Freedom of Information Summary

I. General Information

NADA Number:	NADA 141-111
Sponsor:	Pfizer Inc. 235 East 42nd Street New York, New York 10017
Generic Name:	Carprofen
Trade Name:	Rimadyl® chewable tablets
Marketing Status:	Prescription

II. Indications for Use:

Rimadyl® chewable tablets are indicated for the relief of pain and inflammation associated with osteoarthritis in dogs.

III. Dosage Form, Route of Administration and Recommended Dosage:

A. Dosage Form: Rimadyl® chewable tablets are available as 25 mg, 75 mg, and 100 mg scored tablets.

B. Route of Administration: Oral

C. Recommended Dosage: The recommended dosage for oral administration to dogs is 1 mg/lb of body weight twice daily. Rimadyl® chewable tablets are scored and the dosage should be calculated in half-tablet increments. Tablets can be halved by placing the tablet on a hard surface and pressing down on both sides of the score. Rimadyl® chewable tablets are palatable and willingly consumed by most dogs. Tablets may be fed free choice or placed on food. Care should be taken to ensure that the dog consumes the complete dose.

IV. Effectiveness:

A. Reference is made to information contained in the original FOI Summary for NADA 141-053.

B. Studies

1. Relative Bioavailability of a single 1.0 mg/lb and 3.0 mg/lb dose of orally administered carprofen in caplet and chewable dose forms in dogs (Study No. 2567A-60-97-106).

   a. Type of Study: Plasma Level Bioavailability

   b. Investigator: Dr. Elizabeth I. Evans
   Midwest Research Institute (MRI)
   425 Volker Boulevard
   Kansas City, Missouri

   c. General Design:

      i. Purpose: The objective of the study was to demonstrate comparable relative bioavailability between single doses of 25 mg and 75 mg of carprofen in a caplet formulation and single doses of 25 mg and 75 mg of carprofen in a chewable tablet formulation.

      ii. Test Animals: Sixteen (16) healthy male Beagle dogs approximately 9 months of age and ranging in weight from 20.3-25.0 lb participated in the study.

      iii. Control Group: Rimadyl® caplets (25 mg and 75 mg)

      iv. Dosage Form: Rimadyl® chewable tablets (25 mg and 75 mg). The chewable tablets administered were the same as the proposed market formulation.

      v. Route of Administration: Oral

      vi. Dose: Carprofen 1.0 and 3.0 mg/lb as a single dose.

      vii. Study Design: The study was performed in two phases. Phase I was a two period, two treatment cross-over experimental design, with each replicate being separated by a washout period of 10 days. Study dogs were randomly assigned to two groups (A or B) of eight dogs each. On Day 0, Group A dogs received 1.0 mg/lb of carprofen as a 25 mg caplet; Group B dogs received 1.0 mg/lb of carprofen as a 25 mg chewable tablet. On Day 10, Group A dogs received 1.0 mg/lb of carprofen as a 25 mg chewable tablet; Group B dogs received 1.0 mg/lb of carprofen as a 25 mg caplet. Phase II was a two treatment parallel experimental design with dosing after an 11 day washout period. Study dogs were again randomly assigned to one of two groups (C or D) of eight dogs each. On Day 21, Group C dogs

received 3.0 mg/lb of carprofen as a 75 mg caplet; Group D dogs received 3.0 mg/lb of carprofen as a 75 mg chewable tablet.

viii. Parameters measured: For both study phases, plasma samples were collected for carprofen analysis prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours following dosing. Plasma samples were assayed for carprofen using a validated HPLC method.

d. Results: Means and confidence interval boundary information for the pharmacokinetic variables ($AUC_{0\text{-}LOQ}$, C_{max}, and T_{max}) are summarized in Tables 1 and 2.

