

Approval Date: MAR 25 2003

FREEDOM OF INFORMATION SUMMARY

Supplemental NADA

141-199

**RIMADYL[®] INJECTABLE
(carprofen)**

“... the relief of pain and inflammation associated with osteoarthritis in dogs,
2 mg/lb of body weight once daily or 1 mg/lb twice daily, by subcutaneous injection.”

PFIZER, INC
235 East 42nd Street
New York, NY 10017

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FREEDOM OF INFORMATION SUMMARY**1. GENERAL INFORMATION**

- a. File Number: 141-199
- b. Sponsor: Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Drug Labeler Code: 000069
- c. Established Name: carprofen
- d. Proprietary Name: Rimadyl[®] Injectable
- e. Dosage Form: Injectable solution
- f. How Supplied: This product is available as a 50 mg/ml sterile solution in a 20 ml bottle.
- g. How Dispensed: Prescription (Rx)-U.S. Federal Law restricts this drug to use by, or on the order of, a licensed veterinarian.
- h. Amount of Active Ingredient: Each ml contains 50 mg of Rimadyl[®].
- i. Route of Administration: Subcutaneous injection
- j. Species/Class: dog
- k. Recommended Dosage: The recommended dose for subcutaneous 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.
- l. Pharmacological Category: Non-steroidal, anti-inflammatory drug (NSAID)
- m. Indications: Rimadyl[®] Injectable is indicated for the relief of pain and inflammation associated with osteoarthritis in dogs.

- n. Effect of Supplement: This supplement to NADA 141-199 provides for the addition of a once daily administration of 2 mg/lb (4.4 mg/kg) of body weight in addition to a twice daily administration of 1 mg/lb (2.2 mg/kg) by subcutaneous injection.

2. EFFECTIVENESS

Clinical effectiveness of the recommended dosage of 1 mg/lb body weight twice daily was established in association with the approved Rimadyl[®] oral caplets for dogs [NADA 141-053 (approval dated October 25, 1996)] and Rimadyl[®] Injectable for dogs [NADA 141-199 (approval dated March 3, 2003)]. The pharmacokinetics of carprofen in dogs following repeated oral and subcutaneous administration was demonstrated in the latter NADA. The results indicate that total drug exposure after a single dose, and at steady state, was similar following subcutaneous administration compared to oral dosing. Clinical effectiveness of the 2 mg/lb body weight once daily dose via oral administration was established in a supplement to NADA 141-053 (approval dated September 27, 2001).

Based on the similar bioavailability of carprofen, when administered at the recommended dosage to dogs as either Rimadyl[®] caplets or Rimadyl[®] Injectable, and comparable drug exposure when administered either at one or two sites via subcutaneous injection, no additional clinical effectiveness studies were required for approval of this NADA.

a. Dosage Characterization

The effectiveness of Rimadyl administered orally at a total daily dose of 2 mg/lb, divided and administered twice daily for the relief of pain and inflammation associated with osteoarthritis has been established (NADA 141-053). An equivalent extent of drug exposure (AUC) under both single dose and steady state conditions has been established for the caplet and subcutaneously administered injectable formulation at steady state when administered at a dose of 1 mg/lb twice daily (NADA 141-199). Additional studies confirm that administration of the total daily dose in a single between the shoulders subcutaneous injection does not compromise Rimadyl bioavailability. Therefore, the bioavailability of a single daily subcutaneous injection of 2 mg/lb Rimadyl will be comparable to that of Rimadyl caplets when administered in single or divided daily doses, and to a divided daily dose of the subcutaneous injectable formulation. Accordingly, 2 mg/lb Rimadyl, when administered orally or as a subcutaneous injection given, as a single or divided daily dose will be safe and effective in the control of pain and inflammation associated with osteoarthritis in dogs.

b. Substantial Evidence:

