Date of Approval: September 7, 2007

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-274

ETOGESIC Injectable

etodolac
injectable
Dogs

For the control of pain and inflammation associated with osteoarthritis in dogs.

Sponsored by:

Fort Dodge Animal Health

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number:	NADA 141-274
B. Sponsor:	Fort Dodge Animal Health Division of Wyeth 800 Fifth St. NW. Fort Dodge, IA 50501 Drug Labeler Code: 000856
C. Proprietary Name(s):	ETOGESIC Injectable
D. Established Name(s):	etodolac
E. Pharmacological Category:	NSAID (non-steroidal, anti-inflammatory drug)
F. Dosage Form(s):	Sterile injectable solution
G. Amount of Active Ingredient(s):	Each mL of ETOGESIC Injectable contains 100 mg of etodolac
H. How Supplied:	50 mL vial
I. How Dispensed:	Rx
J. Dosage(s):	The recommended dose of ETOGESIC Injectable is 4.5 to 6.8 mg/lb (10 to 15 mg/kg) body weight as a dorsoscapular subcutaneous (SQ) injection. If needed, the daily dose of ETOGESIC Tablets may be given 24 hours after the injectable.
K. Route(s) of Administration:	Subcutaneous injection
L. Species/Class(es):	Dogs
M. Indication(s):	ETOGESIC Injectable is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

II. EFFECTIVENESS:

A. Dosage Characterization:

Clinical effectiveness of the recommended dose of 10 to 15 mg/kg body weight (b.w.) once daily was established in association with the approved ETOGESIC Tablets for dogs (NADA 141-108, approved July 22, 1998).

The pharmacokinetics of ETOGESIC Injectable were evaluated in a laboratory study confirming comparable systemic drug exposure when dogs were administered 15 mg/kg ETOGESIC Injectable or ETOGESIC Tablets. Refer to the bioequivalence study below (Substantial Evidence).

B. Substantial Evidence:

ETOGESIC Injectable was evaluated in a bioavailability comparison of etodolac plasma concentrations using the injectable and oral formulations.

1. Title: Relative bioavailability comparison of etodolac plasma concentrations when administered to dogs subcutaneously in a 10% w/v injectable solution and in a tablet formulation.

   a) Type of Study: Blood Level Bioequivalence (GLP study)

   b) Study Director: Dr. Charles E. Heird
   Southwest Bio-Labs, Inc.
   Las Cruces, New Mexico

   c) General Design:

      1. Purpose: The objective of this study was to compare the pharmacokinetic profile of ETOGESIC Injectable administered subcutaneously to ETOGESIC Tablets in dogs; and to evaluate injection site reactions following administration of ETOGESIC Injectable.

      2. Study Design: The study was designed as a two-treatment, two-sequence crossover evaluation using 36 dogs, with a 14-day washout interval between treatments. Treatments were as follows:

Table 1. Treatment Groups

Treatment	Formulation	Route	Dose Rate
A	ETOGESIC Injectable	Subcutaneous (right scapular region)	15 mg etodolac/kg b.w.
B	ETOGESIC Tablets	oral	Minimum dose providing at least 10 mg etodolac/kg b.w. using half-tablet increments

Within sexes, animals were placed into groups of two, and animals within each group were randomly assigned to treatment sequence 1 or treatment sequence 2. The 18 dogs in treatment sequence 1 received Treatment A in Period 1 and Treatment B in Period 2; the 18 dogs in treatment sequence 2 received Treatment B in Period 1 and Treatment A in Period 2. Treatments were administered to dogs on Day 0 (Period 1) and Day 14 (Period 2) following an overnight fast. Eating was not permitted for at least three hours after dosing. Blood samples were collected from dogs prior to treatments, then 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 18, 24, 36, and 48 hours after treatment.

3. Test Animals: Thirty-six purpose-bred Beagles (18 females and 18 males) 12 months of age or older
4. Control Drug: none
5. Dosage Form: injectable solution (proposed commercial formulation) and tablets (commercial formulation)
6. Route of Administration: subcutaneous injection and oral route
7. Dosage used: etodolac: 15 mg/kg injectable and a minimum of 10 mg/kg of the tablet formulation based on half-tablet increments
8. Test duration: 22 days
9. Variables Measured: Total (free + bound) concentrations of etodolac in plasma samples were quantified using a non-stereospecific high performance liquid chromatography (HPLC) analytical method. Dogs were observed at least once daily from Day -7 through Day 21. Animals were observed prior to each treatment, immediately post-dosing for injection reactions, at approximately 1, 4, and 12 hours following treatment, and then daily for seven days thereafter.

