Approval Date:July 22, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-108

B. Sponsor

Fort Dodge Animal Health
Cyanamid Agricultural Research Center
P.O. Box 400
Princeton, New Jersey 08543-0400

C. Proprietary Name

EtoGesic™

D. Established Name

Etodolac

E. Dosage Form

Etodolac is a biconvex, half-scored tablet that contains 150 or 300mg of etodolac.

F. Dispensing Status

Rx

G. Dosage Regimen

The recommended dose of EtoGesic™; tablets for dogs is 10 to 15 mg/kg body weight (4.5 to 6.8 mg/lb) given orally once daily.

H. Route of Administration

The product is designed to be administered orally.

I. Indication

Etodolac is recommended for the management of pain and inflammation associated with osteoarthritis in dogs.

II. EFFECTIVENESS

A study was conducted in dogs to demonstrate the efficacy of EtoGesic™; (etodolac) for the management of pain and inflammation associated with osteoarthritis. This combined dose determination and clinical field trial was conducted in four geographically distinct locations by four veterinary orthopedic specialists. The safety of etodolac in the field was also assessed. Results of this study demonstrated that etodolac is efficacious when administered at a daily dose of approximately 15 mg/kg body weight for 8 days.

Dose Determination and Clinical Field Study (P440-C2)

a. Type of Study: Combined Dose Determination and Clinical Field Study

b. Investigators:

Name and Location	**Cases**
Dr. Steven Budsberg Department of Small Animal Medicine and Surgery University of Georgia Athens, GA 30602	22
Dr. Charles DeCamp Department of Small Animal Clinical Sciences Michigan State University East Lansing, MI 48824	20
Dr. Spencer Johnston Department of Small Animal Clinical Sciences Virginia Polytechnic Institute and State University Blacksburg, VA 24061	38
Dr. Peter Schwarz Department of Veterinary Clinical Sciences Colorado State University Fort Collins, CO 80523	36

c. General Design

i. Purpose: The study was conducted to determine an effective dose for EtoGesicTM; tablets in dogs with osteoarthritis associated with chronic hip dysplasia.

ii. Test Animals: One hundred sixteen client-owned dogs from four separate locations entered the study. The dogs were of various breeds, ranged in weight from 26 to 43 kg (57 to 95 lb), and were 1 to 10 years of age. A total of 100 dogs completed the study and were used in the statistical analysis. Sixteen additional dogs received the drug for at least part of the dosing regimen, however, they were not utilized in the analysis for efficacy due to protocol deviations. Young, 1-3 year old, fast growing, giant breeds of dogs and obese chondrodysplastic dogs within the acceptable age and weight ranges were excluded from the study. Dogs were limited to the weight range listed above in order to reduce variables in force plate evaluations.

iii. Placebo Control: Treatment with tablets similar to the proposed market formulation except for the absence of active ingredient.

iv. Diagnosis: Dogs had at least a six-month history of chronic hip dysplasia, were free of confounding diseases, and presented with clinical signs such as lameness or pain. Radiographs were used to confirm the diagnosis of hip

dysplasia.

v. Dosage Form: The tablets were identical to the proposed market formulation.

vi. Route of Administration: Oral.

vii. Dosages used: 135 mg/day to provide approximately 4.5mg/kg/day (2.0 mg/lb/day) and 450 mg/day to provide approximately 15 mg/kg/day (6.8 mg/lb/day). Actual doses administered to the 450 mg/day group ranged from 11.0 to 17.6mg/kg/day.

viii. Treatment Duration: 8 days.

ix. Parameters Measured: Mobility was evaluated twice before the start of therapy and once at the end of therapy by force plate analysis. Prescreening force plate evaluations were performed twice within 5 to 10 days prior to study entry to establish baseline values. The percent difference between mean values of the two force plate vertical impulse area measures taken prior to admission was required to be < 15% for a patient to enter the study. Mobility was also assessed at these times by limb disuse, pain on palpation, and weight bearing scores by a qualified veterinarian.

x. General health was evaluated by physical examinations performed at one week before treatment, just prior to treatment initiation, and at the end of therapy. Samples for serum chemistry, hematology, urinalysis, and fecal parasite analyses were collected before and at the end of treatment

d. Results: When measured objectively as vertical impulse area by force plate technology, etodolac treatment was associated with an increase in the amount of weight carried. Dogs receiving either dose of etodolac exhibited statistically significant increases in vertical impulse area relative to pretreatment values, while only slight improvement was experienced by controls (Table 1). Moreover, the increase in vertical impulse area among dogs receiving the 450 mg dose of etodolac was significantly greater than the corresponding change among controls. The higher dose produced greater improvement in this parameter than did the lower dose.

