HFA-305

SEP 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

FOIS 1

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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-1Z-96-0110:

A masked, postive 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

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.

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

RIMADYL®

(carprofen)

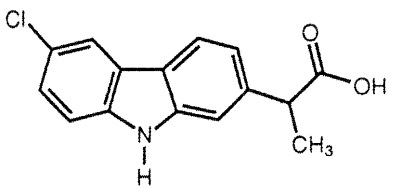
Caplets

***Non-steroidal anti-inflammatory** drug*

For oral use in dogs only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Rimadyl (carprofen) is a non-steroidal anti-inflammatory drug (NSAID) of the proptontc acid class that includes Ibuprofen. naproxen, and ketoprofen. Carprofen is the nonproprietary designation for a substituted carbarofe, 6-chloro-α-methyl-9H-carbazole-2-acetic acid The empirical formula is $C_{15}H_{12}ClNO_2$ and the molecular weight 273 72.



Carprofen is a white, crystalline compound It is freely soluble in ethanol, but practically insoluble in water at 25°C.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equrpotent to indomethacin in animal models 1

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cycfooxygenase activity Two unique cyclooxygenases have been described in mammals 2 The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function The inducible cycfooxygenase, COX.2, generates prostagfandins involved in inflammation Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity The specificity of a particular NSAID for COX-2 versus COX-1 may vary from species to species 3 In an in *vitro* study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.4 Clinical relevance of these data has not been shown Carprofen has *also* been shown to inhibit the release of several prostaglandrns in two inflammatory cell systems. ret polymorphanuctear leukocytes (PMN) and human rheumatoid synovial cells, indicabng inhibition of acute (PMN system) and chronic (synovial cell system] inflammatory reactions.1

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses 5-9 Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF). PGE_1, and PGE_2 by its inhibitory effects on prostaglandin biosynthesis.1

Based upon comparison with data obtained *from* Intravenous administration, carprofen is rapidly and nearly complete& absorbed (more than 90% bioavailable) when administered orally.10 Peak blood plasma concentrations are achieved in 1–3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5–9 8 hours) after single oral doses varying from 1–35 mg/kg of body weight After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog Rimadyl is more than 99% bound to plasma protein and exhrbrts a very small volume of distribution

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of tie resulting metabolites (the ester glucuronide of carprofen and the *ether* glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70–80%) and urine (10–20%) Same enterohepatic circulation of the drug is observed

INDICATIONS: Rimadyl is Indicated for the relief of pain and inflammation associated with osteoarthritis in

concomitant use of Rimadyl with other anti-inflammatory drugs, such as corticosteroids and NSAIDs, should be avoided or very closely monitored. Sensitivity to drug-as sociated adverse reactions varies with the individual patient For example, Rimadyl treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in dogs.

Rimadyl is not recommended for use in dogs with bleeding disorders (e.g., Von Will&and's disease), as safety has not been established in dogs with these disorders. The safe use of Rimadyl in pregnant dogs, dogs used far breeding purposes, or in lactating bitches has not been established. Studies to determine the activity of Rimadyl when administered concomitantly with other protein-bound ar similarly metabolized drugs have nof been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy.

INFORMATION FOR DOG OWNERS:

Rimadyl, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include decreased appetite, vomiting, diarrhea, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. Serious **adverse reactions associated with this drug class can occur without warning and in rare situations result in death** (see **Adverse Reactions**), Owners should be **advised to discontinue Rimadyl therapy and contact their veterinarian** immediately if signs of intolerance are observed. The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated Owners should be advised of the importance of periodic follow up for all dogs during administrabon of any NSAID.

WARNINGS: Keep out of reach of children Not for human use Consult a physician in cases of accidental Ingestion by humans Far use in **dogs only.** Do not use in cats.

All dogs should undergo a thorough history and physical examination before inidabon of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. Owners **should** be advised to **observe for signs of potential** drug toxicity (see Information for Dog Owners **and** Adverse Reactions).

ADVERSE REACTIONS: During investigational studies with twice daily administration of 1 mg/lb, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen- and placebo-treated dogs. Incidences of the fofiowing were observed in both groups vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%) The product vehicle served as control

There were *no* serious adverse events reported during clinical field studies with once daily oral administration of 2 mg/lb The following categories of abnormal health observanons were reported The product vehicle served as control

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2 mg/lb once daily)

Observation	Rimadyf (n=129)	Placebo (n=132)
Inappetance	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PU/PD	0 8	—
SAP increase	7.8	8.3
ALT increase	5.4	4.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketonuria	14.7	9.1

Clinical pathology parameters listed represent reports of increases from pretreatment values; the use of clinical judgement is necessary to determine clinical relevence

Post-Approval Experience

Although not all adverse reacbans are reported, the following adverse reacbons are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are fisted in decreasing order at frequency by body system.