Plasma etodolac concentrations measured in dogs treated with tablets were dose-normalized to a theoretical etodolac dosing rate of 15 mg etodolac/kg b.w. This normalization procedure was corrected for variance in the actual mg/kg dose received by dogs when the oral tablets were administered. To avoid normalization-induced bias in the

treatment variability estimates, etodolac concentrations resulting from the injectable product were also corrected for differences between actual versus targeted (15 mg/kg) doses.

The pivotal pharmacokinetic variables used in the relative bioavailability determination included area under the concentration (AUC) versus time curve from hour 0 – 4 (AUC_{0-4}) and from hour zero to the last quantifiable drug concentration (AUC_{0-LOQ}). The observed peak concentrations (C_{max}), while considered in the overall comparability determination, were evaluated from a safety rather than an effectiveness perspective. AUC_{0-4} was used as a pharmacokinetic surrogate to confirm product comparability in early onset of pain relief. The time to C_{max} (T_{max}) and terminal elimination half life (T½) were considered secondary variables.

Statistical analysis of these data included an analysis of variance procedure, using the following model terms: animal, animal nested within sequence, period, and treatment. Sequence, period and treatment were considered to be fixed effects, while animal was considered to be a random effect. The mean square error associated with this model was used for determining the width of the confidence interval. The error term "animal within sequence" was used to confirm the absence of a statistically significant sequence effect. In an initial analytical step, potential gender differences associated with AUC_{0-LOQ} and C_{max} were analyzed using the model terms sequence, sex nested within sequence, animal nested within sex and sequence, period, treatment, and the interaction term treatment by sex. The effects associated with the terms sex nested within sequence and treatment by sex were not statistically significant. Accordingly, the error associated with these terms was pooled back into the residual sums of squares. The parameter values for $AUC_{0-LOQ,}$ AUC_{0-4} and C_{max} were transformed to their corresponding natural logarithms prior to analysis. The least square means (LSMEAN) for AUC_{0-LOQ}, $AUC_{0-4,}$ and C_{max} among dogs treated with ETOGESIC Injectable were compared to least square means among dogs treated with ETOGESIC Tablets by the 2-one-sided least significant difference (LSD) t-test at the 10% level ($\alpha = 0.05$ for the upper and lower tails, respectively).

d) Results:

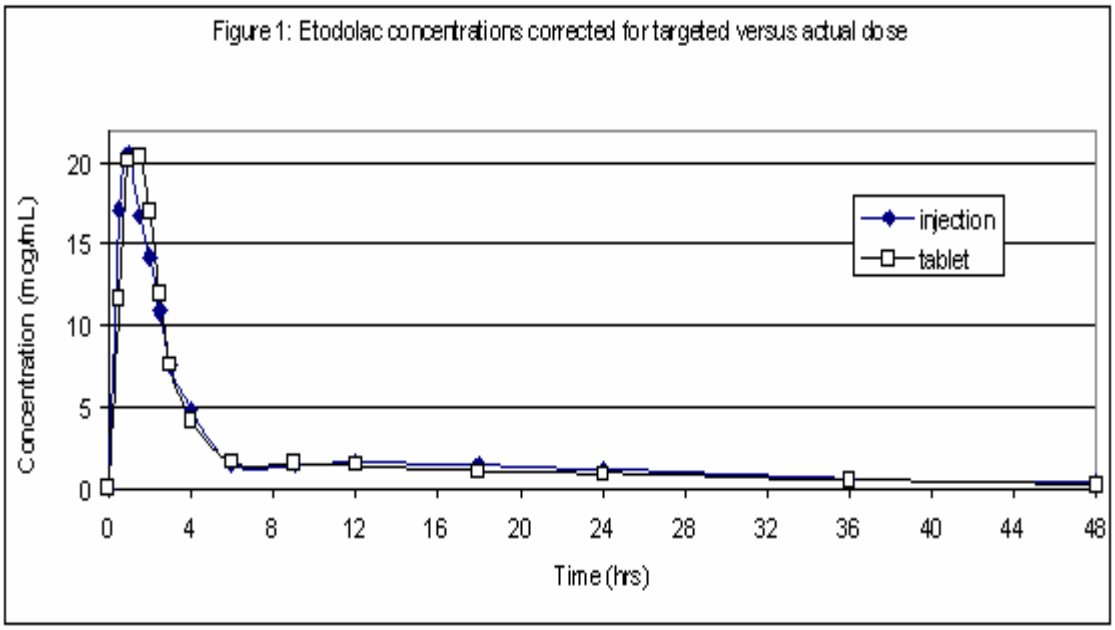
Bioavailability: The composite etodolac blood concentrations resulting from either Treatments A and B were similar, regardless of whether dose-normalized concentrations or actual observed concentrations were considered (Figures 1 and 2). Generally, drug concentrations in the blood appeared slightly sooner (~ 0.5 hr) following administration of the injectable formulation as compared to the tablet, but peak concentrations tended to be slightly higher with the tablet as compared to the injection. Accordingly, the two products demonstrated equivalent total drug exposure (as defined by $AUC_{0\text{-}LOQ}$) and initial exposure (as defined by $AUC_{0\text{-}4}$), but were not equivalent with regard to C_{max} (Table 1). As $AUC_{0\text{-}4}$ is a surrogate for the early onset of pain relief, differences in C_{max} are considered therapeutically inconsequential. Moreover, as peak concentrations were lower after (SQ) as compared to oral administration, these data confirmed that use of the injectable product would not result in unexpected systemic adverse reactions.