Table 1. Effect of etodolac therapy on mobility as measured by force plate analysis.[1]

Daily Dose of Etodolac

Parameter	**Placebo**	**135 mg**	**450 mg**
Vertical impulse area	0.04	0.13[b]	0.22[a,b]

[1] Values are expressed as change from average pretreatment values in units of 100 x N x sec/kg BW for impulse area of the most affected rear leg.

[a] Significantly improved compared to placebo ($P < 0.05$).

[b] Significantly improved from pretreatment ($P < 0.05$).

After therapy with either dose of etodolac, significant improvements were found for all subjective measurements of mobility, i.e. limb disuse, pain on palpation, and weight bearing. Significant improvement was also found among controls**.**

e. Statistical Analysis: Force plate data were analyzed by mixed model analysis of covariance using the average pretreatment values as the covariate. Treatment groups were compared using least square means. All tests were one-sided and conducted at the 0.05 level.

f. Conclusions: This study demonstrated that etodolac administered at a dose of approximately 15 mg/kg/day for 8 days is effective for management of signs associated with osteoarthritis secondary to hip dysplasia in dogs. Etodolac at a dose of 4.5 mg/kg/day provided suboptimal efficacy. This study also demonstrated the safety of etodolac administered at a dose of 15 mg/kg once a day for 8 days under field conditions.

g. Adverse Reactions: Three dogs developed hypoproteinemia during the course of etodolac therapy. One dog was diagnosed with a pre-existing intestinal lymphosarcoma by the Clinical Investigator, and the hypoproteinemia was attributed to this disease. In the two other dogs, the hypoproteinemia resolved after treatment ended.

Other than the hypoproteinemia detailed above, samples collected for clinical pathology showed no statistically significant, dose-dependent changes outside normal physiological ranges in any serum chemistry, hematology, or urinalysis parameters ($P > 0.10$).

Adverse reactions reported during the field trial are tabulated below.

Table 2. Adverse reaction reported during Study P440-C2 (number of dogs=116).

Adverse Reaction	**EtoGesic % 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
inappetance	0.9%	1.7%

III. TARGET ANIMAL SAFETY

Two studies investigated the effects of continuous once daily oral administration of etodolac tablets to adult dogs over a period of six months at dosages up to 90mg/kg body weight and one year at dosages up to 80 mg/kg body weight. These studies show that the primary adverse effect of etodolac is gastrointestinal toxicity.

1. AY-24,236: Etodolic Acid One-Year Oral Toxicity Study – Dog

   a. Type of Study: One Year Oral Toxicity

   b. Investigator:

      Dr. R. D. Hemm
      Ayerst Research Laboratories
      Chazy, NY 12921

   c. General Design

      i. Purpose: To determine the toxicological effects of oral doses of etodolac given once daily for one year.

      ii. Test Animals: Sixteen male and sixteen female beagle dogs were randomly assigned (4 dogs/sex/group) to the four treatment groups. At the start of the study, the dogs ranged from 8-13 kg in weight and 90 to 98 weeks in age.

      iii. Form: Tablets given once daily.

      iv. Placebo Control: Tablets lacking etodolac were given for one year. The number of placebo tablets that were administered was calculated to be the same on a body weight basis as the number of etodolac tablets given to the high dose dogs.

      v. Doses Used:

Dose (mg/kg/d)	**Relative Dose**
0	0X
10	0.7 – 1X
40	2.7 – 4X
80	5.3 – 8X

      vi. Route of Administration: Oral.

      vii. Treatment Duration: 52 weeks.

      viii. Parameters Measured:

         1. General health observations

         2. Food consumption

         3. Body weight

         4. Physical examination

         5. Ophthalmoscopic examination

6. Electrocardiographic analysis
7. Hematology
8. Blood chemistry
9. Urinalysis
10. Gross pathology
11. Histopathology

d. Results:

10 mg/kg: Toxicity of etodolac was minimal with adverse reactions being absent or generally mild and transitory and included mild weight loss and fecal alterations (loose or mucoid feces, diarrhea or presence of blood). The most pronounced effect at this dose was a moderate hypoproteinemia (3.6 g/dl) in one dog at four weeks after the start of etodolac treatment. Serum protein concentration in this dog slowly returned toward normal levels during the remainder of the study but remained below normal at study termination (4.9 g/dl). None of the dogs exhibited any gastrointestinal abnormalities upon necropsy.