DOSAGE AND ADMINISTRATION: The recommended dosage for oral administration to dogs is 2 mg/lb of body weight daily The total daily dose may be administered as 2 mg/lb of body weight once daily or dtvtded and admtntstered as 1 mg/lb twice daily Caplets are scored and dosage should be calculated in half-caplet increments

EFFECTIVENESS: Separate placebo-controlled, masked, multicenter field studtes confirmed the anti-inflammatory and analgesic effectiveness of Rimadyl in various breeds of dogs when dosed at 2 mg/lb of body weight once datiy or when dtvtded and administered at 1 mg/lb twice daily

In these two field studies, dogs dragnosed with osteoarthritis showed significant improvement tn lameness based on masked owner and vetertnartan evaluations when admtntstered at the labeled dosages

ANIMAL SAFETY STUDIES: Laboratory studies and clinical ftefd trials have demonstrated that Rtmadyl is well tolerated in dogs after oral admmtstrattan

In target animal safety studies, Rtmadyl was administered orally to healthy Beagle dogs at 1, 3, and 5 mg/lb twice daily (1, 3 and 5 times the recommended total daily dose) for 42 consecutive days with no stgntfttcant adverse reacbons Serum albumin for a single female dog receiving 5 mg/lb twice daily decreased to 2 1 g/dL after 2 weeks of treatment returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2 3 g/dL at the final 6-week evaluation. Over the &week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with 1 mg/lb twice daily and in 1 dog (2 incidents) treated with 3 mg/lb twice daily Redness of the colonic mucosa was observed in 1 male that received 3 mg/lb twice daily

Two of 8 dogs receiving 10 mg/lb orally twice daily (10 times the recommended total daily dose) for 14 days exhtbtted hypoalbuminemia The mean albumin level tn the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2 88 and 2.93 g/dL, respectively) Three incidents of black or bloody stool were observed in 1 dog five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination Histologic examination of these areas revealed no evidence of ulceration, but dtd show minimal congestion of the lamina propria in 2 of the 5 dogs

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered orally up to 11.4 mg/lb/day (5.7 times the recommended total daily dose of 2 mg/lb) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No grass or histologic changes were seen in any of the treated animals In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU

In the 52-week study, miner dermatologic changes occurred in dogs tn each of the treatment groups but not in the control dogs The changes were described as slight redness or rash and were diagnosed as nonspecific dermatitis The possibility exists that these mild fesions were treatment related, but no dose relationship was observed

Clinical field studies were conducted with 549 dogs of different breeds at the recommended doses for 14 days (297 dogs were included in a study evaluating 1 mg/lb twice daily and 252 dogs were included in a separate study evaluating 2 mg/lb once daily) In both studies the drug was clinically well tolerated and the incidence of clinical adverse reactions for Rtmadyf-treated animals was no htgher than placebo-treated animats (placebo contained inactive ingredients found in Rimadyl). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 1 1 IU greater and 9 IU less than pre-treatment values for dogs receiving Rtmadyl and placebo, respectively. Differences were not statistically srgnthcant For animals receiving 2 mg/lb once daily, the mean post-treatment serum ALT values were 4 5 IU greater and 0.9 IU less than pra-treatment values for dogs receiving Rtmadyl and placebo, respectively In the latter study, 3 Rimadyl-treated dogs developed a 3-fold or greater increase tn (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than t-fold increase in ALT. None of these animals showed clinicat signs associated with the laboratory value changes. Changes in clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant The 1 mg/lb twice daily course of therapy was repeated as needed et 2-week intervals in 244 dogs, same for as fong as 5 years

CONTRAINDICATIONS: Rimadyl should not be used in dogs exhibiting previous hypersensitivity to carprofen or other NSAIDs

PRECAUTIONS: As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid.[11–14] When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which marntarn normal homeostatic function These anti-prostaglandin effects may result tn clinically significant disease in patients with underlying or pre-existing dtsease more often than tn healthy patients [12,14] NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs Patients with underlying renal dtsease for example. may experience exacerbabon or decompensation of their renal disease while on NSAID therapy [11–14]