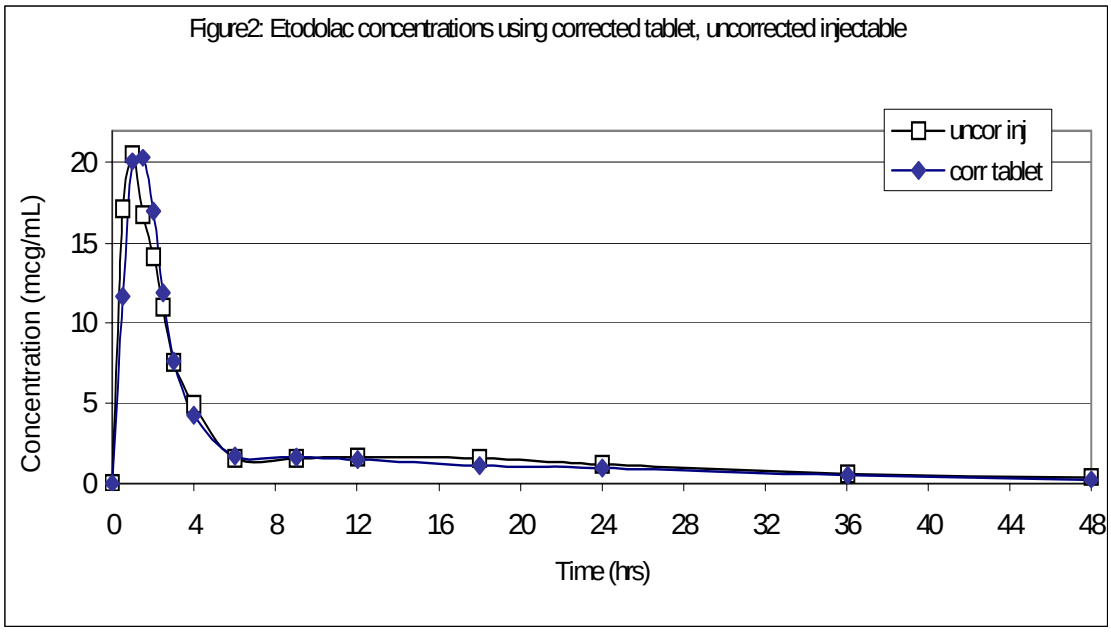
Table 2: Mean Pharmacokinetic Parameters Estimated in 36 Fasted Beagle Dogs After Administration of Etodolac[1] (Arithmetic Mean ± Standard Deviation except as noted)

[1] Based upon concentrations normalized to expected values if actual administered dose = 15 mg/kg

	Injectable Mean	Tablet Mean	Ratio Injectable/Tablet	LCL	UCL
$AUC_{0\text{-}LOQ}$ (mcg*hr/mL)	97 ± 34	90 ± 32	1.08	0.98	1.19
C_{max} (mcg/mL)	21 ± 7	25 ± 9	0.83	0.73	1.02
$AUC_{0\text{-}4}$ (mcg*hr/mL)	48 ± 16	48 ± 26	0.99	0.92	1.06
T_{max} (hr)	1.02 ± 0.46	1.42 ± 0.57			
$T_{1/2}$ (hr)*	12.2 ± 4.3	11.7 ± 4.0			

* harmonic mean, LCL = lower confidence limit, UCL = upper confidence limit





Based upon the systemic etodolac concentrations resulting from the administration of Treatments A and B, the systemic safety and product effectiveness for the control of pain and inflammation associated with osteoarthritis in dogs, resulting from identical doses of the ETOGESIC Tablets and ETOGESIC Injectable are equivalent.

