Approval Date Sept. 27, 2001

FREEDOM OF INFORMATION SUMMARY

Rimadyl® (carprofen) Caplets for Dogs

S/NADA 141-053
August 20, 2001

Pfizer Inc
235 East 42nd Street
New York, New York 10017

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FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

NADA Number: 141-053

Sponsor: Pfizer Inc
235 East 42nd St.
New York, NY 10017

Generic Name: carprofen

Trade Name: Rimadyl® Caplets

Marketing Status: Rx

Effect of Supplement: This supplement provides for flexibility in administration of the total daily dose of Rimadyl® caplets. The drug may be administered orally at 2 milligrams per pound of body weight once daily or 1 milligram per pound of body weight twice daily.

II. INDICATIONS FOR USE

Rimadyl® is indicated for the relief of pain and inflammation associated with osteoarthritis in dogs.

III. DOSAGE FORM, ROUTES OF ADMINISTRATION AND RECOMMENDED DOSAGE

A. Dosage Form: Rimadyl® is available as 25, 75, and 100 mg scored caplets.

B. Route of Administration: Oral

C. Recommended Dosage: The recommended dosage for oral administration to dogs is 2 mg/lb daily. The total daily dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb twice daily.

IV. EFFECTIVENESS

Clinical effectiveness of the recommended dosage of 1 mg/lb body weight twice daily is contained in the original Freedom of Information Summary for NADA 141-053.

A study was conducted in dogs to demonstrate the effectiveness of carprofen administered as a single daily dose of 2 mg/lb of body weight for the relief of pain and inflammation associated with osteoarthritis in dogs. The study was conducted in veterinary practices in thirteen locations. The safety of carprofen in the field was also assessed. Results of this study demonstrated that carprofen is safe and effective when administered at 2 mg/lb body weight once daily.

A. Dosage Characterization

Clinical Study 2167A-12-96-010:

A masked, positive controlled, multicenter clinical field study was conducted to evaluate the effectiveness of carprofen administered orally once daily at a dose of 4 mg/kg (approximately 2 mg/lb) for relief of clinical signs associated with osteoarthritis.

Forty three client-owned dogs presenting with osteoarthritis were treated with Rimadyl® 20 and 50 mg European tablets. Inclusion of dogs in the study was based on physical examination, including a scoring of the severity of the clinical signs and radiographic signs of osteoarthritis. Clinical assessment of the severity of the dog's osteoarthritis was performed by the veterinarian prior to treatment and following five days of therapy. The clinical assessment score was based on a scale of 0 to 4, with 0 defined as clinically normal and 4 defined as nearly incapacitated. Parameters evaluated included gait, overall mobility, and pain on palpation of the affected limb. A case was considered a clinical success when the clinical score had improved between the pre-treatment and post-treatment evaluation.

The percentage of dogs with osteoarthritis that improved after five days of treatment with Rimadyl® was 93% (40/43). Two dogs treated with Rimadyl® experienced mild episodes of vomiting. Increased thirst was reported in one dog treated with Rimadyl®. Three dogs treated with the positive control experienced vomiting. There were no other reports of suspected adverse drug reactions.

The results of this study indicate that carprofen administered at a dose of 4 mg/kg (approximately 2 mg/lb) is effective for relief of pain and inflammation associated with osteoarthritis in dogs.

Dosage Selection Rationale:

Clinical field study 2167A-12-96-010 conducted using the current European approved total daily dose for Rimadyl® of 4 mg/kg (approximately 2 mg/lb) provides evidence of effectiveness for the relief of pain associated with osteoarthritis with once daily dosing. With this clinical field trial support for effectiveness against osteoarthritis following administration of a single daily dose, a dose of 2 mg/lb was selected for confirmation in a US multicenter field study.