Table 1. Means and Confidence Intervals: 25 mg Carprofen Caplet and 25 mg Carprofen Chewable Tablet (Phase I, 1.0 mg/lb Dosing)

Pharmacokinetic Variable	Mean[1]	90% Confidence Interval[2] Lower Bound (%)	Upper Bound (%)
$AUC_{0\text{-}LOQ}$ (μg/mL●hr)			
Caplet	125.2		
Chewable Tablet	119.6	-12.7	4.6
C_{max} (μg/mL)			
Caplet	18.2		
Chewable Tablet	16.3	- 17.4	-2.3
T_{max} (hours)			
Caplet	1.49		
Chewable Tablet	1.81	2.4	44.9

[1]$AUC_{0\text{-}LOQ}$ and C_{max} variables presented as backtransformed geometric means, T_{max} presented as least squares mean.
[2]Confidence Interval = the percentage by which the lower and upper bounds of the 90% confidence interval based on the difference in the mean of the chewable tablet formulation minus the mean of the caplet formulation lie from the caplet formulation reference mean.

Table 2. Means and Confidence Intervals: 75 mg Carprofen Caplet and 75 mg Carprofen Chewable Tablet (Phase II, 3.0 mg/lb Dosing)

Pharmacokinetic Variable	Mean[1]	90% Confidence Interval[2] Lower Bound (%)	Upper Bound (%)
$AUC_{0\text{-}LOQ}$ (μg/mL●hr)			
Caplet	347.2		
Chewable Tablet	311.1	-31.6	18.4
C_{max} (μg/mL)			
Caplet	41.7		
Chewable Tablet	41.3	-25.6	27.8
T_{max} (hours)			
Caplet	1.94		
Chewable Tablet	1.44	-63.1	11.5

[1]$AUC_{0\text{-}LOQ}$ and C_{max} variables presented as backtransformed geometric means, T_{max} presented as least squares mean.
[2]Confidence Interval = the percentage by which the lower and upper bounds of the 90% confidence interval based on the difference in the mean of the chewable tablet formulation minus the mean of the caplet formulation lie from the caplet formulation reference mean.

The area under the curve ($AUC_{0\text{-}LOQ}$), C_{max} and T_{max} were highly similar between the 25 mg dose strengths of each formulation. Ninety percent confidence intervals applied to log transformed data for $AUC_{0\text{-}LOQ}$ and C_{max} for the chewable tablet were within ± 20% of the mean of the caplet for the 25 mg strength but not the 75 mg. strength. For the T_{max} variable, the 90% confidence intervals bounded zero for both dose strengths.

In Phase I, there were no significant ($P > 0.05$) differences between geometric mean plasma concentrations of carprofen administered as a 25 mg caplet versus as a 25 mg chewable tablet at any time point. Similarly, in Phase II, there were no significant ($P > 0.05$) differences between geometric mean plasma concentrations of carprofen administered as a 75 mg caplet versus as a 75 mg chewable tablet at any time point.

e. Statistical Methods: The data were analyzed with a mixed model procedure (SAS/STAT User's Guide, SAS Institute, Cary, North Carolina). Three pharmacological variables [area under curve ($AUC_{0\text{-}LOQ}$, μg/mL•hr), maximum concentration (C_{max}, μg/mL) and time at

maximum concentration (T_{max}, hours)] were calculated for each animal treatment combination. For each of these pharmacological variables the mixed model procedure partitioned the total sum of squares into sources appropriate for the design and estimated the treatment means and their standard deviations. Using the treatment means and their standard deviations, ninety per cent (90%) confidence intervals for the difference between the chewable tablet and the caplet, relative to the caplet, were calculated. The $AUC_{0\text{-}LOQ}$ and C_{max} variables were transformed to the natural log before analysis and the treatment least squares means were backtransformed to geometric means.

f. Suspected Adverse Events: Animals remained healthy for the duration of the study. Two single incidents of abnormal gastrointestinal signs were noted in two dogs (one episode of vomiting and one episode of soft stool occurring within 48 hours and 6 days of dosing, respectively). Abnormal clinical signs were self-limiting and resolved without veterinary care.

g. Conclusions: The area under the time-concentration curve ($AUC_{0\text{-}LOQ}$) and maximum serum carprofen concentration (C_{max}) are statistically equivalent between carprofen 25 mg caplets and 25 mg chewable tablets. The area under the time-concentration curve ($AUC_{0\text{-}LOQ}$) and maximum serum carprofen concentration (C_{max}) were not statistically equivalent between carprofen 75 mg caplets and 75 mg chewable tablets. These data confirm equivalent drug bioavailability between the two formulations for the 25 mg concentration and not the 75 mg concentration.