Injection site reactions: All 36 dogs were monitored for injection site reactions after administration of the labeled dose in the dorsoscapular area. Observable discomfort to the injection was seen in 16 of the 36 dogs

following treatment. Signs included vocalizing and/or whining, scratching, rubbing, licking and/or biting at the injection site, and rolling in the cage. Most signs abated within 30 seconds for 12 dogs. The clinical signs of discomfort lasted between two and 14 minutes in the remaining four dogs.

Injection site examinations over the course of the study showed hyperemia (redness) and/or irritation in seven dogs receiving ETOGESIC Injectable. This lasted up to 12 hours post-injection in six dogs and 24 hours post-injection in one dog.

Abrasions were observed in two dogs receiving ETOGESIC Injectable. This was observed in one dog from Day 2 through Day 5 post-injection, and from Day 10 through Day 13 post-injection in the other dog.

Swellings were observed in three dogs one hour post-injection and resolved by four hours post-injection. Edema was present in three dogs at one hour post-injection. The edema was resolved in two dogs by the four hour post-injection observation and by the 12 hour post-injection observation in the other dog.

e) Conclusions: As equivalence was shown between ETOGESIC Injectable and ETOGESIC Tablets for both $AUC_{0\text{-}LOQ}$ and $AUC_{0\text{-}4}$, these two products were determined to be therapeutically equivalent in terms of systemic safety and effectiveness.

Some dogs experienced irritation, hyperemia and swellings at the injection site. Most reactions were mild and resolved within 24 hours. Some injection site swellings developed a few days following injections and lasted approximately three days.

f) Adverse Reactions: Two dogs vomited during the study (a total of 4 episodes). There was one episode of soft stool in one dog.

III. TARGET ANIMAL SAFETY:

Studies demonstrating the safety of ETOGESIC Tablets for use in dogs are contained in the original FOI summary (NADA 141-108) dated July 22, 1998. No additional animal safety data beyond injection site toleration were required for approval of this NADA.

A. Injection Site Tolerance Study

1) Title**:** Injection site tolerance of 10% w/v etodolac solution injected subcutaneously in canines at the rate of 30 mg/kg b.w. (2X dose).

a) Type of Study: Safety (GLP study)

b) Study Director: Dr. Erin Ivey Weich
Southwest Bio-Labs, Inc.
Las Cruces, New Mexico

c) General Design:

1. Purpose: The objective of this study was to document any injection site reactions in dogs receiving a single, subcutaneous injection of sterile saline (0.3 mL/kg b.w.) or ETOGESIC Injectable (etodolac 30 mg/kg b.w., 0.3 mL/kg b.w.). The ETOGESIC dose tested represents twice the labeled dose.

2. Study Design: Eight dogs (four males, four females) were randomly assigned to either Group A or Group B. Treatments were administered in the dorsoscapular area on Day 0, as follows:

Table 3. Treatment Groups

Tx Group	Dose mg/kg	Number and Sex of Dogs
A	ETOGESIC Injectable 10% (2X)	8 (4M, 4F)
B	Sodium chloride	8 (4M, 4F)

3. Test Animals: Sixteen Beagles (8 females and 8 males) at least 12 months of age.

4. Control Drug: 0.9 % sterile saline

5. Dosage Form: injectable solution (proposed commercial formulation)

6. Route of Administration: subcutaneous injection

7. Dosage used: 30 mg/kg ETOGESIC (etodolac) Injectable or equal quantities of sterile saline

8. Test duration: eight days

9. Variables Measured: Injection sites were evaluated for visible and palpable changes. Evaluated signs included swelling, heat, edema, erythema, ulceration, pain, or any other abnormality to the hair, skin, or underlying tissues. Table 4 shows the variables assessed for the injection site analysis.

   Injection sites were examined prior to injections on Day 0, immediately following injection, and at 1 hour, 4 hours, and 12 hours following injections. Thereafter, the injection sites were examined daily for seven days (at least once daily observations from Day -8 to Day 7).

Table 4: Injection Site Observations

Variable Observed	**Possible Outcome**
Visible Data	
Swelling visually noticeable?	Yes or No
Erythema observed?	Yes or No
Exudate present?	Yes or No
Tactile Data	
Swelling palpable?	Yes or No
Swelling length, long axis	Measured in centimeters (cm)
Swelling width, short axis	Measured in cm
Swelling maximum height	Measured in cm
Nature of swelling	None (score = 0), soft, diffuse (score = 1), firm (score = 2)
Pain on palpation?	Yes or No
Injection site warm to touch?	Yes or No

Physical examinations were performed on each dog pre-study (Day -5). Daily general health observations of all animals included evaluation of behavioral signs for pain, or irritation immediately following injection administration.

d) Results: Actual amounts of etodolac administered during this study ranged from 2.3 to 3.3 mL per dog. Five of the eight dogs treated with ETOGESIC Injectable showed signs of discomfort and/or agitation following injection. Signs included vocalizing, licking, scratching, and/or rubbing at the injection site.