40 mg/kg: Most of the eight dogs showed some adverse reactions. General effects at this dose included more frequent incidences of emesis and fecal alteration, decreases in erythroid parameters, increases in leukocytic parameters and fibrinogen concentration, and decreases in protein, albumin, and globulin concentration. Intestinal ulceration was present in three dogs at necropsy, and less severe lesions ranging from discoloration to erosion were present in the gastrointestinal tract of four other dogs.

80 mg/kg: The effects of this dose were severe, with a mortality rate of 75% among the eight dogs. All deaths resulted from severe ulcerations to the gastrointestinal tract and included two dogs with perforating lesions and peritonitis. One dog died within 3 weeks of treatment initiation while the other 5 died after 3 to 9 months of daily treatment. All deaths were preceded by body weight loss, frequent episodes of emesis or fecal alteration, decreased food intake, pale mucous membranes, and profound changes in hematological and serum biochemical parameters such as decreased erythrocyte counts, increased leukocyte and platelet counts, and hypoproteinemia. One of the two surviving dogs at the high dose did not exhibit signs of toxicity, while the other experienced moderate adverse reactions. One dog in the 80 mg/kg group also showed renal tubular nephrosis at necropsy.

No drug-attributable abnormalities were noted in heart rate, electrocardiograms, or ophthalmoscopic observations, and treatment did not alter organ weights at any dosage. The primary toxicological changes following etodolac administration were attributed to gastrointestinal toxicity with changes in hematological and blood biochemical values resulting from the associated blood loss and peritonitis.

e. Conclusions: This study demonstrated that the adverse effects of etodolac given at the minimum use level of 10 mg/kg/day included weight loss, fecal abnormalities and hypoproteinemia. Administration of etodolac at elevated doses of 40 or 80 mg/kg/day once daily for one year caused severe gastrointestinal toxicity, including death at 80 mg/kg/day.

2. AY-24,236: Etodolic Acid Six-Month Oral Toxicity – Dog

a. Type of Study: Six Month Oral Toxicity

b. Investigator:

Dr. W. J. Tierney
Bio/dynamics, Inc.
Mettlers Road
East Millstone, NJ 08873

c. General Design

i. Purpose: To determine the toxicological effects of oral doses of etodolac given once daily for six months.

ii. Test Animals: Sixteen male and sixteen female beagle dogs were randomly assigned (4 dogs/sex/group) to the four treatment groups. At the start of the study, the dogs ranged from 8.2-11.3 kg in weight and were 10 months of age.

iii. Dosage Form: Tablets given once daily.

iv. Doses Used:

Dose (mg/kg/d)	**Relative Dose**
0	0X
15	1 – 1.5X
45	3 – 4.5X
90	6 – 9X

v. Route of Administration: Oral.

vi. Treatment Duration: 26 weeks.

vii. Parameters Measured:

1. General health observations
2. Food consumption
3. Body weight
4. Physical examination

5. Ophthalmoscopic examination

6. Electrocardiographic analysis

7. Hematology

8. Blood chemistry
9. Urinalysis

10. Gross pathology

11. Histopathology

d. Results:

A dose dependent increase in the incidence of loose, black-tarry, bloody or mucoid stools, and vomiting was observed. Mean body weights in all groups were less than controls with the mean weight of the females in the 90 mg/kg group averaging 10% lower than controls.

15 mg/kg: Toxicological effects on hematological and serum biochemical parameters were absent or small and transitory. Erosions of the intestinal mucosa were described grossly in two dogs but confirmed on histologic examination in only one of the dogs. The other six dogs had less severe gastrointestinal lesions such as mild congestion or hemorrhage.

