. Due to tablet sizes and scoring, dogs weighing less than 5 kg (11 lb) 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. When a satisfactory clinical response is obtained, the daily dose level should be reduced to the minimum effective dose for longer term administration.

CONTRAINDICATIONS

EtoGesic Tablets are contraindicated in animals previously found to be hypersensitive to etodolac or other NSAIDs.

WARNINGS

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

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 should be considered. **Owners should be advised to observe for signs of potential drug toxicity (see Information for Dog Owners and Adverse Reactions).**

For technical assistance or to report a suspected adverse reaction, call (800) 533-8536.

PRECAUTIONS

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

EtoGesic Tablets, as with other nonsteroidal anti-inflammatory drugs, may exacerbate clinical signs in dogs with pre-existing or occult gastrointestinal, hepatic or cardiovascular abnormalities, blood dyscrasias, or bleeding disorders. NSAIDs may also inhibit the prostaglandins, which maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease, thereby unmasking occult disease that has not been previously diagnosed.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Dogs at greatest risk for renal toxicity 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. Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of etodolac with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Studies to determine the activity of EtoGesic Tablets when administered concomitantly with other protein-bound drugs have not been conducted in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of EtoGesic has not been evaluated. Drug compatibility should be monitored closely in patients requiring adjunctive therapy.

The safe use of EtoGesic 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 EtoGesic, alternative analgesia should be considered. The use of another NSAID is not recommended.

INFORMATION FOR DOG OWNERS

EtoGesic, 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 EtoGesic 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.

EFFECTIVENESS

A placebo-controlled, double-blinded study demonstrated the anti-inflammatory and analgesic efficacy of EtoGesic (etodolac) Tablets in various breeds of dogs. In this clinical field study, dogs diagnosed with osteoarthritis secondary to hip dysplasia showed objective improvement in mobility as measured by force plate parameters when given EtoGesic Tablets at the label dosage for 8 days.

ADVERSE REACTIONS

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

Adverse Reaction	EtoGesic 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. 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.

EtoGesic Tablets Post-Approval Experience:

As with other drugs in the NSAID class, adverse responses to EtoGesic Tablets may occur. The adverse drug reactions listed below are based on voluntary post-approval reporting for EtoGesic Tablets. The categories of adverse event 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 responses listed above.

ANIMAL SAFETY

In target animal safety studies, EtoGesic 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 10 mg/kg (4.5 mg/lb) for twelve months or 15 mg/kg (6.8 mg/lb) 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.

Elevated dose levels of EtoGesic 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 EtoGesic 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 EtoGesic Tablets, and during the course of etodolac therapy. Five of the dogs receiving EtoGesic 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 CONDITIONS

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

HOW SUPPLIED

EtoGesic (etodolac) Tablets are available in 150, 300 and 500 mg single-scored tablets and supplied in bottles containing 7, 30 and 90 tablets.

NDC 0856-5520-03 – 150 mg – bottles of 7
NDC 0856-5520-04 – 150 mg – bottles of 30
NDC 0856-5520-05 – 150 mg – bottles of 90
NDC 0856-5530-03 – 300 mg – bottles of 7
NDC 0856-5530-04 – 300 mg – bottles of 30
NDC 0856-5530-05 – 300 mg – bottles of 90
NDC 0856-5550-03 – 500 mg – bottles of 7
NDC 0856-5550-04 – 500 mg – bottles of 30
NDC 0856-5550-05 – 500 mg – bottles of 90

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3. Glaser, KB. Cyclooxygenase selectivity and NSAIDs: cyclooxygenase-2 selectivity of etodolac (Lodine®). *Inflammopharmacol* (1995) 3:335-345.
4. Gervais, F, RR Martel, E Skamene. The effect of the non-steroidal anti-inflammatory drug etodolac on macrophage migration *in vitro* and *in vivo*. *J. Immunopharmacol* (1984) 6:205-214.
5. Cayen, MN, M Kraml, ES Ferdinandi, EL Greselin, D Dvornik. The metabolic disposition of etodolac in rats, dogs, and man. *Drug Metab. Revs.* (1981) 12:339-362.

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