In summary, injection site swellings were observed in three saline-treated dogs through Day 2. Similarly, seven etodolac-treated dogs had visible/palpable injection site swellings through Day 4 at various time points. There were palpable swellings noted in three saline-treated dogs through Day 2. See Table 5 for specific number of dogs represented at each individual observation time.

Table 5: Number of Visible and/or Palpable Injection Site Swellings

Observation/ Time	**saline (n=8)**	**10 % etodolac (n=8)**
Visible swelling		
Pretreatment	0	0
1 hour	0	2
4 hours	2	6
12 hours	1	5
Day 1	2	5
Day 2	2	5
Day 3	0	3
Palpable swelling		
Pretreatment	0	0
1 hour	1	2
4 hours	2	6
12 hours	1	5
Day 1	2	5
Day 2	2	5
Day 3	0	3
Day 4	0	1

Consistency of Swellings: Consistency was scored as 0 = no swelling, 1 = soft, diffuse swelling, or 2 = firm swellings. No dogs in the study scored a "2" (no firm swellings). See Table 6.

Table 6: Consistency Scores for Swelling Observations

	saline		**10% etodolac**	
	Score = 0	**Score = 1**	**Score = 0**	**Score = 1**
Pretreatment	8 dogs	0	8	0
1 hour	7	1	6	2
4 hours	6	2	2	**6**
12 hours	7	1	3	**5**
Day 1	6	2	3	**5**
Day 2	6	2	3	**5**
Day 3	8	0	5	**3**
Day 4	8	0	7	**1**

Bolded numbers = swelling scores are greater for more etodolac dogs compared to the number of saline dogs

Swelling Dimensions (length X width X height, cm): The specific dimensions of any observed swellings were measured in centimeters (cm). There were larger dimensions among the etodolac group compared to the saline group. No measurable swellings were reported for Days 5, 6, and 7. See Table 7.

Table 7: Mean Swelling Dimension Measurements

	saline			**10% etodolac**		
	Long axis (cm)	**Short axis (cm)**	**Height (cm)**	**Long axis (cm)**	**Short axis (cm)**	**Height (cm)**
Pretreatment	0	0	0	0	0	0
1 hour	0.38	0.28	0.05	0.93	0.54	0.14
4 hour	0.66	0.58	0.08	2.65	1.75	0.33
12 hour	0.44	0.44	0.05	2.21	1.59	0.30
Day 1	0.74	0.66	0.09	2.03	1.53	0.24
Day 2	0.73	0.53	0.08	1.88	1.48	0.23
Day 3	0	0	0	0.79	0.75	0.09
Day 4	0	0	0	0.13	0.10	0.03

No swellings were palpated after Day 4.

e) Conclusions: Initial reactions to ETOGESIC injections included vocalizing, rubbing, biting, and scratching at the injection site. There were palpable and/or visible swellings at the injection site through Day 3 (three etodolac-treated dogs) and through Day 4 for one etodolac-treated dog. The swelling present on Day 4 was resolved by Day 5.

B. Bioaccumulation Study

1) Title: Bioaccumulation of etodolac in plasma of dogs injected repeatedly with 10% (w/v) etodolac formulation.

a) Type of Study: Bioaccumulation (GLP study)

b) Study Director: Dr. John Byrd
Southwest Bio-Labs, Inc.
Las Cruces, New Mexico

c) General Design:

1. Purpose: The objective of this study was to evaluate the bioaccumulation of etodolac in plasma from dogs injected repeatedly with ETOGESIC Injectable administered subcutaneously once daily for five consecutive days.

2. Study Design: The study utilized a single-treatment group. ETOGESIC Injectable product was administered subcutaneously for five consecutive days in the dorsoscapular region. Injection sites were alternated between the right dorsoscapular and left dorsoscapular sites each day:

Table 8. Drug Administration

Formulation	Route	Dose Rate
ETOGESIC Injectable	Subcutaneous (scapular region, alternating sides daily)	15 mg etodolac/kg b.w.

Dogs were adult, purpose-bred, female beagles of at least one year of age. Seven of the 14 dogs used in the study were randomly selected for treatment initially on the right dorsoscapular area and seven were selected for treatment initially on the left dorsoscapular area. All treatments followed an overnight fast, and dogs were not fed for at least three hours after dosing. Blood samples were collected from dogs prior to the first, third and fifth treatments, and at the following times following the first, third and fifth injections: 0.5, 1, 1.5, 2, 4, 6, 12, 18 and 23.5 hours.