Carprofert is an NSAID, and as with others in that class, adverse reacbons may occur with tts use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologrc, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepabc dysfunction Since many NSAIDs possess the potential to induce gastrointestinal ulceration,

Gastrointestinal *Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal inflammation, gastrointestinal bleeding, pancreatbs*

Hepattc *Inappetence, vomiting, jaundice,* acute *hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, bilirubinuria, hypoalbuminemia Approxima tely one-fourth afhepabc reports were in Labrador Retrievers*

Neurologic *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation*

Urinary *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities including acute tubular necrosis, renal tubular acidosis, glucosuria*

Behavioral *Sedation, lethargy, hyperactivity, restlessness, aggressiveness*

Hematologtc *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis.*

Immunologic or hypersensitivity *Facial swelling, hives, erythema*

In rare situations, death has been associated with some of the adverse reactions fisted above

To report a suspected adverse reaction call 1-800-366-5288.

STORAGE: Store at controlled room temperature 15°–30°C (59°–86°F).

HOW SUPPLIED: Rtmadyi caplets are scored, and contain 25 mg, 75 mg, or 100 mg of carprofen per caplet. Each caplet size is packaged in bottles containing 14, 60, or 180 caplets.

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For a copy of the Matertal Safety Data Sheet (MSDS) or to report adverse reactions call Pfizer Animal Health at 1-800-366-5288

NADA #141-053, Approved by FDA

TAKE TIME  OBSERVE LABEL DIRECTIONS

Distributed by:

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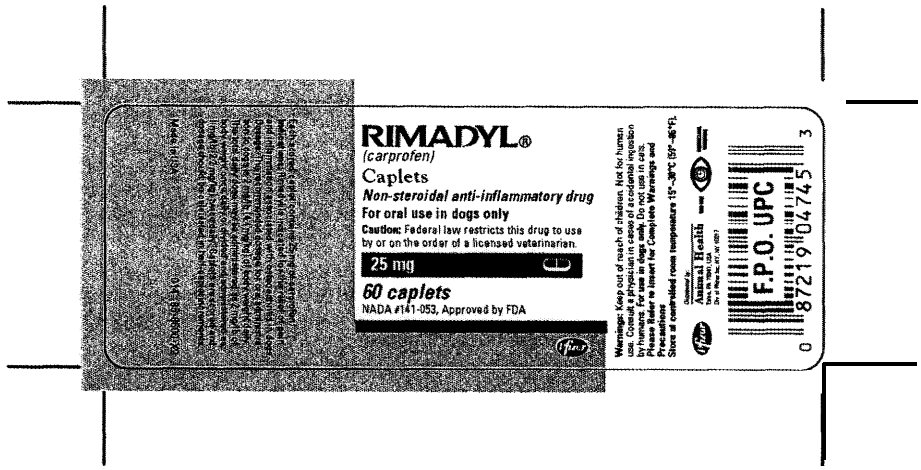
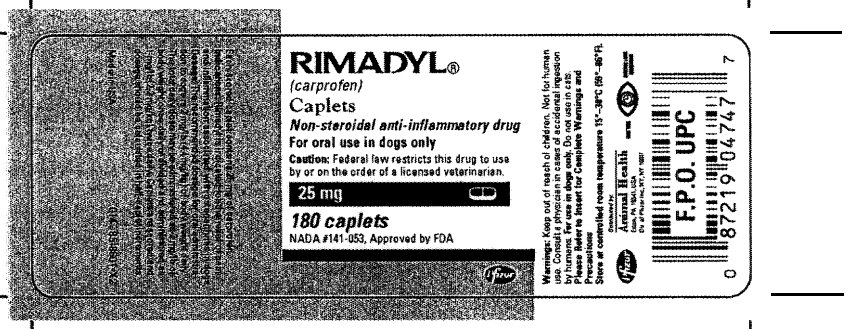
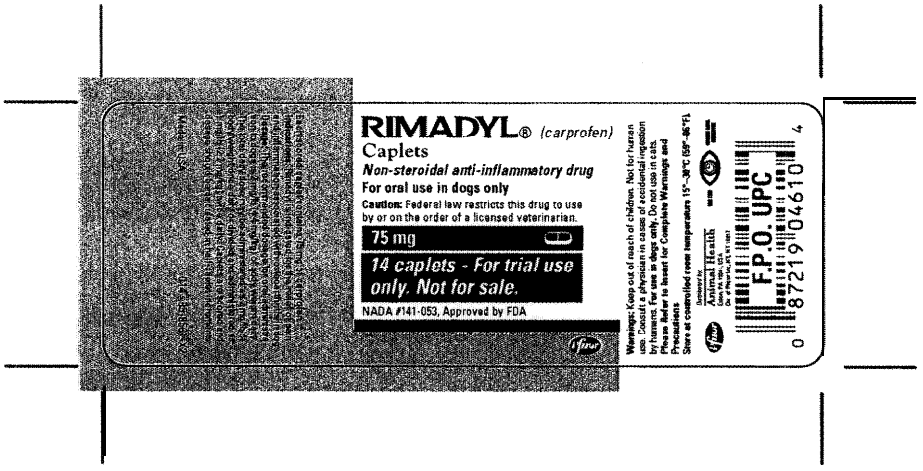
Coordinator	Paige Hofpar				
Artist	Ron VanValkenburg	PMS 116	PMS 330	PMS 286	PMS 254	Black
Proofreader	Diane Mattison				SKU: 8560000



