FREEDOM OF INFORMATION SUMMARY

S/NADA

141-053

Rimadyl® Caplets
(carprofen)

"for the control of postoperative pain associated with soft tissue and orthopedic surgery in dogs."

PFIZER, INC.
235 East 42nd Street
New York, NY 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

Established Name: carprofen

Trade Name: Rimadyl® Caplets

Marketing Status: Rx: U.S. Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

Effect of Supplement: The supplement to NADA 141-053 provides revisions to 21 CFR 520.309 *Indications for Use.* To add a claim for the control of postoperative pain associated with soft tissue and orthopedic surgery in dogs.

II. INDICATIONS FOR USE

Rimadyl® Caplets are indicated for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgery 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 (4.4 mg/kg) of body weight daily. The total dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb (2.2 mg/kg) twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure. Caplets are scored and dosage should be calculated in half-caplet increments.

IV. EFFECTIVENESS

A. Dosage Characterization:

Clinical effectiveness of the recommended dosage of 1 mg/lb body weight twice daily for the relief of pain associated with osteoarthritis was established in association with the

approval of Rimadyl® caplets for dogs (NADA 141-053). Clinical effectiveness of the dosage of 2 mg/lb body weight once daily for the relief of pain associated with osteoarthritis was demonstrated by a supplement to NADA 141-053, dated August 20, 2001.

Field study data supplied in the supplement to NADA 141-053, for administration of 2 mg/lb body weight once daily, demonstrated effectiveness of Rimadyl® caplets for the relief of pain and inflammation associated with osteoarthritis. With support for effectiveness for the relief of pain associated with osteoarthritis following the administration of a single daily dose of Rimadyl® caplets, a dose of 2 mg/lb once daily was selected for effectiveness confirmation in the control of postoperative pain in a U.S. multicenter field study.

B. Substantial Evidence:

The effectiveness of Rimadyl® caplets for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs presented as veterinary patients was evaluated in three controlled studies involving a variety of surgical procedures. The studies were conducted at twenty-one veterinary clinics throughout the U.S. Results of these studies demonstrate that Rimadyl® caplets are safe and effective when administered at a dose of 2 mg/lb of body weight once daily.

The intensity of surgical pain varied with the procedure performed, the duration of the procedure, the surgical technique used, and individual response to pain; therefore, the requirement for pain control may have varied for different surgical procedures. The safety of Rimadyl® caplets in the field was also assessed.

Surgical inductions included the use of combinations of tranquilizers, barbiturates, inhalant anesthetics, anticholinergics, antibiotics and parenteral fluids.

C. Field Efficacy and Safety for the Relief of Postoperative Pain Associated with Surgical Repair of Cruciate Injuries in Dogs (Study No. 1963C-60-99-304)

1. Type of Study: Multicentered Field Study

2. Investigators:

Name
Dr. Jeffrey L. Berzon Vet Specialists of Connecticut West Hartford, CT 06117
Dr. James F. Biggart Veterinary Surgery Service, Inc. Berkeley, CA 94710
Dr. R.Scott Buzhardt The Animal Center Zachary, LA 70791
Dr. James M. Fingeroth Vet Specialists of Rochester Rochester, NY 14623
Dr. Paul E. Howard Vermont Veterinary Surgical Center Colchester, VT 05446

Name
Dr. Stephen L. Jones Lakeside Animal Hospital Moncks Corner, SC 29461
Dr. Steven A. Martinez Washington State University Pullman, WA 99164
Dr. Rodney Oakley Veterinary Specialty Hospital of the Carolinas, Cary, NC 27511
Dr. Roger L. Sifferman Bradford Park Vet Hospital Springfield, MO 65804

3. General Design:

a. Purpose: The objective of the study was to evaluate the effectiveness and safety of Rimadyl® at a dosage of 2 mg/lb (4.4 mg/kg) administered orally approximately 2 hours prior to surgery, then once daily as needed for 3 days, for the control of postoperative pain associated with surgical repair of cruciate injuries in dogs.