3. Test Animals: Fourteen purpose-bred, female Beagles 12 months of age or older

4. Control Drug: None

5. Dosage Form: injectable solution (proposed commercial formulation)

6. Route of Administration: subcutaneous injection

7. Dosage used: 15 mg etodolac/kg ETOGESIC Injectable

8. Test duration: 12 days

9. Variables Measured: Total (free + bound) concentrations of etodolac in plasma samples were quantified using a non-stereospecific high performance liquid chromatography (HPLC). Dogs were observed at least once daily from Day –7 through Day 11. Animals were observed prior to each treatment, at approximately 1, 4, and 12 hours following each treatment, and then once daily for seven days following the fifth treatment.

   Pivotal pharmacokinetic variables compared to evaluate bioaccumulation were area under the concentration (AUC) versus time curve from hour zero to infinity following the first dose ($AUC_{0-\infty}$) versus etodolac concentrations over a single dosing interval ($AUC_{0-\tau}$) following the third and fifth doses of etodolac. Maximum observed plasma etodolac concentration (C_{max}), time to C_{max} (T_{max}), and the terminal elimination rate constant (K_e) were considered secondary variables.

   The statistical model evaluated the within-subject fixed effects of treatment day by comparing $AUC_{0-\infty}$ on Day 0 to $AUC_{0-\tau}$ on either Day 2 or Day 4. Comparisons were based upon the use of Ln-transformed AUC values. Ln-transformed $AUC_{0-\infty}$ values for Day 0 were compared to the Ln-transformed $AUC_{0-\tau}$ values estimated during Days 2 and 4.

d) Results:

The results from this experiment (Table 6) showed that the mean $AUC_{0-\infty}$ following the first treatment of dogs with 10% (w/v) Etodolac Injectable at the rate of 15 mg etodolac/kg b.w. on Day 0 (Dose 1) was not statistically different ($P > 0.05$) than $AUC_{0-\tau}$ following the third and fifth treatments at the same dosing rate.

Table 9. Means of Primary and Secondary Pharmacokinetic Variables from Experiment 0790-C-US-03-05

Variable[1]	Day 0	Day 2	Day 4
Primary parameters			
$AUC_{0-\infty}$, mcg•hr/mL	109 ± 75	NA	NA
$AUC_{0-\tau}$, mcg•hr/mL	81 ± 31	110 ± 41*	93 ± 15*
Secondary parameters			
C_{max}, mcg/mL	15.88 ± 4.54	21.64 ± 5.33	23.33 ± 4.59
T_{max}, hr	1.82 ± 0.32	1.43 ± 0.33	1.21 ± 0.47
K_e, mcg•mL/hr	0.09 ± 0.02	0.08 ± 0.02	0.11 ± 0.03
$T_{1/2}$, hr	8.39 ± 2.89	9.76 ± 4.21	6.90 ± 2.08

[1] Arithmetic treatment means ± standard deviations of secondary variables. Statistical comparison of secondary variables was not performed.

* Value of $AUC_{0-\tau}$ (μg•hr/mL) is not different than value of $AUC_{0-\infty}$ (μg•hr/mL) following treatment on Day 0 by the 2-sided t-test ($P < 0.05$).

Injection site reactions: All 14 dogs were monitored for injection site reactions from before the first treatment through Day 7. Of the 14 study dogs, no lesions were observed at any time on three dogs (except for scratches and abrasions present before treatment). The remaining 11 dogs had injection site observations that included soft, diffuse swellings that persisted up to 12 hours after treatment. Eight of the 14 dogs had evidence of these transient swellings after one or more of the injections with 10% (w/v) Etodolac Injectable.

One dog had soft, diffuse swelling at 1, 4, 12, and 25 hours after injection on Day 1. This dog also had injection site hyperemia 25 and 28 hours after the Day 1 injection and at 4 and 12 hours after the Day 2 injection. The Day 2 injection site remained tender through Day 8. Injection sites on six dogs appeared tender following repeated injections. Tenderness at the injection sites correlated with affected sites receiving two or three injections per area. In summary, soft diffuse swellings appeared transient and most resolved by 12 hours post-injection. Tenderness was noted on several dogs following repeated injections at the same site.

e) Conclusions: Results from this experiment showed that the mean $AUC_{0-\infty}$ following the first treatment of dogs with 10% (w/v) Etodolac Injectable at the rate of 15 mg etodolac/kg b.w. was not statistically different ($P > 0.05$) than $AUC_{0-\tau}$ following the third and fifth treatments at the same dosing rate. Therefore, the observed magnitude of etodolac bioaccumulation, as estimated on the basis of the ratios of C_{max} values and $AUC_{0-\tau}$ values across study days, is consistent with linear pharmacokinetics. Observations of injection sites suggested that treatment of dogs with ETOGESIC Injection at a rate of 15 mg etodolac/kg b.w. caused transient swellings at the injection site in some dogs.

