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
ETOGESIC is a sterile, isotonic, aqueous suspension of etodolac, USP, for subcutaneous (SQ) or intramuscular (IM) administration in dogs. The empirical formula for etodolac is C16H18NO4. The molecular weight of the base is 287.37. It has a pKa of 3.85 and an octanol: water partition coefficient of 3.6 at pH 7.4. ETOGESIC 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; 3% benzylic alcohol; and 0.9% sodium bisulfite, and g. 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/kg body weight (10 to 15 mg/kg) given as a 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.

DOGS
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, 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, or diarrhea and/or fecal incontinence; increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, tachypnea, increased mucous membrane thickness, or behavioral changes. Serious adverse reactions associated with this drug class may 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-steroidal, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, anti-pyretic, and analgesic activity (9). 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 (9). Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiological processes, e.g., platelet aggregation, gastric mucosal protection, and renal perfusion (9). It also constitutively expressed in the brain, spinal cord, and reproductive tract (9). 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 (9). COX-2 mRNA has been identified in the dog liver, ovary, lung, cerebral cortex, and gastrointestinal tract (9). Cyclooxygenase-3 (COX-3) is also constitutively expressed in the canine and human brain and also the human heart (9).

In vitro experiments have shown that etodolac selectively inhibits COX-2 activity (9). Inhibition of COX-1 and COX-2 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. Because of the importance of macrophage 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. 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 fasted 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 dorsocapular subcutaneous route). The study was conducted in 36 fasted, Beagle dogs, at least 12 months of age (18 males and 18 females). Formulation was assessed using pharmacokinetic 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 major and minor metabolite accumulation that occurs after repeated administration of the oral versus parenteral formulations.

Specifically, comparative 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-time curve from 0 to 4 hour post-dose (AUG4)) and the total
systemic drug exposure (AUC_{\text{total}}). 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 ETODGESIC®

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>ETODGESIC Injectable</th>
<th>ETODGESIC Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{\text{total}} (mcg-hours/mL)</td>
<td>97 ± 34</td>
<td>90 ± 32</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>21 ± 7</td>
<td>25 ± 9</td>
</tr>
<tr>
<td>AUC_{\text{total}} (mcg-hours/mL)</td>
<td>48 ± 16</td>
<td>48 ± 26</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.02 ± 0.46</td>
<td>1.42 ± 0.57</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>12.2 ± 4.3</td>
<td>11.7 ± 4.0</td>
</tr>
</tbody>
</table>

1 Based upon concentrations normalized to expected values if actual administered dose = 15 mg/kg.
2 * Harmonic mean

Figure 1: Biocomparison of ETODGESIC Injectable to ETODGESIC Tablets: Etdolac 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.

**EFFECTIVENESS**

A placebo-controlled, double-blinded study demonstrated the anti-inflammatory and analgesic effectiveness of ETODGESIC (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 ETODGESIC 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**

ETODGESIC 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 20 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 ETODGESIC Injectable resulted in minimal drug accumulation. The main 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 ETODGESIC 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, mucous, mucus-containing feces or diarrhea), and hyperproteinemia. 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 ≥60 mg/kg/day (36 mg/lb/day, 5.3X the maximum daily dose), 6 of 9 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 necrosis 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 reticulocytes, leukocytes, and platelet counts.

In an additional study which evaluated the effects of ETODGESIC 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 the dogs in the weeks prior to initiation of treatment with ETODGESIC Tablets, and during the course of this oral etodolac therapy. Five of the dogs receiving ETODGESIC 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 necropy.

**STORAGE INFORMATION**

Store at or below 25°C (77°F).

**HOW SUPPLIED**

ETODGESIC (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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