b. Test Animals: Seventy-six client-owned dogs (40 females and 36 males) from 9 locations, ranging in age from 10 months to 14 years, entered the study. Dogs presenting in the course of clinical practice for surgical repair of cruciate injury were admitted to the study. A total of 38 dogs were treated with Rimadyl® and 38 dogs received placebo; these groups represented 42 pure-bred and 34 mixed-bred dogs. Surgical procedures included joint stabilization and/or arthrotomy (fabellar suture, imbrication, and fibular head transposition).

c. Control Drug: Placebo (same as carprofen formulation without the active ingredient).

d. Dosage Form: The caplets administered were the same as the market formulation.

e. Route of Administration: Oral

f. Dosages used: 2 mg/lb administered approximately 2 hours prior to surgery, then once daily as needed, for 3 days.

g. Test Duration: 4 days

h. Parameters measured: Clinical assessment of pain was performed by the veterinarian prior to surgery (Day -1 or Day 0), approximately 4, 8, and 12 hours post-surgery, twice daily on Days 1, 2, 3, and once on Day 4. The procedure for assessing the animals' pain included observation of demeanor, attention and response, interest in food and water, movements in a confined space, palpation of the surgical site and flexing and extending the affected joint. The degree of pain was quantified using a Visual Analog Scale (VAS).

Hematology, clinical chemistry, coagulation, urine and fecal occult blood analyses were performed prior to treatment, and upon study completion (Day 4). Approximately 24 hours post-surgery (Day 1), coagulation status was measured.

Effectiveness was based upon *a priori* contrasts among least squares means of VAS scores to assess the difference between placebo and Rimadyl® treatments. In addition, the number of animals withdrawn from the study due to lack of effectiveness was compared for each treatment.

Safety was evaluated by comparing the clinical pathology results from samples collected prior to surgery to the results from samples collected on Day 1 and Day 4. In addition, the abnormal health observations following treatment were summarized.

4. Results: Sixty-three of the 76 dogs enrolled in the study were included in the complete effectiveness analysis. Thirteen dogs were excluded from part (n = 7) or the entire (n = 6) efficacy analysis due to protocol deviations or failure to meet the enrollment criteria. Duration of treatment is summarized in Table 1. Rimadyl®-treated dogs were significantly less painful 4, 12, 24, approximately 28 hours post-surgery, on the second assessment on Day 3, and on the final assessment on Day 4 after surgery ($P \leq 0.05$). Results of pain assessment using VAS are provided in Table 2. Five placebo-treated dogs and 1 Rimadyl®-treated dog were withdrawn due to lack of effectiveness.

Table 1. Duration of Treatment

Treatment Days	Treatment		Overall
	Placebo	Rimadyl®	
Day 0	6	3	9
Days 0 and 1	3	3	6
Days 0, 1, and 2	5	2	7
Days 0, 2, and 3	1	0	1
Days 0, 1, 2, and 3	23	29	52
Total	38	37	75

Table 2. Analysis of Pain Assessment Using a Visual Analog Scale

Assessment	**Visual Analog Scale Score (mm)**				
	Placebo		**Rimadyl®**		P-values
	n[a]	LSM [b]	n[a]	LSM [b]	
Day 0					
preoperative	32	8.33 ± 3.92	31	7.14 ± 4.03	0.7030
1st postoperative	32	39.25 ± 3.94	33	31.54 ± 4.02	0.0200
2nd postoperative	31	36.65 ± 3.95	33	30.60 ± 4.02	0.0629
3rd postoperative	30	35.70 ± 3.95	33	28.36 ± 4.02	0.0271
Day 1					
1st assessment	30	34.26 ± 3.95	33	27.54 ± 4.02	0.0412
2nd assessment	30	32.20 ± 3.95	33	24.79 ± 4.02	0.0257
Day 2					
1st assessment	30	29.06 ± 3.95	33	24.21 ± 4.02	0.1320
2nd assessment	30	28.53 ± 3.95	33	22.18 ± 4.02	0.0526
Day 3					
1st assessment	30	25.20 ± 3.95	33	20.09 ± 4.02	0.1138
2nd assessment	30	25.30 ± 3.95	33	18.33 ± 4.02	0.0349
Day 4					
1st assessment	30	23.50 ± 3.95	33	16.09 ± 4.02	0.0258

[a] Not all animals had every pain assessment completed, therefore, the sum of animals listed under Day 0 to Day 3 may not equal the number of treated animals.