Swollen areas were mild, and appeared to resolve quickly. Tenderness at some injection sites may be a result of dogs being injected in the same area on more than one occasion.

f) Adverse Reactions: One dog had blood in the stool on Days 3 and 4. A definitive cause for the presence of blood in feces from this dog was not determined.

C. Comparison of Two Etodolac Injectable Formulations (Two Studies):

A study comparing two etodolac formulations administered in the dorsoscapular area of dogs.

1) Title**:** Evaluation of injection site acceptability of two etodolac injectable formulations following subcutaneous administration into the dorsal scapular region in dogs.

a) Type of Study: Safety (non-GLP study)

b) Study Director: Dr. Deborah Dietrich
Fort Dodge Animal Health
Charles City, IA

c) General Design:

1. Purpose: The purpose of this experiment was to compare two formulations of etodolac for clinical signs of irritation and injection site acceptability following administration of the formulations subcutaneously into the dorsoscapular region of the dogs. Treatment B was a non-GMP laboratory scale batch of the proposed final market formulation.

2. Study Design: Dogs were randomly assigned to either Treatment A or Treatment B. Treatments were administered in the scapular (shoulder) area as follows:

Table 10. Treatment Groups

Treatment Group	Day 0	Day 4	Number/Sex of Dogs
1	Treatment A	Treatment B	8 (4M, 4F)
2	Treatment B	Treatment A	8 (4M, 4F)
3		Four dogs – Treatment A Four dogs – Treatment B	4 (2M, 2F) 4 (2M, 2F)

Treatment A was a 10% w/v etodolac formulation with a lower osmolality than the final market formulation.

Treatment B was a 10% w/v etodolac formulation (non-GMP laboratory scale batch of the proposed final market formulation).

3. Test Animals: Twenty-four healthy dogs (12 females and 12 males) at least 12 months of age

4. Control Drug: none

5. Dosage Form: injectable solution

6. Route of Administration: subcutaneous injection

7. Dosage used: The test articles were administered subcutaneously once on each test day, at 0.15 mL/kg b.w. (15 mg/kg etodolac) in the scapular region. Injections on Day 0 and Day 4 were administered in alternating scapular areas.

8. Test duration: 29 days

9. Variables Measured: All injection sites were evaluated at the time of administration and for approximately four minutes following injection.

d) Results: A total of 20 dogs received Treatment A and 20 dogs received Treatment B. Only data pertaining to the proposed final market formulation (Treatment B) are presented below. Seventeen dogs receiving Treatment B showed signs of discomfort. See Table 11.

Table 11: Results of Behavioral Signs Following Treatment B (etodolac) Injections

Behavioral Sign	Treatment B
# scratched at site	16
# bit at site	8
# rubbed at site	3
# circled	2
# turned head to site	1
# vocalized	1

Most dogs reacted within 30 seconds to the etodolac injections by intermittently scratching and/or biting at the injection site for a few seconds to greater than four minutes.

There were no cases of severe swelling. There were transient, mild swellings for all injections that resolved within 24-48 hours for Treatment B.

In 17 of 20 dogs, no swelling was noted after Day 2 through Day 28. One dog had swelling that lasted through the last observation on Day 28. Two dogs had reoccurrence of swelling on Day 14. The swelling persisted through Day 18 for one dog, and through the last observation on Day 28 for the remaining dog. These latter swellings were different from the soft swellings initially observed and were usually characterized as firm nodules.

e) Conclusions: There were signs of discomfort following Treatment B (non-GMP laboratory scale batch of the proposed final market formulation) after subcutaneous injection into the scapular region. The most common behavioral signs included scratching and biting at the injection site.

Subcutaneous injections caused soft, initial swellings in most dogs. The initial swellings generally resolved within 24-48 hours post-injection. Delayed firm nodules were also noted in 15% of the dogs administered Treatment B.

A study comparing two etodolac injectable formulations administered in the dorsoscapular area, mid-neck, and left flank.

1) Title: Evaluation of injection site acceptability of 10% w/v etodolac injectable formulation with 3% w/v benzyl alcohol (non-GMP laboratory scale batch of the proposed final market formulation) following subcutaneous administration in dogs.

a) Type of study: Safety (non-GLP)

b) Study Director: Dr. Deborah Dietrich
Fort Dodge Animal Health
Charles City, IA

c) General Design:

1. Purpose: To evaluate injection sites following administration of two etodolac formulations and observe for clinical signs of irritation following subcutaneous administration in dogs. The results were compared to a saline control.

