Clinical Effectiveness and Safety of a New NSAID, Firocoxib: A 1,000 Dog Study*

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CLINICAL RELEVANCE

For the Previcox (firocoxib, Merial) Experience Trial, practicing veterinarians across the United States were asked to enroll dogs diagnosed with osteoarthritis. At an initial visit, owners of dogs deemed suitable for NSAID therapy were given Previcox and instructed to maintain a daily diary and to return 10 and 40 days after treatment began. Approximately 86% of 1,002 enrolled dogs completed the study. The withdrawal rate associated with gastrointestinal side effects was low (2.9% of dogs), and no serious drug-related adverse events were reported. Investigators and owners rated 93% and 91% of dogs, respectively, as improved, and 86% of owners rated their dogs "happier" or "more active" after treatment with firocoxib. The improvements observed following initiation of firocoxib therapy were independent of gender, breed, starting body weight, age, and prior NSAID use. These results support previous findings that firocoxib is well tolerated and effective when used under field conditions.

INTRODUCTION

Previcox (firocoxib, Merial) is a cyclooxygenase (COX)-2–selective/COX-1–sparing NSAID developed specifically for veterinary use following demonstration in canine whole blood assays that it is approximately 380-fold selective for COX-2 over COX-1.[1] While these COX enzymes are believed to play a role in the health and repair of the gastrointestinal mucosa, the failure of nonselective NSAIDs to spare COX-1 has been indicted as the major factor contributing to the adverse effects associated with their use.[2] Serum levels of firocoxib necessary to provide peak inhibition of COX-2 have little impact (0%–3%) on COX-1 activity, and field trials have demonstrated

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that firocoxib is associated with fewer side effects and improved efficacy over less COX-1–sparing NSAIDs against which it has been compared, including carprofen and etodolac.[3,4]

The objective of the Previcox Experience Trial (PET) was to familiarize veterinarians with the clinical utility of Previcox for the relief of canine osteoarthritis (OA)-related inflammation and pain. The clinical acceptability would be demonstrated by the assessments of participating veterinarians (investigators) and dog owners (owners) of the acceptability and tolerability of firocoxib and the improvement in lameness that it produced. Although the study was undertaken to allow veterinary practitioners and specialists to gain experience with firocoxib, it also allowed the expansion of an already extensive clinical performance database compiled during registration studies.

TABLE 1. NSAID and Steroid Withholding Guidelines for Trial Participation

Agent	*Withdrawal Time*
NSAIDs	
Carprofen (oral)	2–3 d
Carprofen (injectable)	1 d
Deracoxib	1–2 d
Etodolac	2–3 d
Meloxicam	3–5 d
Tepoxalin	2–3 d
Aspirin	10–14 d
Steroids	
Short acting (hydrocortisone and cortisone)	2 d
Intermediate acting (prednisone, prednisolone, methylprednisolone)	7 d
Long acting (dexamethasone, triamcinolone, betamethasone)	4 wk
Repositol type (methylprednisolone acetate, triamcinolone acetonide)	6 wk

MATERIALS AND METHODS

Investigator Qualification and Patient Recruitment

Practicing veterinarians were invited to participate in a live Webcast or to review a Webcast archive that provided an overview of clinical use of NSAIDs in dogs for treatment of OA, a presentation on the newly registered firocoxib, and an outline of the trial protocol. Veterinarians who chose to enroll as investigators were assigned a site number, and identifying information was entered in the PET database.

A trial binder containing the protocol and relevant study forms was then shipped by the Trial Data Coordinator to the participating practices. Firocoxib to be used in the study was also shipped directly to the clinics.

Study Enrollment

Exclusion criteria were provided by Merial, but the decision as to whether a given patient was enrolled in the PET was the responsibility of each investigator, based on his or her clinical assessment of the needs of each patient. Investigators were informed of exclusion criteria, which included recent elective surgery; pregnancy or lactation; concomitant conditions such as gastrointestinal, renal, or hepatic disease; or any evidence of systemic disease or infectious arthritis. Owners of dogs that were receiving an NSAID or corticosteroid at the time of the enrollment visit were asked to observe a washout period thought to be sufficient for clearance before initiating treatment with firocoxib (Table 1).

The enrollment objective was 10 dogs/site at a minimum of 100 sites. Enrollment occurred from the date of the Webcast on April 21, 2005, through October 8, 2005.