[b] Least squares means ± standard error of the mean (SEM)

5. Statistical Analysis: *A priori* contrasts among least squares means of the VAS scores using a repeated measures model were used to assess the difference between placebo and Rimadyl® treatments at each time point. The analyses were performed using SAS

6.12 (Statistical Analysis System). Statistical difference was assessed at the 5% level of significance ($P \leq 0.05$).

6. Conclusions: Under clinical conditions of use, Rimadyl® administered orally at 2 mg/lb (4.4. mg/kg) approximately 2 hours prior to surgery and once daily thereafter, as needed, for 3 days is safe and effective in controlling postoperative pain associated with cruciate injury repair in dogs.

7. Adverse Reactions: Clinical pathology data indicated that Rimadyl® was well tolerated. Changes in clinical pathology variables were similar in dogs administered Rimadyl® compared with the placebo cases. One Rimadyl®-treated dog had a two-fold increase in alkaline phosphatase. No clinical signs associated with this laboratory change were seen. There were no notable differences in mean values for hematology (including platelet counts), clinical chemistry, urinalysis results, or fecal occult blood detection between treatment groups. There were no notable differences in mean values for variables measuring coagulation status (prothrombin time, partial thromboplastin time and fibrinogen) between treatment groups. There were no serious adverse drug experiences or mortalities related to Rimadyl®. Similar types and numbers of abnormal health observations were reported between placebo and Rimadyl®-treated dogs and are summarized in Table 3.

Table 3. Abnormal Health Observations reported during field study (number of dogs = 76)

Abnormal Health	**Rimadyl® (% of dogs)**	**Placebo (% of dogs)**
Diarrhea/soft stool[a]	5.3	0.0
Traumatic Pain and Swelling of Limbs	2.6	2.6
Dermatitis/skin lesion	2.6	2.6
Wound Drainage	2.6	0.0
Oral/periodontal Disease	2.6	0.0
Urinary tract disease	2.6	0.0
Vomiting	2.6	0.0
Ocular Disease	2.6	0.0
Pyrexia	0.0	5.3
Salivation	0.0	2.6

[a] Includes soft stool, fecal incontinence

D. Field Efficacy and Safety for the Relief of Postoperative Pain Associated with Soft Tissue Surgery in Dogs (Studies 1963C-60-99-305 and 1963C-60-99-306)

1.Type of Study: Multicentered Field Studies

2.Investigators:

Name	Name
Dr. Douglas C. Andrews Falmouth Veterinary Hospital Falmouth, ME 04105	Dr. David Lukof Harleysville Veterinary Hospital Harleysville, PA 19438
Dr. H. Lee Butler Huntingdon Animal Clinic Huntingdon, TN 38344	Dr. Mark Marks Marks Veterinary Hospital Lawrence, KS 66047
Dr. R.Scott Buzhardt The Animal Center Zachary, LA 70791	Dr. John Means North Hampton Animal Hospital North Hampton, NH 03862
Dr. Peter Davis Pine Tree Veterinary Hospital Augusta, ME 04330	Dr. Dean Rund Grant Avenue Pet Hospital Springfield, MO 65807
Dr. Stuart Gluckman Mendon Village Animal Care Mendon, NY 14506	Dr. Roger L. Sifferman Bradford Park Vet Hospital Springfield, MO 65804
Dr. David Hancock Perinton Animal Hospital Victor, NY 14564	Dr. Susan B. Thompson Pet Vet Animal Hospital Mt. Pleasant, SC 29464
Dr. Stephen L. Jones Lakeside Animal Hospital Moncks Corner, SC 29461	Dr. Paul Urband East Haddam Veterinary Clinic East Haddam, CT 06423
Dr. Sharon Lachette White Haven Veterinary Hospital White Haven, PA 18661	

3. General Design:

a. Purpose: The objective of these studies was to evaluate the effectiveness and safety of Rimadyl® at a dosage of 2 mg/lb (4.4 mg/kg) administered orally approximately 2 hours prior to surgery and once daily thereafter, as needed for 2 days, for the control of postoperative pain associated with soft tissue surgery (ovariohysterectomy and aural procedures) in dogs.

