NADA 141-274, Approved by FDA

FORT DODGE®

5960A

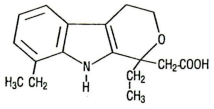
EtoGesic®
(etodolac)

STERILE INJECTABLE SOLUTION
NON-STEROIDAL ANTI-INFLAMMATORY
FOR 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 mL contains 100 mg of etodolac.

The concentrations of components in this product are 10% etodolac; 33% polyethylene glycol 400, NF; 3% benzyl alcohol, NF; 0.3% sodium bisulfite; and *q.s.* with water for injection. Sodium hydroxide, NF and phosphoric acid, NF are used to adjust the pH.

INDICATIONS

ETOGESIC Injectable is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of ETOGESIC and other treatment options before deciding to use ETOGESIC. Use the lowest effective dose for the shortest duration consistent with individual treatment response.

The recommended dose of ETOGESIC Injectable in dogs is 4.5 to 6.8 mg/lb body weight (10 to 15 mg/kg) as a dorsoscapular subcutaneous (SQ) injection. If needed, daily doses of ETOGESIC Tablets may begin 24 hours after the last injectable treatment. **Read package insert carefully before use.**

Use alternate injection sites. The likelihood of injection site reactions increases when administered near previous injection sites.

CONTRAINDICATIONS

ETOGESIC Injectable is contraindicated in animals previously found to be hypersensitive to etodolac.

WARNINGS

Not for human use. Keep out of the reach of children. Consult a physician in cases of accidental exposure by humans. **Do not use in cats. For SQ injectable 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).**

For technical assistance or to report a suspected adverse reaction, call 1-800-533-8536.

PRECAUTIONS

The safe use of ETOGESIC Injectable and 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.** For subcutaneous use only. The safety of IV or IM administration has not been established. 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. The long term use of the injectable has not been studied.

As a class, cyclo-oxygenase 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 existing 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 produce gastrointestinal ulceration and/or gastrointestinal perforation, concomitant use of ETOGESIC with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided.

The use of concomitantly protein-bound drugs with ETOGESIC 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 ETOGESIC 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.

ETOGESIC Injectable should not be administered if signs such as inappetence, emesis, fecal abnormalities, or anemia have been experienced following treatment with the oral etodolac formulation. 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.

ETOGESIC Injectable, 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 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 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 subsequently returned to normal.

ETOGESIC Tablets Post-Approval Experience:
As with other drugs in the NSAID class, adverse responses to ETOGESIC Tablets may occur. Although not all adverse reactions are reported, the adverse 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 reactions listed above. For technical assistance, to report a suspected adverse reaction, or to obtain a Material Safety Data Sheet, call 1-800-533-8536.

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).** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care 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 also constitutively expressed in the canine and human brain and also 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 was initially approved in a tablet formulation for use in dogs. Etodolac is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration. The relative bioavailability of the tablet formulation when given with or without food is essentially 100%. Although the terminal half-life increases in a nonfasted state, minimal drug accumulation (less than 30%) is expected after repeated dosing (i.e., steady-state). Etodolac bioavailability was compared following administration of an oral tablet or the injectable formulation (right dorsoscapular subcutaneous injection). The study was conducted in 36 fasted, Beagle dogs, at least 12 months of age (18 males and 18 females) utilizing a single dose, two-period crossover design. The comparability of the product's systemic safety and effectiveness was based upon pharmacokinetic comparisons (plasma drug concentrations) and upon an assessment of the magnitude of bioaccumulation that occurs after repeated administration of the oral versus parenteral formulations.

Specifically, comparable effectiveness was based upon an inter-product comparison of the extent of drug exposure during the first four hours following administration [the area under the concentration versus time curve from 0 to 4 hour post-dose ($AUC_{0\text{-}4}$)] and the total

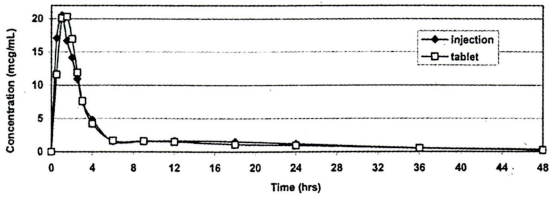
systemic drug exposure ($AUC_{0\text{-}LOQ}$). The safety of the injectable formulation was based upon the presence of peak plasma drug concentrations that were equal to, or less than, those observed following administration of the approved oral formulation and upon the confirmation that the pharmacokinetic characteristics of the injectable product does not change after repeated daily subcutaneous injections. The results of these comparisons are provided in Table 1 and Figure 1. All concentrations represent the observed normalization values for the ratio of the actual versus targeted dose (15 mg/kg).