45 mg/kg: Toxicological reactions at this dose were absent or generally mild. Dogs at this dose experienced decreases in erythroid parameters, increases in leukocytic parameters, and decreases in protein, albumin, globulin, and bilirubin concentrations. At necropsy, two of the eight dogs exhibited erosions in the small intestine.

The other six dogs had less severe gastrointestinal abnormalities such as mild congestion.

90 mg/kg: Adverse reactions at this dose ranged from mild to severe. One of the eight dogs died as the result of an ileal intussusception into the colon, and exhibited many hematological and blood biochemical changes prior to death. Decreases in erythrocyte counts, alanine aminotransferase activity, and protein, albumin, globulin, and bilirubin concentrations, and increases in leukocytic parameters and fibrinogen concentration were mild to severe in all dogs. At necropsy, two of the seven surviving dogs had ulcers in the colon and two others had erosions in the small intestine. The three other surviving dogs had mild abnormalities of the gastrointestinal tract.

e. Conclusions: This study demonstrated that etodolac given at 15mg/kg/day caused erosions in the gastrointestinal tract in one dog when given once daily for up to six months. Administration of etodolac at elevated doses of 45or90mg/kg/day caused more severe gastrointestinal toxicity with ulceration occurring at 90 mg/kg.

3. Study P440-C6

   a. Investigator:

      Dr. Peter Schwarz
      Department of Veterinary Clinical Sciences
      Colorado State University
      Fort Collins, CO 80523

   b. General Design

      i. Purpose: To evaluate the effects of etodolac at doses of approximately 15 mg/kg dose when administered for approximately 9.5 weeks.

      ii. Test Animals: Twelve dogs were randomly assigned to etodolac and placebo control treatments (3 dogs/sex/group). Dogs weighed between 24 to 35 kg (53 to 77 lb) at the start of treatment.

      iii. Placebo Control: Treatment with tablets similar to the proposed market formulation except for the absence of active ingredient.

      iv. Dosage and Route of Administration: The tablets were identical to the proposed market formulation. Dogs received approximately 15 mg/kg body weight (6.8 mg/lb) orally once daily.

      v. Disease System: Dogs exhibited normal musculoskeletal condition at the start of the study. Osteoarthritis was induced in the stifle joint by transection of the cranial cruciate ligament in one rear leg. Four weeks later, the stifle joint was stabilized using a modified surgical imbrication technique. The study ended eight weeks after stabilization surgery. Etodolac treatment administration began 10 days prior to stifle stabilization surgery and continued until the end of the study for a duration of 9.5weeks.

      vi. Parameters Measured: General health was evaluated by daily, including observations for alertness and evidence of vomiting, diarrhea, or inappetance. Physical examinations were performed at approximately 4 week intervals. Samples for serum chemistry, hematology, urinalysis, and fecal parasite analyses were collected at the time of each physical examination. At the end of the study, all dogs were euthanized and complete necropsies were performed. Any lesions noted on gross necropsy were submitted for histologic evaluation.

   c. Adverse Reactions: Five of six dogs treated with etodolac exhibited excessive hemorrhage during the stifle stabilization surgery compared to two of six control dogs. Instances of diarrhea and vomiting occurred occasionally among dogs receiving etodolac. These instances occurred in the same frequency prior to initiation of etodolac treatment, and with a similar frequency among dogs receiving placebo tablets. Clinico-pathologic analyses did not suggest any adverse drug reactions.

d. Conclusions: This study evaluated the safety of etodolac administered at a dose of approximately 15 mg/kg/day for 9.5 weeks. The significant adverse effect noted was increased bleeding during surgery in 5 of 6 dogs receiving etodolac treatment, versus 2 of 6 dogs receiving placebo.

Pharmacokinetics and Bioavailability

Studies were conducted in dogs to investigate the pharmacokinetics and bioavailability of etodolac following oral administration. Results of these studies demonstrated that etodolac is rapidly and efficiently absorbed from the gastrointestinal tract.