b. Test Animals: Two hundred and twenty-one (180 females and 41 males) client-owned dogs from 15 locations, ranging in age from 4 weeks to 12 years, entered the study. Dogs presenting in the course of clinical practice for aural (ear) surgery or elective ovariohysterectomy were admitted to the study. The preponderance of females was due to the inclusion of ovariohysterectomy as

one of the soft tissue surgeries. A total of 110 dogs were treated with Rimadyl® and 111 dogs received placebo; these groups represented 164 purebred and 57 mixed-bred dogs. Aural surgeries included hematoma repair, ear crop, lateral canal resection, bullae osteotomy, and growth removal.

c. Control Drug: Placebo (same as carprofen formulation without the active ingredient).

d. Dosage Form: The caplets administered were the same as the market formulation.

e. Route of Administration: Oral

f. Dosages used: 2 mg/lb administered approximately 2 hours prior to surgery, then once daily as needed for 2 days.

g. Test Duration: 3 days

h. Parameters measured: Clinical assessment of pain was performed by the veterinarian prior to surgery (Day -1 or Day 0), approximately 4, 8, and 12 hours post-surgery, twice daily on Days 1, 2, and once on Day 3. The procedure for assessing the animals' pain included observation of demeanor, attention and response, interest in food and water, movements in a confined space and palpation of the surgical site. The degree of pain was quantified using a Visual Analog Scale (VAS).

Hematology, clinical chemistry, coagulation, urine and fecal occult blood analyses were performed prior to treatment, and upon study completion (Day 3). Approximately 24 hours post-surgery (Day 1), coagulation status was measured.

Effectiveness was based upon *a priori* contrasts among least squares means of VAS scores to assess the difference between placebo and Rimadyl® treatments. In addition, the number of animals withdrawn from the study due to lack of effectiveness was compared for each treatment.

Safety was evaluated by comparing the clinical pathology results from samples collected prior to surgery to the results from samples collected on Day 1 and Day 3. In addition, the abnormal health observations following treatment were summarized.

4. Results: Two hundred and four of the 221 dogs enrolled in the study were included in the complete effectiveness analysis. Seventeen dogs were excluded from part (n = 11) or the entire (n = 6) effectiveness analysis due to protocol deviations or failure to meet the enrollment criteria. Duration of treatment is summarized in Table 4. Dogs treated with Rimadyl® were significantly less painful 4, 8, 12, 24, 30, and 54 hours post-surgery ($P \leq 0.05$). Results of pain assessment using VAS are provided in Table 5. One placebo-treated dog and 1 Rimadyl®-treated dog were withdrawn due to lack of effectiveness.

Table 4. Duration of Treatment

Days of Test Article Administration	Treatment		Overall
	Placebo	Rimadyl®	
Day 0	61	74	135
Days 0 and 1	24	11	35
Days 0 and 2	2	1	3
Days 0, 1, and 2	23	21	44
Total	110	107	217

Table 5. Analysis of Pain Assessment Using a Visual Analog Scale

Assessment	**Visual Analog Scale Score (mm)**				
	Placebo		**Rimadyl®**		P-values
	n[a]	LSM [b]	n[a]	LSM [b]	
Day 0					
preoperative	105	0.71 ± 1.97	100	1.67 ± 1.978	0.5389
1st postoperative	109	21.34 ± 1.963	104	17.27 ± 1.971	0.0098
2nd postoperative	109	22.20 ± 1.963	104	16.74 ± 1.973	0.0007
3rd postoperative	109	20.34 ± 1.963	104	15.52 ± 1.974	0.0025
Day 1					
1st assessment	109	18.48 ± 1.964	104	15.22 ± 1.974	0.0380
2nd assessment	108	14.87 ± 1.964	104	10.79 ± 1.974	0.0097
Day 2					
1st assessment	108	11.45 ± 1.965	104	9.25 ± 1.974	0.1580
2nd assessment	108	9.67 ± 1.965	104	5.80 ± 1.974	0.0141
Day 3					
only assessment	107	8.30 ± 1.968	104	6.31 ± 1.974	0.2034

[a] Not all animals had every pain assessment completed, therefore, the sum of animals listed under Day 0 to Day 3 may not equal the number of treated animals.
[b] Least squares means ± standard error of the mean (SEM)

5. Statistical Analysis: *A priori* contrasts among least squares means of the VAS scores using a repeated measures model were used to assess the difference between placebo and Rimadyl® treatments at each time point. The analyses were performed using SAS 6.12 (Statistical Analysis System). Statistical difference was assessed at the 5% level of significance ($P \leq 0.05$).