Study Design

The protocol, prepared in consultation with

an advisory committee of American College of Veterinary Surgeons–boarded surgeons, required three scheduled office visits:

- Initial enrollment visit (day –3 to day –1)
- A visit 7 to 10 days after initiation of treatment (~day 10 post–treatment initiation)
- Final visit or study end (~day 40 post–treatment initiation)

All candidate dogs enrolled in the trial were to have been diagnosed with OA by an investigator as a prerequisite for inclusion in the trial. Whether such diagnosis included radiology was left to the discretion of each investigator. At the initial visit (day –3 to day –1), the investigator determined that a given patient might be a candidate for the PET (i.e., the dog had a preexisting diagnosis of OA), conducted a physical examination, obtained the required blood samples for comprehensive serum chemistry and hematology analyses, completed a Case Details (Enrollment) Form, dispensed a 10-day supply of firocoxib, and handed out the Owner Observation Form (i.e., owner diary). After a review of the laboratory results, the investigator determined a patient's eligibility for study participation and contacted the owner accordingly.

For the ~day 10 assessment, the patient was returned to the investigator for a physical examination and a repeat of the laboratory work. The owner also brought his or her initial Owner Observation Form for review. The investigator completed a ~day 10 evaluation, which consisted of one question answered separately by the owner and the investigator: "How would you describe the dog's lameness since initial visit?"

Investigators and owners chose from the following:

- Greatly improved
- Moderately improved
- Mildly improved
- Not improved
- Worse

The procedure was similar for the final visit, at which point the investigator reviewed and collected the Owner Observation Form. Owners were asked questions about palatability (whether the dog readily accepted the tablet), convenience (palatability and ease of administration if the dog did not accept the tablet readily), and their impression of the dog's quality of life. After the final visit of the last dog enrolled at each clinic, investigators compiled their PET forms in the PET Binder issued to each investigator before the start of the study.

RESULTS

Enrollment

Investigators at 106 sites in 36 states enrolled 1,002 dogs in the trial. Of these, 954 dogs returned for the ~day 10 evaluation; evaluations for 864 dogs were submitted at the final (~day 40) evaluation. Dogs enrolled slightly favored females over males; ages ranged from 6 months to 16 years, and weights ranged from 4 to 199 lb (1.8–90.5 kg). Mixed-breed dogs represented the largest enrollment category, followed by Labrador retrievers, golden retrievers, and German shepherds. OA was diagnosed in a single joint for approximately half of the enrolled dogs; multiple joint involvement was diagnosed in the remaining animals.

Of the 1,002 dogs enrolled in the study, 458 (46%) were reported as having been treated previously with at least one NSAID; 544 (54%) were reported by investigators as having no history of NSAID treatment. Approximately 23% had a history of treatment with carprofen, 12% with deracoxib, and 11% with meloxicam at some point before initiation of treatment with firocoxib.

NSAIDs used within the week (7 days) before initiation of treatment with firocoxib in-

cluded aspirin, carprofen, deracoxib, etodolac, meloxicam, piroxicam, and tepoxalin. On the Case Details Forms, investigators identified 195 dogs (19.5% of enrollees) as having been treated with carprofen, deracoxib, or meloxicam within the week before treatment with firocoxib.

Trial Noncompleters, Blood Analysis Results, and Potential Adverse Events

From a preliminary screening of 1,135 dogs, 1,002 were enrolled in the study. In general, investigators did not convey their reasons for disqualifying dogs after the preliminary blood screening. However, elimination may be attributed to factors such as blood test results that either were deemed unsatisfactory by the veterinarian or indicated the presence of disease precluding treatment with an NSAID, owner schedules, and other owner-related considerations.

Of the 1,002 dogs enrolled in the study, 135 (13.5%) were withdrawn (Table 2), including 11 reported to have died or been euthanized for reasons not linked to treatment (Table 3). Of the dogs that were withdrawn, the most common single reasons were vomiting (1.9% of the total dogs enrolled) and elevations in blood chemistry (most commonly blood urea nitrogen) that were of concern to the investigator. Although additional events of vomition were recorded in the owner diaries, these episodes were transient and mild and generally were not attributed to treatment. None of the deaths that occurred during the trial were attributable to the types of gastrointestinal, renal, or hepatic events that typically have been associated with NSAID use.