2. Bioavailability of 75 mg caplets and 75 mg chewable tablets (Study # 2567-60-98-090)

a. Type of Study: Relative Bioavailability

b. Investigator: Dr. Elizabeth I. Evans
Midwest Research Institute (MRI)
45 Volker Boulevard
Kansas City, Missouri

c. General Design:

i. Purpose: The objective of this study was to demonstrate comparable relative bioavailability between single doses of 75 mg of carprofen in a caplet formulation and single doses of 75 mg of carprofen in a chewable tablet formulation. This study was conducted as a follow-up study due to the failure to show comparable bioavailability between

the 75 mg caplet formulation and the chewable formulation in Phase II of Study # 2567A-60-97-106.

ii. Test Animals: 20 healthy male Beagle dogs approximately 8-9 months of age and ranging in weight from 20.8-31.1 lb were selected for the study.

iii. Control Group: Rimadyl® caplets (75 mg)

iv. Dosage Form: Rimadyl® chewable tablets (75 mg) and the proposed market chewable formulation of Rimadyl.

v. Route of Administration: Oral

vi. Dose: 3.0 mg/lb of carprofen as 75 mg caplet and 75 mg chewable tablet.

vii. Study Design: The study was a two-period, two treatment crossover experimental design, with each replicate being separated by a washout period of 10 days. Dogs were randomly assigned to two groups (A or B) of 10 dogs each and dosed with approximately 3.0 mg/lb of carprofen as a 75 mg caplet or a 75 mg chewable tablet.

viii. Parameters measured: Plasma samples were collected for carprofen analyses prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 ,24, 36, and 48 hours following dosing. Plasma samples were assayed for carprofen using a validated HPLC method.

d. Results: Means and confidence interval boundary information for the pharmacokinetic variables (AUC_{LOQ}, $C_{max,}$ and T_{max}) are summarized in Table 1.

Table 1. Means and Confidence Intervals: 75 mg Carprofen Caplet and 75 mg Carprofen Chewable Tablet (Phase II, 3.0 mg/lb Dosing)

Pharmacokinetic Variable	Mean[1]	90% Confidence Interval[2] Lower Bound (%)	Upper Bound (%)
$AUC_{0\text{-}LOQ}$ (μg/mL●hr)			
Caplet	381.2[a]		
Chewable Tablet	382.0[a]	-5.9	6.8
C_{max} (μg/mL)			
Caplet	44.5[a]		
Chewable Tablet	44.0[a]	-11.1	10.1
T_{max} (hours)			
Caplet	1.48[a]		
Chewable Tablet	2.23[b]	25.5	76.2

[1] $AUC_{0\text{-}LOQ}$ and C_{max} variables presented as back-transformed geometric means, T_{max} presented as least squares mean.
[2] Confidence Interval = the percentage by which the lower and upper bounds of the 90% confidence interval based on the difference in the mean of the chewable tablet formulation minus the mean of the caplet formulation lie from the caplet formulation reference mean.
[a,b] Means within pharmacological variables with unlike superscripts are significantly ($P \leq 0.05$) different.

There were no significant ($P > 0.05$) differences between the 75 mg caplet and chewable tablet formulations for the area under the curve ($AUC_{0\text{-}LOQ}$) and maximum plasma carprofen concentration (C_{max}) variables. Ninety percent confidence intervals applied to log transformed data for $AUC_{0\text{-}LOQ}$ and C_{max} for the chewable tablet were within $\pm$ 20% of the mean of the caplet for the 75 mg strength. These data confirm equivalent drug bioavailability between the two formulations as administered.