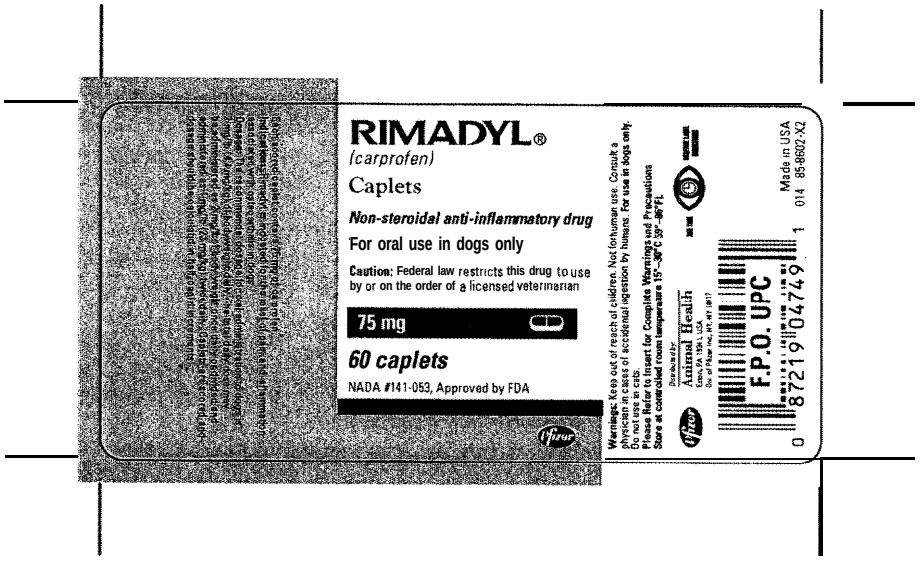
Pfizer PACKAGE DESIGN & DEVELOPMENT Animal Health	Project Name	Part Number	Draft#	Date	Dimensions
	Rimadyl	85-8600-X2	1	02AUG01	1 3/8" x 3 3/4"
	Project Number	Country USA			Visual Code Bar(s)
	1884	Die (CAD)#			Code(s) UPC
Editor	Michele Brettmann	Colors:			
Coordinator	Paige Hofpar	PMS 116	PMS 330	PMS 286	Black
Artist	Ron VanValkenburg				
Proofreader	Diane Mattison				SKU: 8600000