**(1) Absorption Kinetics of Rimadyl[®] Administered Subcutaneously in Dogs
(Study 1560N-60-99-369)**

(a) Type of Study: Pharmacokinetic

(b) Study Director: Dennis J. Margitich, B.S.
Oread, Inc.
Oread BioSafety Center (OBC)
400 Farmington Avenue
Farmington, CT 06032-1959

(c) General Design:

- 1 Purpose: The objective of this study was to determine if the rate and extent of carprofen absorption after subcutaneous injection is affected by the dose amount administered within a single site.
- 2 Study Design: The investigation was designed as a two period, two sequence, crossover study. Dogs in Sequence A received 2 mg/lb carprofen once at one subcutaneous site in Period 1 and 1 mg/lb carprofen at two separate sites in Period 2. Dogs in Sequence B received 1 mg/lb carprofen each at two separate subcutaneous sites in Period 1 and 2 mg/lb carprofen once at one subcutaneous site in Period 2. A ten-day washout separated study periods.

For each sequence, blood samples were collected from the dogs pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 12, 24, and 48 hours after administration of the first dose of each period.
- 3 Test Animals: Eighteen healthy male Beagle dogs were used for the study.
- 4 Control Drug: None
- 5 Dosage Form: Injectable solution (proposed commercial formulation)
- 6 Route of administration: Dorsoscapular subcutaneous injection
- 7 Dosages used: carprofen: 2 mg/lb once at one subcutaneous site or 1 mg/lb carprofen at two separate sites
- 8 Test Duration: 12 days

- 9 Parameters measured: Carprofen concentrations in plasma were determined using a specific, validated, high performance liquid chromatographic method with fluorescence detection. Plasma concentration data were used to determine the maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC_{0-last} and AUC_{0-inf}), time to peak concentration (T_{max}), elimination constant (K_{el}), and elimination half-life ($T_{1/2}$).

(d) Results: see Table 1.

Table 1: Carprofen bioavailability when the total daily dose is administered in one versus two injection sites.

Parameter	Mean (%CV) One site	Mean (%CV) Two sites	Ratio One site/two sites	90% Confidence limits
AUC_{0-last}	178.5 (26)	163.0 (28)	1.09	0.96 – 1.26
C _{MAX}	12.7 (23)	14.0 (26)	0.91	0.82 – 1.04
T _{MAX}	3.86 (66)	2.56 (45)		
THALF	8.68 (22)	8.40 (22)		

AUC = area under the concentration-time curve, C_{MAX} = maximum plasma concentration, T_{MAX} = time to peak concentration, $THALF$ = elimination half-life
 CV = coefficient of variation

- (e) Conclusions: The statistical results of the study are within the limits established for declaring two treatments as bioequivalent. Therefore, based upon the blood level comparison between one site and two site subcutaneous administrations, it is concluded that the rate constant (expressed as min^{-1}) and extent (F) of carprofen absorption following subcutaneous injection will be equivalent whether carprofen is administered as a once daily or twice daily dose.
- (f) Adverse reactions: There were no adverse effects related to Rimadyl® in any of the dogs in this study.

3. TARGET ANIMAL SAFETY

Target animal safety for Rimadyl® following oral administration is addressed in NADA 141-053. Target animal safety study requirements for approval of the Rimadyl® Injectable were limited to an injection site toleration study provided in NADA 141-199 (approval dated March 3, 2003). No new animal safety data were required for approval of this supplement.

4. 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 cases of accidental human exposure."

5. AGENCY CONCLUSIONS

The data 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 demonstrate that Rimadyl[®] Injectable for dogs, when administered under labeled conditions of use, is safe and effective for the relief of pain and inflammation associated with osteoarthritis.

Rimadyl[®] Injectable is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose canine osteoarthritis and to monitor response to treatment.

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this supplemental approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the 2 mg/lb dosage once daily by subcutaneous injection, for the claim of relief of pain and inflammation associated with osteoarthritis for which this supplement is approved.

