Approval Date: March 3, 2003

FREEDOM OF INFORMATION SUMMARY

New Animal Drug Application

141-199

RIMADYL® INJECTABLE
(carprofen)

" …for the relief of pain and inflammation associated with osteoarthritis in dogs at a dose of 1 mg/lb (2.2 mg/kg) of body weight twice daily."

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 dosage for subcutaneous administration to dogs is 1 mg/lb (2.2 mg/kg) of body weight 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.

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, approved October 25, 1996). The pharmacokinetics of carprofen in dogs following repeated oral and subcutaneous administration was

evaluated in a laboratory study. The results indicate that total drug exposure after a single dose, and at steady state, was similar following subcutaneous administration compared to oral dosing.

The pharmacokinetics of carprofen in dogs following a single administration orally, and by intravenous and subcutaneous injection, were also evaluated in a laboratory study. The results indicate that total drug exposure after a single dose was similar following subcutaneous administration compared to oral dosing.

Based on the similar bioavailability of carprofen, when administered at the recommended dosage to dogs as either Rimadyl® oral caplets or Rimadyl® Injectable solution, no additional clinical effectiveness studies were required for approval of this NADA.

a. Dosage Characterization

The Rimadyl® Injectable dosage of 1 mg/lb bodyweight administered subcutaneously twice daily for the relief of pain and inflammation associated with osteoarthritis was selected for evaluation based on the dosage of the approved oral caplet for this indication (NADA 141-053). Pharmacokinetic data, following a single oral or subcutaneous administration of Rimadyl® demonstrated similar bioavailability of these two formulations (study 2567A-60-97-167). The extent of carprofen absorption for both the oral and injectable formulations was comparable when evaluated under steady state conditions (study 1560N-60-99-302). At steady state, the extent of drug exposure (AUC) for Rimadyl® Injectable administered subcutaneously between the shoulders twice daily at a dosage of 1 mg/lb was equivalent to twice daily oral administration of Rimadyl® caplets. Although small differences were observed in the rate of carprofen absorption from the two formulations, under chronic use conditions, Rimadyl® Injectable (subcutaneous administration) is expected to have comparable systemic safety and will be equally effective in the relief of pain and inflammation associated with osteoarthritis in dogs.

b. Substantial Evidence

(1) Pharmacokinetics of Rimadyl® Following Oral Administration or Subcutaneous Injection in Dogs (Study 1560N-60-99-302)

(a) Type of Study: Pharmacokinetic

(b) Study Director: Karol Bice Godwin, D.V.M.
HTI Bio-Services, Inc.
10326 Roselle Street
San Diego, California 92121

(c) General Design:

1 Purpose: The objective of the study was to evaluate, under laboratory conditions, the relative bioavailability of a 25 mg dose of Rimadyl® administered twice daily as either the approved caplet or as an injectable formulation for subcutaneous administration.

2 Study Design: The investigation was designed as a two period, two sequence, two treatment crossover trial. Treatments were administered twice daily for seven days. A ten-day washout interval separated study periods. For each treatment, blood samples were obtained pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 12 hrs following the first administration. Blood sampling was repeated immediately prior to the last dose and at hrs 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 12, 24, 48, 72, and 96 post-treatment.

Pivotal assumptions supporting data analysis:

There are no active first pass metabolites that affect the safety and effectiveness of carprofen. This information is supported by the corroborative study data where the absolute bioavailability of both the oral and subcutaneous dose were found to exceed 90% (refer to study 2, pg. 7 of this FOI).

Steady state peak-to-trough carprofen concentrations achieved with twice daily SC dosing are comparable to that achieved at steady state with oral carprofen administration. This was confirmed in this study.

Repeated SC injections of the proposed formulation do not alter the product absorption kinetics. This was confirmed in this study.