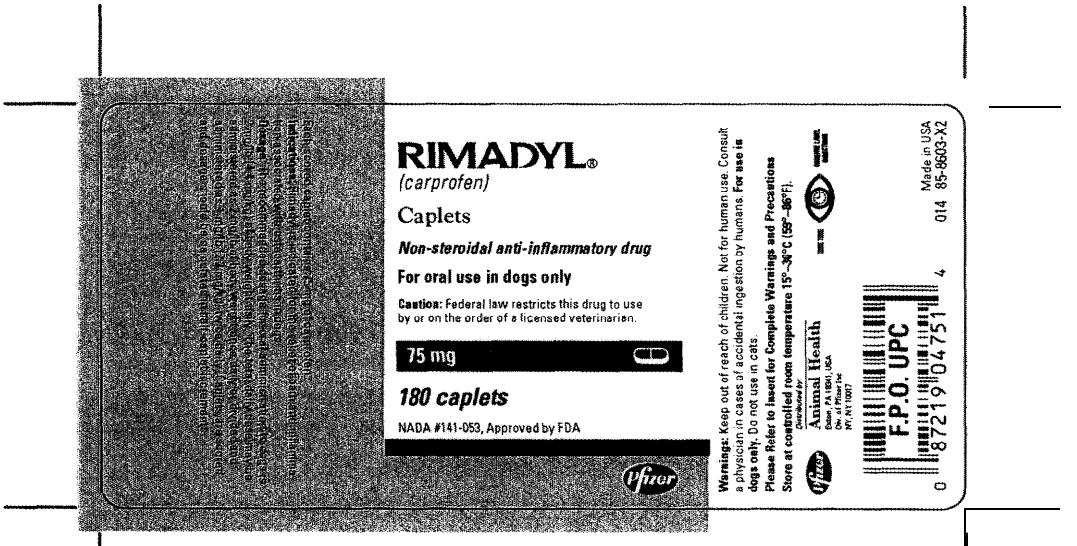
PACKAGE DESIGN & DEVELOPMENT Animal Health	Project Name	Part Number	Draft#	Date	Dimensions
	Rimadyl	85-8601-X2	1	02AUG01	1 3/8" x 3 3/4"
	Project Number	Country USA			Visual Code Bar(s)
	1884	Die (CAD)#			Code(s) UPC
Editor	Michele Brettmann	Colors:			
Coordinator	Paige Hofpar				
Artist	Ron VanValkenburg	PMS 116	PMS 330	PMS 286	Black
Proofreader	Diane Mattison				SKU: 8601000



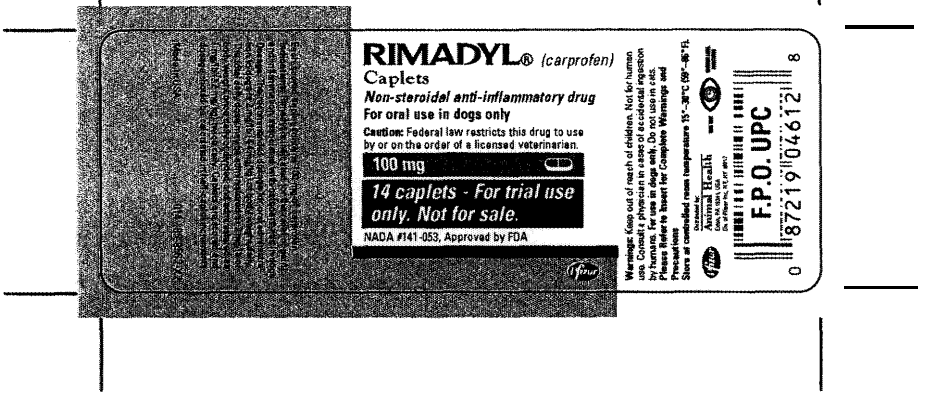
Pfizer PACKAGE DESIGN & DEVELOPMENT Animal Health	Project Name	Part Number	Draft#	Date	Dimensions
	Rimadyl	85-8561-X2	1	02AUG01	1 3/8" x 3 3/4"
	Project Number	Country USA			Visual Code Bar(s)
	1884	Die (CAD)#			Code(s) UPC
Editor	Michele Brettmann	Colors:			
Coordinator	Paige Hofpar				
Artist	Ron VanValkenburg	PMS 116	PMS 330	PMS Rhodamine Red	PMS 254 Black
Proofreader	Diane Mattison				SKU: 8561000



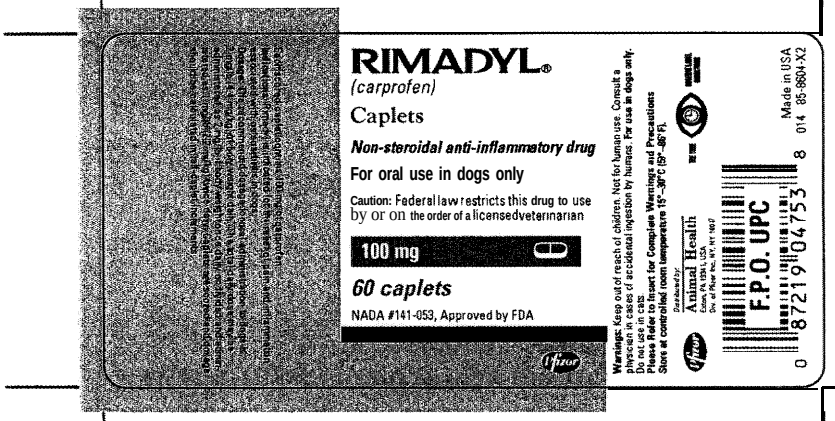
Pfizer PACKAGE DESIGN & DEVELOPMENT Animal Health	Project Name	Part Number	Draft#	Date	Dimensions
	Rimadyl	85-8602-X2	1	02AUG01	1 7/8" x 3 3/4"
	Project Number	Country USA			Visual Code Bar(s)
	1884	Die (CAD)#			Code(s) UPC
Editor	Michele Brettmann	Colors:			
Coordinator	Paige Hofpar	PMS 116	PMS 330	PMS Rhodamine Red	Black
Artist	Ron VanValkenburg				
Proofreader	Diane Mattison				SKU: 8602000