In accordance with 21 CFR 514.106(b)(2)(iv) this is a Category II supplemental application that did not require a reevaluation of safety or effectiveness data in the parent application.

Rimadyl[®] Injectable is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
US 4,882,164	February 19, 2008
US 6,013,808	April 15, 2019

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

- a. Veterinary Package Insert
- b. Bottle
- c. Carton

RIMADYL®

(carprofen)



Sterile Injectable Solution

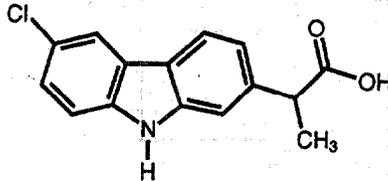
50 mg/mL

Non-steroidal anti-inflammatory drug

For subcutaneous use in dogs only

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

DESCRIPTION: Rimadyl Injectable is a sterile solution containing carprofen, a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the non-proprietary designation for a substituted carbazole, 6-chloro- α -methyl-9H-carbazole-2-acetic acid. The empirical formula is $C_{15}H_{12}ClNO_2$ and molecular weight 273.72. The chemical structure of carprofen is:



Each mL of Rimadyl Injectable contains 50.0 mg carprofen, 30.0 mg arginine, 88.5 mg glycocholic acid, 169.0 mg lecithin, 10.0 mg benzyl alcohol, 6.17 mg sodium hydroxide, with additional sodium hydroxide and hydrochloric acid as needed to adjust pH, and water for injection.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent 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 cyclooxygenase 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 cyclooxygenase, COX-2, generates prostaglandins 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 prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating 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 (DAF), PGE₁, and PGE₂ by its inhibitory effects on prostaglandin biosynthesis.¹

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely 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 exhibits a very small volume of distribution.

Comparison of a single 25 mg dose in Beagle dogs after subcutaneous and oral administration demonstrated that the dorsoscapular subcutaneous administration results in a slower rate of drug input (as reflected by mean peak observed concentrations) but comparable total drug absorption within a 12 hour dosing interval (as reflected by area under the curve from hours zero to 12 postdose).

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the 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%). Some enterohepatic circulation of the drug is observed.

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

DOSAGE AND ADMINISTRATION: The recommended dosage for subcutaneous administration to dogs is 2 mg/lb (4.4 mg/kg) of body weight 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 (2.2 mg/kg) twice daily.

EFFECTIVENESS: Confirmation of the effectiveness of carprofen in controlling osteoarthritis (both once daily and twice daily dosing schedules) was demonstrated in placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of Rimadyl (carprofen) caplets in various breeds of dogs. Dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered Rimadyl at labeled dose. Based upon the blood level comparison between subcutaneous and oral administration, Rimadyl effectiveness after dorsoscapular subcutaneous and oral administration should be similar, although there may be a slight delay in onset of relief after subcutaneous injection.

ANIMAL SAFETY STUDIES: Laboratory studies in unanesthetized dogs and clinical field studies with caplets have demonstrated that Rimadyl is well tolerated in dogs after oral and dorsoscapular subcutaneous administration.

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ANIMAL SAFETY STUDIES: Laboratory studies in unanesthetized dogs and clinical field studies with caplets have demonstrated that Rimadyl is well tolerated in dogs after oral and dorsoscapular subcutaneous administration. In target animal safety studies, Rimadyl 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 significant adverse reactions. 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 6-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 exhibited hypoalbuminemia. The mean albumin level in 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 did 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 gross 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, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral 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 Rimadyl-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in Rimadyl). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving Rimadyl and placebo, respectively. Differences were not statistically significant. 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 pre-treatment values for dogs receiving Rimadyl and placebo, respectively. In the latter study, 3 Rimadyl-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical 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

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

Observation	Rimadyl (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 pre-treatment values; medical judgment is necessary to determine clinical relevance.

Post-Approval Experience: Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting with the oral formulation. The categories of adverse reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: Vomiting, diarrhea, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.