B. Dose Confirmation

Rimadyl® (carprofen) clinical field trial at small animal clinics
(Study No. 1960C-60-98-271)

a. Type of Study: Multicentered Clinical Field study

b. Investigators:

Name	Cases
Dr. Mark Albin Pieper-Olson Veterinary Hospital Middletown, CT	12
Dr. Douglas Andrews Falmouth Veterinary Hospital Falmouth, ME	21
Dr. Joshua Atz Manchester Veterinary Clinic Manchester, CT	6
Dr. Lynn Buzhardt The Animal Center, Inc Zachary, LA	35
Dr. Geoffrey Clark Dover Veterinary Hospital Dover, NH	6
Dr. Peter Davis Pine Tree Veterinary Hospital Augusta, ME	26
Dr. Sonnya Dennis Stratham Veterinary Hospital Newfields, NH	25

Name	Cases
Dr. Donald Hamryka Sugar Hill Animal Hospital Sugar Hill, GA	12
Dr. Stephen Jones Lakeside Animal Hospital Monck's Corner, SC	21
Dr. David Lukof Harleysville Veterinary Hospital Harleysville, PA	35
Dr. John Means North Hampton Animal Hospital North Hampton, NH	24
Dr. Susan Thompson Pet Vet Animal Hospital Mount Pleasant, SC	23
Dr. Phillip Waguespack Siegen Lane Animal Clinic Baton Rouge, LA	22

c. General Design:

i. Purpose: The objective of the study was to evaluate, under field conditions, the safety and effectiveness of Rimadyl® (carprofen) for the relief of pain and inflammation associated with canine osteoarthritis.

ii. Test Animals: Two hundred sixty eight client owned dogs from thirteen locations entered the study. A total of 132 dogs were treated with Rimadyl® and 136 dogs were treated with placebo. Dogs had clinical and radiographic evidence of osteoarthritis and satisfactory clinical pathology test results within 14 days prior to starting the study. With regard to age, sex, weight, breed and the severity of the osteoarthritic condition, dogs were well represented across both treatment groups. Dogs ranged from 8 months to 15 years and weighed from 8 to 163 pounds. Dogs were randomly assigned to either carprofen or placebo treatment groups. The data from 248 animals were suitable for inclusion in the complete effectiveness analysis. Twenty four dogs were excluded from part (n=2) or the entire (n=22) analysis due to incomplete observations or protocol deviations.

iii. Control Drug: Placebo (same as carprofen caplet formulation except for the omission of the active ingredient).

iv. Dosage Form: The caplets administered were the market formulation.

v. Route of Administration: Oral

vi. Dosages used: 2 mg/lb of carprofen given orally once daily.

vii: Test Duration: 14 days

viii. Parameters measured: Clinical assessment of the severity of the dog's osteoarthritis was performed by the owner and veterinarian prior to treatment (Day 0) and on Day 13 of the study. The owner made a single assessment of the severity of the dog's condition before and after treatment. The veterinarian performed a composite assessment as well as individual assessments of lameness/weight-bearing, joint mobility, willingness to raise contralateral limb, and pain. The clinical assessment score was based on a scale of 0 to 4, with 0 defined as clinically normal and 4 defined as nearly incapacitated.

Hematology, clinical chemistry, urine, and fecal occult blood analyses were performed prior to treatment, and following treatment.

Effectiveness was evaluated based on two independent assessments of response: (1) a veterinary evaluation of the overall response to therapy (based on physical evaluation, observation of the gait and mobility, general condition and clinical signs, and a graded lameness evaluation) and (2) an owner evaluation based on the assessment of response to therapy. Improvement in the assessment score was evaluated for a reduction in score of one grade or more and for improvement of two grades or more.

Safety was assessed by determination of baseline clinical pathology values prior to the start of the study and at the end (hematology, clinical chemistry, urinalysis, and fecal occult blood). The owner was contacted on day 5, 6, or 7 to discuss the dog's progress.

d. Results: Results of the carprofen and placebo treatments, as evaluated by veterinarians and owners, are provided in Tables 1 & 2. Progress from Day 0 to Day 13 was assessed as positive or negative on a masked basis. Improvements were statistically significantly higher among carprofen treated dogs versus placebo for reductions of one grade or more for both owner and veterinarian composite assessments. Improvements in lameness/weight-bearing, joint mobility, pain on palpation of joints(s), and willingness to bear weight on the contralateral limb for dogs treated with carprofen were statistically significantly different from placebo for a reduction in score of one grade or more.

Improvements were also statistically significantly higher among carprofen treated dogs versus placebo for reductions of two grades or more based upon both veterinarian and owner composite assessments.