2. Study Design: The study evaluated two etodolac formulations following subcutaneous injections at three different injection sites. On Day -13, the 18 dogs were randomly assigned to treatment groups. Treatments were as follows:

Table 12. Treatment Groups

Treatment Group	Treatment	Dose (mL/kg b.w.)	Number/Sex of Dogs
A	0 (saline)	0.15 mL/kg	1M, 1F
B	10% w/v etodolac	0.15 mL/kg	5M, 3F
C	10% w/v etodolac	0.15 mL/kg	4M, 4F

Treatment group B received a 10% w/v etodolac formulation containing 1% benzyl alcohol. Treatment group C received a 10% w/v etodolac formulation containing 3% benzyl alcohol, and represented a non-GMP laboratory scale batch of the proposed final market formulation.

3. Test Animals: 18 healthy Beagles (10 male, 8 female)

4. Control Drug: 0.9% sodium chloride (sterile)

5. Dosage form: injectable solutions

6. Route of Administration: subcutaneous injection

7. Dosage used: All three test articles were administered subcutaneously once a day, at 0.15 mL/kg b.w. Animals in Treatment groups B and C received 15 mg/kg etodolac.
   Day 0 - the dorsoscapular region
   Day 1 - the mid-neck area
   Day 2 - the left dorsal flank

8. Test duration: 32 days

9. Variables measured: All injection sites were evaluated via visible and palpation examinations at 1, 2, 4, and 7 hours post-injection, then daily (Days 3-7) and twice weekly (Days 10-31). Evaluations included observations of swelling, heat, edema, pain or any other abnormality to the skin or underlying tissue. Swellings were also measured in centimeters (length X width X height).

d) Results:

Only data pertaining to the proposed final market formulation (Treatment C) and the saline control (Treatment A) are presented below.

Results of injections administered in the scapular region (above the shoulder blades): Treatment A – There were no abnormalities for the saline group (n = 2). Treatment C – All eight dogs had visible swelling one hour post-injection. The swollen areas were largest at the 4 hour post-injection observation (average swelling size = 5.4 X 4.9 X 0.6 cm). All swollen areas resolved by 24 hours.

Results of injections administered in the mid-neck region: Treatment A – There were no abnormalities for the saline group (n = 2). Treatment C – All eight dogs had visible swelling one hour post-injection. The swollen areas were largest (n = 7) at the 7 hour post-injection observation (average swelling size = 6.1 X 4.7 X 0.6 cm). All swollen areas resolved by 24 hours.

Results of injections administered in the flank area: Treatment A – There were no abnormalities for the saline group (n = 2). Treatment C – All eight dogs had visible swelling one to two hours post-injection. The swollen areas were largest at the 4 hour post-injection observation (average swelling size = 5.1 X 4.9 X 0.7 cm). Swollen areas resolved in seven hours for four dogs, by 24

hours for three dogs, and within 48 hours for one dog. Four Treatment C dogs developed palpable, firm nodules at the injection sites 12-26 days post-injection. The four nodules lasted 3 days (n = 1), 4 days (n = 1), 11 days (n = 1), and 13 days (n=1), respectively.

e) Conclusions: Injection of etodolac may cause injection site reactions in the initial 24 hours post-injection. There may also be delayed nodule formation at the site of injection, noted approximately two weeks post-injection and lasting between 3 - 13 days.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ETOGESIC:

"Not for human use. Keep this and all drugs out of the reach of children. Consult a physician in case of accidental exposure by humans."

The following items were examined to ensure human user safety: the MSDS for etodolac, the FOI Summary for ETOGESIC Tablets (NADA 141-108), and the data submitted in support of this NADA. According to the MSDS for the active ingredient (dated 1996, Fort Dodge), the active ingredient is toxic when absorbed through inhalation and ingestion. Absorption of the active ingredient from ETOGESIC Injectable by inhalation or ingestion is unlikely, as the product is for injection.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that ETOGESIC Injectable, when used according to the label, is safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs. Additionally, data demonstrate that residues in food products derived from dogs treated with ETOGESIC Injectable will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose canine osteoarthritis and to monitor response to treatment. Furthermore, the veterinarian monitors patients for possible adverse reactions to the drug.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. This exclusivity is based on the bioequivalence and injection site tolerance studies conducted for this approval.

C. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling:
a. Veterinary Package insert
b. Bottle – 50 mL
c. Carton – 50 mL