Hepatic: Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function tests, hyperbilirubinemia, bilirubinuria, hypalbuminemia. Approximately one-fourth of hepatic 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, glycosuria.

Behavioral: Sedation, lethargy, hyperactivity, restlessness, aggressiveness.

Hematologic: Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.

Dermatologic: Pruritus, increased shedding, alopecia, pyodermatitis, 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 listed above.

HOW SUPPLIED: Rimadyl injectable is supplied in 20-ml, amber, glass, sterile, multi-dose vials.

REFERENCES: 1. Baruth H, et al: In Anti-inflammatory and Anti-Rheumatic Drugs, Vol. II, Newer Anti-inflammatory Drugs, Rainford KD, ed. CRC Press, Boca Raton, pp. 33-47, 1986.

2. Vane JR, Botting RM: Mechanism of action of anti-inflammatory drugs. *Scand J Rheumatol* 25:102, pp. 9-21.

3. Grossman CJ, Wiseman J, Lucas FS, et al: Inhibition of constitutive and inducible cyclooxygenase activity in human platelets and mononuclear cells by NSAIDs and COX-2 inhibitors. *Inflammation Research* 44:253-257, 1995.

4. Rickerts AP, Lundy KM, Seibel SB: Evaluation of selective inhibition of canine cyclooxygenase 1 and 2 by carprofen and other nonsteroidal anti-inflammatory drugs. *Am J Vet Res* 59:11, pp. 1441-1446, November 1998.

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6. Ceuppens JL, et al: Endogenous prostaglandin E₂ enhances polyclonal immunoglobulin production by ionically inhibiting T suppressor cell activity. *Cell Immunol* 70:41, 1982.

7. Schlemmer RP, et al: The effects of prostaglandin synthesis inhibition on the immune response. *Immunopharmacology* 3:205, 1981.

8. Leung KH, et al: Modulation of the development of cell mediated immunity: possible roles of the products of cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism. *Int J Immunopharmacology* 4:195, 1982.

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11. Kore AM: Toxicology of nonsteroidal anti-inflammatory drugs. *Veterinary Clinics of North America, Small Animal Practice* 20, March 1990.

12. Bins SH: Pathogenesis and pathophysiology of ischemic injury in cases of acute renal failure. *Compend for Cont Ed* 16:1, January 1994.

13. Boothe DM: Prostaglandins: Physiology and clinical implications. *Compend for Cont Ed* 6:11, November 1984.

14. Rubin S: Nonsteroidal anti-inflammatory drugs, prostaglandins, and the kidney. *JAVMA* 188:9, May 1986.

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

NADA #141-199, Approved by FDA

Manufactured by:
Vertore Limited
Dundee, United Kingdom

Distributed by:
Pfizer Animal Health

Sensitivity to drug-associated 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 Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of Rimadyl in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Safety has not been established for IV administration. Studies to determine the activity of Rimadyl when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It is suggested to use different sites for additional injections. If additional pain medication is warranted after administration of the total daily dose of Rimadyl, alternative analgesia should be considered. The use of another NSAID is not recommended.

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 drug is discontinued. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

WARNINGS: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental human exposure. For use in dogs only. Do not use in cats.

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematology 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 for the caplet formulation 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 following 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 of osteoarthritis with once daily oral administration of 2 mg/lb. The following categories of abnormal health observations were reported. The product vehicle served as control.

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

Observation	Rimadyl (n=129)	Placebo (n=132)
Inappetance	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
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PU/PD	0.8	—
SAP increase	7.8	8.3
ALT increase	5.4	4.5
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BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketouria	14.7	9.1

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

Post-Approval Experience: Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reports.

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

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral 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 Rimadyl-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in Rimadyl). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving Rimadyl and placebo, respectively. Differences were not statistically significant. 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 pre-treatment values for dogs receiving Rimadyl and placebo, respectively. In the latter study, 3 Rimadyl-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical 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 at 2-week intervals in 244 dogs, some for as long as 5 years.