Table 1: Mean Pharmacokinetic Parameters Estimated in 36 Fasted Beagle Dogs After Administration of ETOGESIC[1] (Arithmetic Mean ± Standard Deviation)

Pharmacokinetic Parameter	ETOGESIC Injectable	ETOGESIC Tablets
$AUC_{0\text{-}LOQ}$,* (mcg•hours/mL)	97 ± 34	90 ± 32
Cmax, (mcg/mL)	21 ± 7	25 ± 9
$AUC_{0\text{-}4}$, (mcg•hours/mL)	48 ± 16	48 ± 26
Tmax (hr)	1.02 ± 0.46	1.42 ± 0.57
T1/2** (hr)	12.2 ± 4.3	11.7 ± 4.0

[1] Based upon concentrations normalized to expected values if actual administered dose = 15 mg/kg.
* AUC measured from time zero to last quantifiable concentration.
** Harmonic mean

Figure 1: Biocomparison of ETOGESIC Injectable to ETOGESIC Tablets: Etodolac concentrations corrected for targeted versus actual dose.



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 as 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 study demonstrated the anti-inflammatory and analgesic effectiveness of ETOGESIC (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 ETOGESIC Tablets at the label dosage for 8 days. A pharmacokinetic comparison of the tablet and injectable etodolac formulations was evaluated in healthy Beagle dogs (see Clinical Pharmacology). As the injectable product was associated with plasma etodolac concentrations comparable to that of the tablet, it is expected that the therapeutic response to these two formulations will be equivalent.

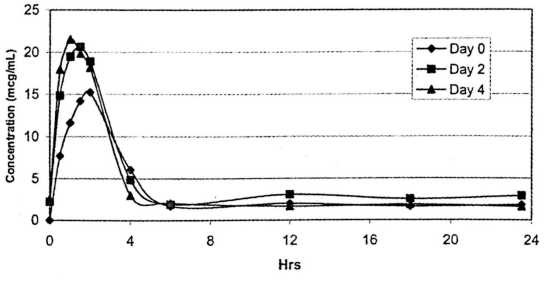
ANIMAL SAFETY

ETOGESIC Injectable may induce signs of discomfort upon administration. In two laboratory studies the injectable formulation caused signs of discomfort in some dogs including scratching, vocalizing, rubbing, and rolling. These signs occurred in 44% of the dogs and usually resolved in 30 seconds, although signs persisted in some dogs for 2-14 minutes. Localized injection site swellings were visible and palpable usually one hour post-administration, with the largest swellings occurring four hours post-administration (average swelling dimension 2.65 X 1.75 X 0.33 cm).

Swellings usually resolved within 24 hours, although some lasted 3-4 days. Additional studies suggested delayed nodule formation may occur at the site of injection approximately two weeks post-injection and may last 3-13 days.

A pharmacokinetic study showed that repeated treatment of dogs with once-daily 15 mg/kg (6.8 mg/lb) body weight injections of ETOGESIC Injectable resulted in minimal drug accumulation. The mean plasma etodolac profiles obtained after repeated daily subcutaneous injection (15 mg/kg) is provided in Figure 2. In this study, blood was observed in the feces of one of the 14 dogs following four daily subcutaneous injections. The safety of ETOGESIC Injectable has not been evaluated in dogs larger than 20 kg.

Figure 2: Assessment of bioaccumulation with repeated injections: Mean concentration/time profiles across injection days.



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 etodolac administered orally, 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 this oral 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 INFORMATION

Store at or below 25°C (77°F).

HOW SUPPLIED

ETOGESIC (etodolac) 10% Injectable is available in 50 mL vials, and each mL contains 100 mg etodolac - NDC 0856-5953-02.

REFERENCES

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