Approval Date: March 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 ($AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$), 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
$AUC_{0\text{-}last}$	178.5 (26)	163.0 (28)	1.09	0.96 – 1.26
CMAX	12.7 (23)	14.0 (26)	0.91	0.82 – 1.04
TMAX	3.86 (66)	2.56 (45)		
THALF	8.68 (22)	8.40 (22)		

AUC = area under the concentration-time curve, CMAX = maximum plasma concentration, TMAX = 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.S. Patent Number	Date of Expiration
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