TABLE 2. Categorization of Dogs Not Completing the Study

Explanation for Withdrawal	*No. of Dogs*	*% of Dogs*
Miscellaneous[a]	26	2.6%
Owner noncompliance	24	2.4%
No reason given	20	2.0%
Vomiting	19	1.9%
Elevated laboratory values (mainly elevations in BUN)	12	1.2%
Ineffectiveness	8	0.8%
Euthanasia (see Table 3)	8	0.8%
Diarrhea	6	0.6%
Owner moved	5	0.5%
Death (see Table 3)	3	0.3%
Vomiting and diarrhea	4	0.4%

[a]Includes concurrent use of corticosteroids or other NSAIDs, alternative diagnosis made, new disease developed, Hurricane Katrina–related reasons, surgery required, mitral valve disease diagnosed, dog was lost, palatability, dog weighed <7 lb (minimum weight limit for Previcox per product label), and incontinence.

Laboratory Results

Despite the recommended guidelines to exclude dogs with signs of renal or liver disease, 7% of dogs enrolled in the trial had elevated blood urea nitrogen (BUN) values and 26% had elevated alanine transaminase values. Nonetheless, mean BUN levels remained within the normal range throughout the study. For any dogs with elevated BUN and creatinine levels or increased alanine transaminase or aspartate aminotransferase levels combined with an increased alkaline phosphatase level, owner records were reviewed in detail to determine if such blood chemistry changes were associated with any clinical signs of disease. Total bilirubin results were also assessed in dogs that had elevated liver enzymes, and all were found to be unremarkable.

Blood test results were reviewed to determine if any elevations in blood values could be temporally associated with gastrointestinal events described in an owner's diary but not necessarily reported to the investigator. No di-

rect links were noted. Even though some owners observed instances of vomiting and/or diarrhea in their dogs and noted them on the Owner Observation Form, generally neither the owner nor the investigator considered these episodes to be a concern or a reason to discontinue use of firocoxib.

Efficacy Results

Similar improvements in OA were observed in male and female dogs and in dogs of different breeds, weights, and ages evaluated at each assessment. There was also essentially no difference in rate and degree of improvement between dogs with a history of NSAID use and those without such a history.

Investigator and Owner Evaluations

At the first post–enrollment visit (~day 10; n = 954), investigators rated 88.2% of dogs as improved (mildly to greatly improved) and 11.8% as unimproved (Figure 1). Owners rated 87.4% of animals as improved and 12.6% as unimproved (Figure 2). At study end (~day 40; n = 864[a]), investigators rated 92.8% of dogs as improved whereas owners rated 90.8% of animals as improved. Both the investigator and owner assessments demonstrate that improvement occurred throughout the course of the study, with more dogs showing overall improvement and more dogs showing great improvement at ~day 40 than at ~day 10.

Veterinary evaluation of those dogs demonstrating the higher degrees of improvement ("moderately improved" and "greatly improved") increased from 57.3% at ~day 10 to 75.8% by the end of the trial (~day 40). Owner evaluations reflected the same trend throughout the trial, as dogs demonstrating great or moderate improvement climbed from 60.2% at the intermediate visit (~day 10) to 75.2% by the end of the trial (~day 40).

Similar improvements in signs of OA were observed in male and female dogs and in dogs of different breeds, weights, and ages. Additionally, when the participating animals were segregated into these subsets, similar patterns and tendencies of improvement were seen regardless of the category or breakdown. For example, results for each subgroup at the ~day 40 investigator analysis for each weight band (Figure 3) were very similar to the ~day 40 investigator results in Figure 1.

The reported improvements in dogs with a history of receiving carprofen, meloxicam, or deracoxib in the week before enrollment did

TABLE 3. Classification of All Reports of Death and Euthanasia during the Study

Cause	*Total Cases*	*Classified Cause*
Euthanasia	8	Splenic tumor
		Cervical tumor
		Tumor
		Pulmonary masses
		Paralysis
		Lymphosarcoma
		"Dog went down"
		Lumbosacral disease
Death	3	Died under the care of another veterinarian (no records, no necropsy)
		Heart base tumor (found dead)
		Spleen and liver abscesses[a]

[a]Postmortem findings included abscesses of the liver and spleen, thrombosis of the liver and splenic vessels, and disseminated intravascular coagulation with shallow 1- to 2-mm ulcers identified near the pylorus.

[a]Owner diary information and final blood test results were available for an additional three dogs that received medication throughout and completed the study. However, there was no final investigator or owner evaluation available for these dogs with submission of the raw data.