Table 1. Percent of positive improvement of one grade or more for individual & composite components of lameness evaluation

Assessment	Placebo (Number Improved/Total)	Carprofen (Number Improved/Total)	*P*-value[a]
Lameness/weight-bearing	37.3% (47/126)	56.5% (70/124)	0.002
Joint mobility	15.9% (20/126)	37.1% (46/124)	<0.001
Pain on palpation of joint(s)	35.7% (45/126)	59.7% (74/124)	<0.001
Willingness to bear weight on contralateral limb	28.8% (36/125)	42.7% (53/124)	0.014
Veterinarian Composite	41.3% (52/126)	57.3% (71/124)	0.008
Owner Composite	42.1% (53/126)	55.6% (69/124)	0.029

[a] statistically significant

Table 2. Percent of positive improvement of two grades or more for composite components of lameness evaluation

Assessment	Placebo (Number Improved/Total)	Carprofen (Number Improved/Total)	*P*-value[a]
Veterinarian Composite	4.0% (5/126)	12.1% (15/124)	0.011
Owner Composite	7.1% (9/126)	15.4% (19/124)	0.041

[a] statistically significant

Adverse Reactions: There were no clinically relevant differences in the mean values for all laboratory tests between the placebo and carprofen treated dogs. For both groups, the mean serum alkaline phosphatase (SAP) value was above the laboratory reference range pre-treatment and post-treatment. Three carprofen treated dogs developed a three fold or greater increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) during the course of therapy. For two of these dogs, the increase in the ALT and AST was greater than four fold. None of these dogs showed clinical signs associated with the laboratory value changes. One dog, which experienced a transient decrease in appetite, had elevated ALT and serum alkaline phosphatase (SAP) values at the time of enrollment. During the study, the ALT increased and the SAP decreased. The dog completed the study. The carprofen treated dogs with ALT increases during the course of therapy had a mean rise of 4.1 fold between pre- and post-treatment levels. Placebo dogs with ALT increases had a 1.5 fold mean increase between pre- and post-treatment levels. No other samples collected for clinical pathology showed significant changes outside normal physiologic ranges. Adverse reactions reported during the field trial are summarized in Table 3.

Table 3. Adverse reactions reported during the clinical field study

Category of Adverse Events	Placebo N=132 total		Rimadyl® N=129 total	
	Number of Dogs	Percentage	Number of Dogs	Percentage
Inappetance	2	1.5	2	1.6
Vomiting	5	3.8	4	3.1
Diarrhea/Soft stool	6	4.5	4	3.1
Behavior change	1	0.76	1	0.78
Dermatitis	1	0.76	1	0.78
Polyuria/Polydipsia	0	-	1	0.78
SAP increase	11	8.3	10	7.8
ALT increase	6	4.5	7	5.4
AST increase	1	0.76	3	2.3
BUN increase (Blood urea nitrogen)	2	1.5	4	3.1
Bilirubinuria	16	12.1	21	16.3
Ketonuria	12	9.1	19	14.7

Clinical pathology parameters listed represent reports of increases from pre-treatment values; the use of clinical judgement is necessary to determine clinical relevance.

e. Statistical Analysis: Incidence of positive responses obtained from the veterinarian and owner assessments were compared for total carprofen treated cases versus placebo cases using the Cochran-Mantel-Haenszel procedure (Fleiss, 1984, Statistical Methods for Rates and Proportions, 2nd ed.) for combining evidence from multiple investigators or clinics. The analyses were performed using PROC FREQ in SAS 6.12 (Statistical Analysis System). Statistical difference was assessed at the 5% level of significance ($P<0.05$).

f. Conclusions: Carprofen, administered orally at a dose of 2 mg/lb once daily, is safe and effective for the relief of pain and inflammation associated with canine osteoarthritis.

V. ANIMAL SAFETY

Studies demonstrating the safety of Rimadyl® Caplets for use in dogs are contained in the original FOI summary dated October 25,1996. Animal safety data from the clinical study were evaluated and found to be acceptable. Refer to section IV.

VI. HUMAN SAFETY

Human Safety Relative to Food Consumption:

Data on human food safety, pertaining to consumption of drug residues in food, were not required for approval of this supplement. Rimadyl® Caplets are approved for use in dogs only.

Human Safety Relative to Possession, Handling and Administration:

Labeling contains adequate caution/warning statements.

VII. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that Rimadyl® Caplets (carprofen), when used under labeled conditions of use, are safe and effective.

Rimadyl® Caplets are 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.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non-food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the alternate dosing regimen of 2 mg/lb body weight once daily for which the supplemental application was approved.

Pfizer Inc Patent Nos. US 4,264,500 expires February 28, 2003
US 6,013,808 expires April 15, 2019

VIII. LABELING

Package insert
Bottle