e. Statistical Methods: The data were analyzed with a mixed model procedure (SAS/STAT User's Guide, SAS Institute, Cary, North Carolina). Three pharmacological variables [area under curve ($AUC_{0\text{-}LOQ}$, μg/mL•hr), maximum concentration (C_{max}, μg/mL) and time at maximum concentration (T_{max}, hours)] were calculated for each animal treatment combination. For each of these pharmacological variables the mixed model procedure partitioned the total sum of squares into sources appropriate for the design and estimated the treatment means and their standard deviations. Using the treatment means and their standard deviations, ninety per cent (90%) confidence intervals for the difference

between the chewable tablet and the caplet, relative to the caplet, were calculated. The $AUC_{0\text{-}LOQ}$ and C_{max} variables were transformed to the natural log before analysis and the treatment least squares means were backtransformed to geometric means.

f. Suspected adverse events: Animals remained healthy for the duration of the study. Two single incidents of abnormal gastrointestinal signs were noted in two dogs (one episode of vomiting after consumption of bandage material and one episode of loose stool which occurred within 8 hours and 36 hours after dosing, respectively). A third dog was noted to have superficial carpal lesions at approximately 24 hours after dosing, likely due to self-induced trauma from rubbing and /or catheter tape. Abnormal clinical signs were self-limiting and resolved without veterinary care.

g. Conclusions: Based on confidence intervals, the $AUC_{0\text{-}LOQ}$ and the C_{max} were equivalent between the 75 mg carprofen caplet and chewable tablet formulations. These data confirm equivalent drug bioavailability between the two formulations at the 75 mg dosage strength.

3. Palatability of twice-daily chewable tablets containing 25 mg or 100 mg of carprofen. (Study No. 2767A-60-97-105).

a. Type of Study: Palatability

b. Investigator: Dr. David R. Young
Young Veterinary Research Services
Turlock, California

c. General Design:

i. Purpose: The objective of this study was to demonstrate in small and large dogs the palatability of twice-daily chewable tablet formulations containing either 25 mg carprofen (for small dogs) or 100 mg carprofen (for large dogs) compared to the same formulation containing no drug.

ii. Test Animals: Thirty (30) adult mixed breed and purebred dogs (15 small dogs and 15 large dogs) of mixed sexes and ranging in age from 2 to 8 years participated in the study.

iii. Control Group: Placebo (same as Rimadyl® chewable tablet formulation with the omission of the active ingredient).

iv. Dosage Form: Rimadyl® chewable tablets (25 mg and 100 mg). The chewable tablets administered were the same as the proposed market formulation.

v. Route of Administration: Oral

vi. Dose: 25 mg to small dogs (8.3-16.9 kg) and 100 mg to large dogs (23.4-34.7 kg) twice daily for 14 days. Placebo: 0 mg of carprofen twice daily for 14 days.

vii. Study Design: On Days -3 to -1, each dog was pre-conditioned to a two position palatability testing rack and testing procedures by offering commercially available dog treats in each of the two test positions. From Day 0 through Day 13, dogs were offered the two chewable tablet formulations twice daily (morning and afternoon) via the testing rack. Small dogs were offered tablets containing 25 mg carprofen (Tablet A) or no drug (Tablet B), while large dogs were offered tablets containing 100 mg carprofen (Tablet C) or no drug (Tablet D). Food was removed at least two hours prior to morning testing and was not available until completion of the afternoon testing. The position location for each tablet on each day (both morning and afternoon) was randomly determined with the restriction that each formulation (placebo or active) was offered in each position of the rack an equal number of times during the study period.

viii. Parameters measured: An observer blinded to treatment determined if a dog consumed a tablet. A tablet was not considered consumed until it was completely swallowed. A Yes or No consumption score was recorded for each tablet for each dog. Five minutes was allowed for each palatability test. Dogs were observed twice daily for adverse reactions and for general physical health.

d. Results: 27 of the 30 dogs consumed every tablet offered at every trial. This gives a 95% confidence interval of (73.5%, 97.9%) for the percentage of dogs in the target population who are likely to consume every tablet offered on repeated trials. One dog refused both tablets on only one trial but consumed both tablets for the other 27 trials. Two dogs refused both tablets on 13 of the 28 trials. Of these two dogs, one ate only the drug tablet on two of the trials, ate only the placebo tablet on one of the trials, and consumed both tablets on the remaining 12 trials. The other dog ate only the placebo tablet on one of the other trials, and consumed both tablets on the remaining 14 trials.