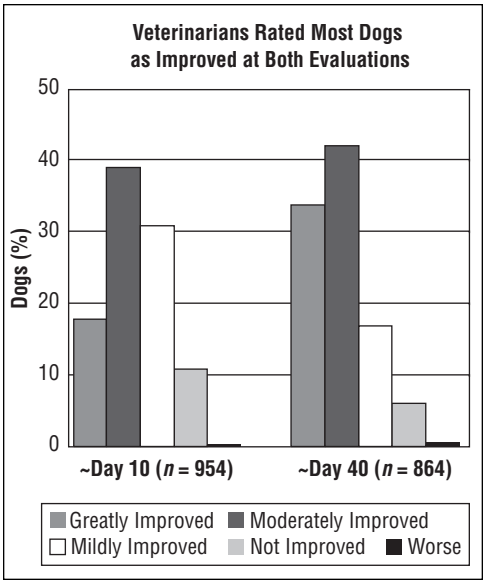

Figure 1. *Investigator evaluation: ~day 10 and study end (~day 40). Expressed as a percentage of dogs presented on ~day 10* (n = *954) and ~day 40* (n = *864).*

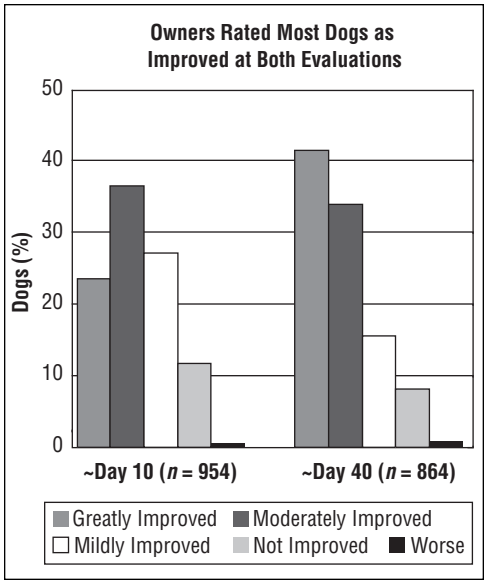

Figure 2. *Owner evaluation: ~day 10 and study end (~day 40). Expressed as percentage of dogs presented on ~day 10* (n = *954) and ~day 40* (n = *864).*

not appear to differ from those that had no such history (Figure 4).

Among owners responding to questions on palatability and convenience of administration of the firocoxib formulation, just over 90% rated the firocoxib flavored tablet as convenient to administer and 79% reported that their dogs found firocoxib palatable. Among owners responding to each question on their perception of their dog's attitude ("Is your dog more active since starting treatment?" "Is your dog happier since starting treatment?"), 86% reported that the dog was more active and 86% that the dog was happier.

DISCUSSION

With more than 1,000 dogs enrolled and more than 100 investigators involved, the Previcox Experience Trial is the largest single canine NSAID postmarketing study ever undertaken. The results substantiate earlier studies showing favorable effectiveness, tolerability, and overall safety of firocoxib. The absence of a control group and of investigator and owner blinding and the related absence of a valid statistical analysis precludes definitive conclusions on the overall efficacy of firocoxib; however, this national trial (1) addresses the need for more information on newly approved products, (2) generates in-clinic experience that normally builds over an extended period, and (3) provides systematic records of important aspects of product performance. Large-scale postregistration clinical studies are well accepted and well established in human medicine, and similarly, this trial should be beneficial for veterinarians.

The PET demonstrated that dogs prescribed firocoxib for treatment of OA showed substantial improvement within 10 days of initiation of treatment and that the pattern of improvement continued over time. A larger percentage of dogs showed improvement at the end of the tri-

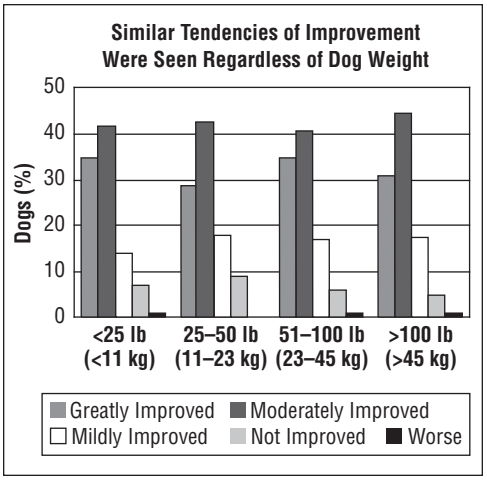

Figure 3. *Investigator evaluation: Study end (~day 40) improvement by weight band.*