Swelling and warmth were associated with the injection site after subcutaneous administration of Rimadyl Injectable. These findings were not clinically significant. Long term use of the injectable has not been studied.

CONTRAINDICATIONS: Rimadyl should not be used in dogs exhibiting previous hypersensitivity to carprofen.

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 maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in 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 disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy.¹¹⁻¹⁴

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, 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 hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously, with appropriate monitoring. Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of Rimadyl with other anti-inflammatory drugs, such as corti-

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pathways of arachidonic acid metabolism. *Immunopharmacology*
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For a copy of the Material Safety Data Sheet (MSDS) or to report adverse
reactions call Pfizer Animal Health at 1-800-366-5288.

NADA #141-199, Approved by FDA

Manufactured by:

Vericore Limited
Dundee, United Kingdom



Distributed by:



Animal Health

Exton, PA 19341, USA
Div. of Pfizer Inc.
NY, NY 10017

1701715

75-0304-X3
October 2002
Printed in USA

RIMADYL®
(carprofen)

Injectable 50 mg/mL



**Non-steroidal
anti-inflammatory drug**

*For subcutaneous use
in dogs only*

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

Contents: 20 mL

NADA #141-199,
Approved by FDA



Each mL of Rimadyl Injectable con-
tains 50 mg of carprofen.

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

Dosage: The recommended dosage
for subcutaneous administration to
dogs is 2 mg/lb (4.4 mg/kg) of body
weight 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
(2.2 mg/kg) twice daily.

Warnings: Keep out of reach
of children. Not for human use.
Consult a physician in cases of
accidental human exposure.
**For use in dogs only. Do not
use in cats.**

**Please Refer to Insert for
Complete Warnings and
Precautions**

Store under refrigeration at

2°-8°C (36°-46°F).

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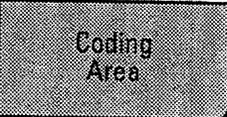
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85-0304-X3

1701714

LOT

EXP



150%

RIMADYL®
(carprofen)
Injectable 50 mg/mL
Contents: 20 mL



1701716

Each mL of Rimadyl contains 50 mg of carprofen. The active ingredient, carprofen, is a non-steroidal anti-inflammatory drug (NSAID) that is used to relieve pain and inflammation associated with osteoarthritis and other musculoskeletal conditions. Rimadyl is indicated for the treatment of pain and inflammation associated with osteoarthritis in dogs. Rimadyl is contraindicated in dogs with a known hypersensitivity to carprofen or any of the other ingredients. Rimadyl should be used with caution in dogs with a history of gastrointestinal, renal, or hepatic disease. Rimadyl should be used with caution in dogs with a history of bleeding disorders. Rimadyl should be used with caution in dogs with a history of hypotension. Rimadyl should be used with caution in dogs with a history of dehydration. Rimadyl should be used with caution in dogs with a history of hypoproteinemia. Rimadyl should be used with caution in dogs with a history of hypokalemia. Rimadyl should be used with caution in dogs with a history of hypocalcemia. Rimadyl should be used with caution in dogs with a history of hypomagnesemia. Rimadyl should be used with caution in dogs with a history of hypophosphatemia. Rimadyl should be used with caution in dogs with a history of hypoglycemia. Rimadyl should be used with caution in dogs with a history of hypothermia. Rimadyl should be used with caution in dogs with a history of hypotension. Rimadyl should be used with caution in dogs with a history of hypovolemia. Rimadyl should be used with caution in dogs with a history of hypoxemia. Rimadyl should be used with caution in dogs with a history of hypoxia. Rimadyl should be used with caution in dogs with a history of hypoxemia. Rimadyl should be used with caution in dogs with a history of hypoxia. Rimadyl should be used with caution in dogs with a history of hypoxemia. Rimadyl should be used with caution in dogs with a history of hypoxia.



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Pfizer Inc.
New York, NY 10017
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