Pfizer PACKAGE DESIGN & DEVELOPMENT Animal Health	Project Name	Part Number	Draft#	Date	Dimensions
	Rimadyl	85-8603-X2	1	02AUG01	2 1/8" x 4 1/2"
	Project Number	Country USA			Visual Code Bar(s)
	1884	Die (CAD)#			Code(s) UPC
Editor	Michele Brettmann	Colors:			
Coordinator	Paige Hofpar	PMS 116	PMS 330	PMS Rhodamine Red	Black
Artist	Ron VanValkenburg				
Proofreader	Diane Mattison				SKU: 8603000



Pfizer PACKAGE DESIGN & DEVELOPMENT Animal Health	Project Name	Part Number	Draft#	Date	Dimensions	
	Rimadyl	85-8562-X2	1	02AUG01	1 3/8" x 3 3/4"	
	Project Number	Country USA			Visual Code Bar(s)	
	1884	Die (CAD)#			Code(s) UPC	
Editor	Michele Brettmann	Colors:				
Coordinator	Paige Hofpar	PMS 116	PMS 330	PMS 3275	PMS 254	Black
Artist	Ron VanValkenburg					
Proofreader	Diane Mattison					SKU: 8562000



Project Name	Part Number	Draft#	Date	Dimensions
Rimadyl	85-8604-X2	1	02AUG01	1 7/8" x 3 3/4"

PACKAGE DESIGN & DEVELOPMENT Animal Health

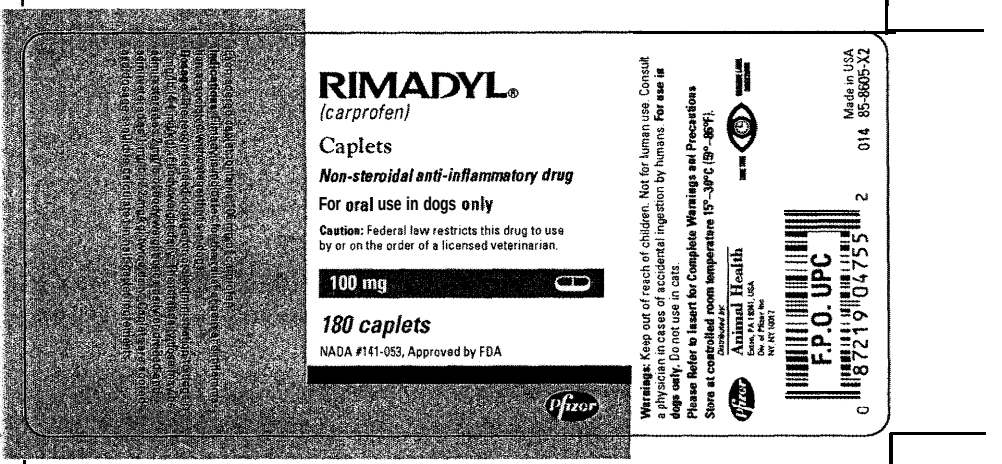
Project Number	Country USA	Visual Code Bar(s)
1884	Die (CAD)#	Code(s) UPC

Editor	Michele Brettmann	
Coordinator	Paige Hofpar	
Artist	Ron VanValkenburg	
Proofreader	Diane Mattison	

Colors:

PMS 116 PMS 330 PMS 3275 Black

SKU: 8604000



Pfizer PACKAGE DESIGN & DEVELOPMENT Animal Health	Project Name	Part Number	Draft#	Date	Dimensions
	Rimadyl Cap fac	85-8605-X2	1	02AUG01	2 1/8" x 4 1/2"
	Project Number	Country USA			Visual Code Bar(s)
	1884	Die (CAD)#			Code(s) UPC
Editor	Michele Brettmann	Colors:			
Coordinator	Paige Hofpar	PMS 116	PMS 330	PMS 3275	Black
Artist	Ron VanValkenburg				
Proofreader	Diane Mattison				SKU: 8605000