6. Conclusions: Under clinical conditions of use, Rimadyl® administered orally at 2 mg/lb (4.4 mg/kg) approximately 2 hours prior to surgery, then once daily, as needed

for 2 days, is safe and effective in controlling postoperative pain associated with soft tissue surgery in dogs.

7. Adverse Reactions: Clinical pathology data indicated that Rimadyl® was well tolerated. Changes in clinical pathology variables were similar in dogs administered Rimadyl® compared with the placebo cases. Nineteen Rimadyl®- and 12 placebo-treated dogs had normal baseline and positive Day 3 fecal occult blood results. One Rimadyl®-treated dog had a greater than two-fold increase in ALT (alanine transferase). One Rimadyl®-treated dog had an elevated baseline ALT, which additionally increased greater than two-fold by Day 3. Sixteen Rimadyl®- and 14 placebo-treated cases had normal baseline and elevated Day 3 WBCs (white blood cell counts). Three Rimadyl®- and 1 placebo-treated dog had a greater than two-fold increase in GGT (gamma-glutamyl transpeptidase). None of these animals showed clinical signs associated with these laboratory changes. There were no notable differences in mean values for hematology (including platelet counts), clinical chemistry, urinalyses, or fecal occult blood detection between treatment groups. There were no notable differences in mean values for variables measuring coagulation status (prothrombin time, partial thromboplastin time and fibrinogen) between treatment groups. There were no serious adverse drug experiences or mortalities related to Rimadyl®. Similar types and numbers of abnormal health observations were reported between placebo and Rimadyl®-treated dogs and are summarized in Table 6.

Table 6. Abnormal Health observations reported during field study
(number of dogs = 221)

Abnormal Health	**Rimadyl® (% of dogs)**	**Placebo (% of dogs)**
Vomiting	12.7	18.0
Diarrhea/soft stool	6.4	8.1
Ocular Disease	2.7	0.0
Inappetence	1.8	0.0
Apnea	1.8	0.0
Dermatitis/skin lesion	1.8	0.0
Dehydration	0.9	0.0
Abscess	0.9	0.0
Abdominal Distension	0.9	0.0
Constipation	0.9	0.0
Oral/periodontal disease	0.9	0.0
Pyrexia	0.9	0.0
Wound Drainage	0.9	0.0
Urinary Tract Disease	0.9	1.8
Cyanosis	0.9	0.0
Dysrhythmia	0.9	0.0
Hypothermia	0.9	0.0

[a] Includes soft stool, fecal incontinence

V. TARGET ANIMAL SAFETY

Studies demonstrating the safety of Rimadyl® for use in dogs are contained in the original FOI summary dated October 25, 1996. No new animal safety data were required for approval of this supplement.

VI. HUMAN 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, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Keep out of reach of children. Not for human use. Consult a physician in case of accidental ingestion by humans."

VII. 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 of the implementing regulations. The data demonstrates that Rimadyl® caplets for dogs, when administered under labeled conditions of use are safe and effective for the intended use.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and provide guidance in the control of postoperative pain. Furthermore, the veterinarian monitors patients for possible adverse effects of the drug.

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 indication for control of postoperative pain for which the supplemental application was approved.

U.S. Patent Number	Date of Expiration
US 4,264,500	February 28, 2003
US 6,013,808	April 15, 2019

VIII. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Package Insert

Client Information Sheet

Bottle:

25 mg- bottles of 14, 60 and 180 caplets
75 mg- bottles of 14, 60 and 180 caplets
100 mg- bottles of 14, 60 and 180 caplets