3 Test Animals: Eighteen healthy male Beagle dogs were used in the study.

4 Control Drug: None

5 Dosage Form: Injectable solution (proposed commercial formulation) and caplets (commercial formulation)

6 Route of Administration: Dorsoscapular subcutaneous injection and oral

7 Dosage used: carprofen: 25 mg

8 Test Duration: 24 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 following the first administration of each dosing period were used to determine the maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) over the first dosing interval (AUC_{0-12}). Following the final dose, plasma concentration data were used to assess peak concentrations ($Cmax_{ss}$), trough concentrations (Cmin) and steady state AUC values (AUC_{ss}). It should be noted that AUC_{ss} is equivalent to AUC extrapolated to time infinity ($AUC_{0-\infty}$) following a single dose. To confirm that the fluctuations in steady state plasma carprofen concentrations after subcutaneous dorsoscapular injection were less than or equal to that observed after oral administration, peak to trough ratios and differences were also assessed after the final dose.

(d) Results: see Table 1

Table 1: Geometric means for response variables for oral and subcutaneous (SC) administration.

	AUC_{ss}*	$Cmax_{ss}$**	$Cmax_{ss}$/ Cmin***	$Cmax_{ss}$- Cmin***	AUC_{0-12}*	Cmax**
Oral	101.92	18.73	3.80	14.12	69.44	15.91
SC	111.01	14.71	2.25	8.14	64.29	7.96
Ratio SC/Oral	1.09	0.79	0.59	0.58	0.93	0.50
Lower Conf Lim	1.02	0.69	0.50	0.44	0.84	0.43
Upper Conf Lim	1.16	0.89	0.69	0.71	1.03	0.58

AUC_{ss} = area under the concentration-time curve at steady state, $Cmax_{ss}$ = maximum plasma concentration at steady state, Cmin = minimum concentration
*expressed as μg*hr/mL
**expressed as μg/mL
***arithmetic means

(e) Conclusions: The results of the study indicate that the two treatments result in equivalent total drug exposure after the first dose and under steady state conditions. Thus, repeated SC injections do not alter product absorption kinetics. However, significantly lower peak concentrations were observed following a single dose. The magnitude of the differences in peak concentrations decreased when measured under steady state conditions. The reduction in difference between

Cmax values observed at steady state is attributable to slower drug absorption following SC vs. oral Rimadyl® administration. This slower absorption process also results in higher Cmin values and significantly smaller peak to trough differences (fluctuations in plasma drug concentrations) as compared to that of oral administration.

Based upon the blood level comparison between subcutaneous and oral administration, carprofen effectiveness after subcutaneous and oral administration should be similar, although there may be a slight delay in the onset of relief after subcutaneous injection.

(f) Adverse reactions: There were no clinically significant adverse effects related to Rimadyl® in any of the dogs in this study.

(2) Relative Bioavailability of Rimadyl® Following Oral, Subcutaneous or Intravenous Administration in Dogs (Study 2567A-60-97-167)

(a) Type of Study: Pharmacokinetic

(b) Study Director: Elizabeth I. Evans, D.V.M.
Midwest Research Institute
425 Volker Boulevard
Kansas City, Missouri 64110

(c) General Design:

1 Purpose: The objective of the study was to evaluate, under laboratory conditions, the absolute bioavailability of Rimadyl® when administered orally or by dorsoscapular subcutaneous injection, and to determine the differences in rate of absorption when Rimadyl® is administered orally or by subcutaneous injection. Absolute oral bioavailability (i.e., the ratio of AUC0-∞ values for oral administration versus intravenous administration) was used to confirm the absence of extensive first pass drug loss when Rimadyl® is orally administered.

2 Study design: The investigation was designed as a three period, three sequence, three-treatment crossover trial. Blood samples after oral and SC doses were collected into heparinized tubes pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, and 48 hrs post-dose. After IV administration, blood was collected pre-dose, 2, 5, 10, 15, and 30 minutes and at hrs 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, and 48 post-dose.

3 Test Animals: Nine healthy male Beagle dogs were used in the study.

4 Control Drug: None

5 Dosage Form: Injectable solution (proposed commercial formulation) and caplets (commercial formulation)

6 Route of Administration: Dorsoscapular subcutaneous and intravenous injection, and oral

7 Dosage used: carprofen: 25 mg

8 Test Duration: 24 days following administration of a single dose in each of three crossover trials.

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}) and area under the concentration-time curve ($AUC_{0\text{-}LOQ}$). Since terminal samples had no quantifiable concentration, values of $AUC_{0\text{-}LOQ}$ closely approximate $AUC_{0\text{-}\infty}$.