1. Three-Way Oral Tablet and Oral Gavage Crossover Bioavailability Study with Etodolac in Dogs (P440-C7)

    a. Type of Study: Oral Bioavailability Study

    b. Investigator:
    Dr. Anthony Kiorpes
    Hazleton Wisconsin, Inc.
    Madison, WI 53707

    c. General Design

        i. Purpose: To compare the bioavailability of etodolac when administered as a single oral tablet to fasted and nonfasted dogs and as an oral gavage solution to fasted dogs.

        ii. Test Animals: Male and female beagles were assigned at random to three treatment groups (3 dogs/sex/group) in a three-way crossover design. Dogs were approximately 5 months old and 7-11 kg in weight at treatment initiation. Fasting was achieved by withholding food overnight until two hours after dose administration.

        iii. Dosage Form: The tablets were identical to the proposed market formulation. Etodolac in aqueous solution was used for the oral gavage treatment.

        iv. Doses Used: The dose was approximately 150 mg of etodolac.

        v. Route of Administration: Oral.

        vi. Treatment Duration: Single dose.

        vii. Parameters Measured:

            1. Plasma etodolac concentrations

            2. General health observations

            3. Body weight

d. Results: 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 is 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., at steady-state). Pharmacokinetic parameters estimated in a crossover study (fed vs. fasted) in eighteen 5 month beagle dogs are summarized in the following table:

Table 3. 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} (mg/mL)	22.0 + 6.42	16.9 + 8.84
T_{max} (hours)	1.69 + 0.69	1.08 + 0.46
$AUC_{0-¥}$(ug· 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

e. Conclusions: 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.

f. Adverse Reactions: All three etodolac dosing regimens were well tolerated, and all dogs gained weight during the study.

2. Pharmacokinetics in Dogs with Reduced Kidney Function

a. Type of Study: Pharmacokinetics

b. Investigator:

Dr. M. Kraml
Ayerst Research Laboratories
Chazy, NY 12921

c. General Design:

i. Purpose: The study was conducted to determine the pharmacokinetics of etodolac and effects on renal function in dogs in which kidney mass had been surgically reduced by 75%.

ii. Test Animals: A total of 12 Beagles weighing 10 to 12 kg body weight were employed in a series of three experiments.

iii. Experiments: Four dogs received 200 mg of etodolac daily for five days before and after surgical reduction of kidney mass. Four dogs received a single dose of 200 mg of etodolac before and after surgical reduction of kidney mass. In 4 dogs with reduced kidney mass, clearance of p-aminohippurate before or one hour after a single dose of 200 mg of etodolac was measured.

iv. Dosage Form: Etodolac powder.

v. Route of Administration: Oral.

vi. Treatment Duration: Single oral doses up to 5 days.

vii. Parameters Measured: Concentrations of etodolac in the serum, hematological and blood biochemical determinations, and urinalysis

d. Results: In the first experiment, four dogs were administered an etodolac regimen of five daily doses before and after surgical reduction of kidney mass. Etodolac bioavailability as measured by area under the concentration by time curve (AUC) was unaffected. This finding was expected due to the low contribution of urinary excretion to elimination of etodolac in normal dogs.

In the second experiment, renal function in dogs with reduced kidney mass was studied before and after a single administration of etodolac. Etodolac treatment had no effect on serum albumin or total protein concentrations, or urine volume. Similarly, excretion of potassium, sodium, chloride, or creatinine were unaffected.

A third experiment, using dogs with reduced kidney mass, measured the clearance of p-aminohippurate before or one hour after a single dose of etodolac. Clearance of p-aminohippurate was unaffected by etodolac treatment.

e. Conclusions: 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 very little etodolac is cleared by the kidneys in normal animals. Most of etodolac and its metabolites are eliminated via the liver and feces. In addition, etodolac is believed to undergo enterohepatic recirculation. (See Cayen, M.N., M. Kraml, E.S. Ferdinandi, El Greselin, D. Dvornik. The Metabolic Disposition of Etodolac in Rats, Dogs, and Man. Drug Metab. Revs. (1981) 12:339-362.)

IV. HUMAN FOOD SAFETY

Data on human food safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is to be labeled for use in dogs, which are non-food animals. Human Safety Relative to Possession, Handling, and Administration: Labeling contains adequate warning statements relative to user safety.

V. AGENCY CONCLUSIONS

Data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrate that EtoGesic™; (etodolac), when used according to labeled conditions, is safe and effective.

EtoGesic™; is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is required to determine when a dog has a condition such as osteoarthritis, and to monitor the dog for signs of adverse reactions.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for five years of marketing exclusivity beginning on the date of approval because no active ingredient, including any ester or salt of the active ingredient, of the drug has been approved in any other application.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.