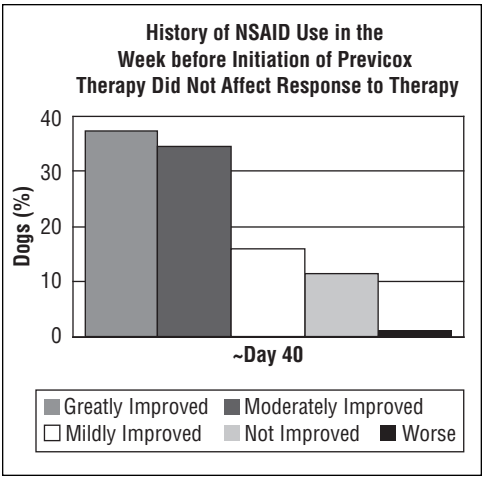

Figure 4. *Owner assessment of improvement at study end (~day 40) in dogs taking carprofen, deracoxib, or meloxicam in the week before PET (*n = *195).*

al (~day 40) than at the intermediate visit (i.e., 1 week to 10 days after treatment began). Whereas studies of extended duration are desirable to confirm the continuing efficacy and safety of firocoxib (or any canine NSAID) over long-term use, the results of this study suggest a cumulative benefit that becomes more apparent with continued therapy. Possible reasons for such continued improvement might include a return of muscle tone associated with increased use of the affected limb or a progressive reduction in inflammation around the affected joint.

More than 90% of dogs were rated as improved (mildly, moderately, and greatly) by investigators and owners, and rating patterns over the course of the study were similar for investigators and owners. Because the clinic and home environments are so dissimilar and would be expected to affect animal disposition, this consistency is particularly interesting.

Improvement was seen regardless of age, gender, breed, body weight, or prior NSAID use. This study suggests that for dogs receiving a different NSAID, there can be clinical benefits associated with switching to firocoxib. Moreover, owner responses indicating that in 86% of cases their dogs were "happier" or "more active" suggest the benefit of treatment with firocoxib on quality of life.

The low rate of gastrointestinal events sufficiently severe to withdraw a dog from the study matches observations reported in earlier studies with firocoxib.[5] Consistent with expectations, many of the dogs entering this study were advanced in years and thus more susceptible to concomitant conditions, including exposure to other medications (with or without the investigator's knowledge) and to NSAID toxicities. In fact, some dogs were presented with underlying illnesses in addition to OA, and approximately one-third of enrolled dogs had elevations beyond the normal range in at least one blood chemistry measurement before starting the trial. However, this may be attributed to the "real-life" trade-off between the risks of exacerbating an existing pathology by repeated NSAID treatment and the benefit of quality-of-life improvement gained by use of the NSAID.

Despite the enrollment of dogs with condi-

tions that would be expected to lead to increased susceptibility to NSAID side effects, overall results of clinical observations and blood chemistry are consistent with earlier reports of overall safety and acceptability of firocoxib. Nonetheless, as would be expected for any NSAID used in the population of dogs enrolled in this study, there were some elevations in BUN, creatinine, and liver enzyme levels (albeit generally without any outward clinical sign) in a small number of dogs during the treatment period. These findings confirm the ongoing need for monitoring of blood chemistry and clinical presentation of any dog undergoing NSAID therapy.

For many practices, participation in a clinical trial was a new challenge that presented organizational hurdles related to coordinating owners' return visits with investigators' in-clinic schedule. An impression that arose from telephone discussions with investigators and from other contacts with PET sites is that the clinics that adapted best to the trial routine were those with a capable technician who maintained the trial organization.

Entries in owner diaries ranged from cursory to exhaustive and provide a potentially useful view of how owners approach evaluating and balancing the health and quality of life of their dogs. Some observations focused on behaviors, others on level and type of activity, and still others on patterns related to appetite, elimination, and other gastrointestinal factors. In some instances, experiences and expectations specifically in terms of NSAIDs were fairly clear. For example, some owners offered comparisons of firocoxib to other NSAIDs, and some owners appeared to be anticipating the appearance of gastrointestinal side effects. Overall, more than 90% of dogs were rated as improved (mildly, moderately, or greatly), and rating patterns over the course of the study were similar for investigators and owners.

SUMMARY

One hundred six veterinary practices in 36 states enrolled 1,002 dogs in a 40-day field study of Previcox. Side effects associated with firocoxib treatment were typical for the NSAID class and consistent with earlier studies that demonstrated a favorable tolerability profile for firocoxib relative to less selective NSAIDs. Responding owners rated firocoxib overall as convenient to administer and palatable, with 86% rating their dogs as happier or more active after starting treatment. The PET confirmed the results of registration and field trials conducted worldwide and demonstrated that under clinical conditions, client-owned dogs diagnosed with OA and treated with firocoxib experienced improvement in lameness and quality of life. Overall improvement of treated dogs appeared to increase with time over the 40-day study.

ACKNOWLEDGMENT

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