(d) Results: see Table 2

Table 2: Geometric means for response variables for oral, intravenous (IV) and subcutaneous (SC) administration.

Cmax (μg/mL)	Mean	Ratio SC/oral	Lower Conf Limit (SC vs Oral)	Upper Conf Limit (SC vs Oral)
Oral	16.4			
IV	37.7			
SC	9.7	0.59	0.5	69
$AUC_{0\text{-}LOQ}$ (μg*hr/mL)		Ratio TRT/IV		
	102	0.91*		
	112			
	105	0.94**	91	116

AUC = area under the concentration-time curve, Cmax = maximum plasma concentration, TRT = treatment
*Oral/IV
**SC/IV

(e) Conclusions: The results of the study indicate that carprofen is equally bioavailable after both oral and subcutaneous administration. In both cases, absolute bioavailability exceeds 90%. This confirms that there is little or no drug lost by first pass metabolism when Rimadyl® is orally administered. As seen in Study #1560N-60-99-302,

subcutaneous injection results in lower peak carprofen values as compared to that observed when Rimadyl® is administered orally.

(f) Adverse reactions: There were no clinically significant adverse effects related to Rimadyl® in any of the dogs in this study.

3. TARGET ANIMAL SAFETY

Studies demonstrating the safety of Rimadyl® caplets for use in dogs are contained in the original FOI summary (NADA 141-053) dated October 25, 1996. No additional animal safety data beyond injection site toleration were required for approval of this NADA.

a. Injection Site Toleration of Rimadyl® Administered Subcutaneously as a Mixed Micelle Formulation in Dogs (Study 1463N-60-99-310)

(1) Type of Study: Safety

(2) Study Director: John W. Campbell, Ph.D.
Southwest Bio-Labs, Inc.
Las Cruces, NM 88005

(3) General Design:

(a) Purpose: The objective of the study was to evaluate injection sites in dogs after dorsoscapular subcutaneous administration of 2 mg/lb (4.4 mg/kg; total daily dose) and 4 mg/lb (8.8 mg/kg; 2x total daily dose) of Rimadyl® Injectable.

(b) Test Animals: 24 purpose-bred Class A Beagle dogs

(c) Control Drug: 0.9% sterile saline

(d) Dosage Form: Injectable solution (proposed commercial formulation)

(e) Route of Administration: Subcutaneous injection

(f) Dosages used: T01 = 0.04 mL/lb saline
T02 = 0.08 mL/lb saline
T03 = 2 mg/lb, 0.04 mL/lb Rimadyl®
T04 = 4 mg/lb, 0.08 mL/lb Rimadyl®

(g) Test Duration: 3 days

(h) Parameters measured: Animals were observed for discomfort upon injection, pain upon palpation, temperature of the overlying skin,

redness and swelling (measured with calipers to the nearest millimeter in the cranial/caudal and medial/lateral dimensions). Injection site observations were made at pre-dosing and at approximately 1, 4, 12, 24, 36, 48, 60, and 72 hours post-dosing.

(i) Results: The animals appeared healthy throughout the study. Animals treated with saline or Rimadyl® showed no observable discomfort during injection of the control or Rimadyl® Injectable. Following subcutaneous administration of Rimadyl® a transient, soft, nonpainful swelling was commonly observed. This was not detected after 24 hours at the label dose and 48 hours at 2X (the maximum width and length recorded for the two doses were 4 cm and 6.5 cm, and 6 cm and 8.5 cm, respectively).

(4) Statistical Analysis: none

(5) Conclusions: There was swelling and warmth associated with the injection site after left or right dorsoscapular subcutaneous administration of Rimadyl®. These findings were not of clinical significance. The injectable formulation is acceptable for subcutaneous administration.

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)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval.

Rimadyl® Injectable is under the following U.S. patent number:

U.S. Patent Number	Date of Expiration
US 4,882,164	February 19, 2008

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

a. Veterinary Package Insert

b. Bottle

c. Carton