e. Statistical Methods: The data from the small and large dogs were pooled. The dog was considered to be the independent experimental unit of the

analysis, and 95% confidence intervals were calculated from exact procedures for the percentage of dogs in the target population that could be expected to consume all tablets on repeated trials.

f. Suspected adverse events: Vomitus or material possibly representing vomitus was observed in the runs of two dogs during palatability testing. Soft feces was observed in the runs of four dogs during palatability testing. One of these dogs was also reported to be depressed on one of the days soft feces was noted. These clinical signs were mild, self-limiting and resolved without veterinary care. In general, dogs remained healthy throughout the study and maintained their body weight.

g. Conclusions: Carprofen as a 25 mg chewable tablet (for small dogs) and carprofen as a 100 mg chewable tablet (for large dogs) was highly palatable and well tolerated by both weight classes of dogs.

4. Relative dissolution of 25, 75 and 100 mg dose strengths of carprofen in caplet and chewable tablet formulations (Study No.: 2567A-60-97-137).

a. Type of study: *In vitro* dissolution

b. Investigator: Ronald G. Holtgrewe
Pfizer Animal Health
601 W. Cornhusker Hwy.
Lincoln, Nebraska

c. General Design

i. Purpose: The objective of the study was to demonstrate dissolution profiles of 25, 75 and 100 mg dose strengths of the carprofen chewable tablet formulation and the equivalent dose strengths of the carprofen caplet formulation. These dissolution data support the approval of the 100 mg chewable tablet.

ii. Control Group: Rimadyl® caplets (25 mg, 75 mg and 100 mg). The caplets were the same as the commercially marketed formulation.

iii. Dosage Form: Rimadyl® chewable tablets (25 mg, 75 mg and 100 mg). The chewable tablets were the same as the proposed market formulation.

iv. Study Design: Two identical dissolution apparatuses (USP apparatus 2) were used, one for the chewable tablets and one for the caplets. Six chewable tablets and six caplets (two of each dose strength) were tested daily. The dissolution media consisted of USP simulated intestinal fluid

without enzymes, pH 7.5. Dissolution of the chewable tablets was performed at 100 rpm for 120 minutes with samples collected at seven time periods (5, 15, 30, 45, 60, 90 and 120 minutes). There was no attempt to break or pulverize chewable tablets prior to addition to the dissolution media. Carprofen caplets were tested at 50 rpm for 30 minutes, with samples collected at three time periods (5, 15 and 30 minutes).

v. Parameters Measured: Carprofen content of each chewable tablet sample was determined by high performance liquid chromatography (HPLC). Carprofen content of each caplet sample was determined by measuring spectrophotometric absorbance. The percent of drug released from each dose strength for each formulation was calculated at each timepoint.

d. Results:

Although the *in vitro* dissolution rate for the chewable tablets was significantly slower than that of the caplets, both formulations succeeded in demonstrating greater than 87% dissolution by the end of the respective sampling periods (see Tables 6 and 7). The mean percent release at 30 minutes for the 25 mg and 100 mg caplet formulations were 97.0% and 93.4% respectively, a difference of approximately 3.6%. The mean percent release at 120 minutes for the 25 mg and 100 mg chewable tablets were 91.4% and 88.3% respectively, a difference of approximately 3.1%.

There were significant differences ($P \leq 0.05$) in the percent release between the 25 mg and 75 mg caplets and 25 and 100 mg caplets at all three sampling times (5, 15 and 30 minutes). There were also significant differences ($P \leq 0.05$) between the 75 mg and 100 mg caplets at 5 and 15 minutes, but not ($P > 0.05$) at 30 minutes.

Table 6. Mean Percent Carprofen Release - Caplets

	Time (minutes)		
Dose	5	15	30
25 mg	85.9	94.7	97.0
75 mg	59.1	88.7	94.6
100 mg	77.2	91.0	93.4
Contrast			
25 mg vs. 75	*	*	*
25 mg vs.	*	*	*
75 mg vs.	*	*	ns

* = significant difference ($P \leq 0.05$) ns = no significant difference ($P > 0.05$)

There were no significant differences ($P > 0.05$) in percent release between the 25 mg and 75 mg chewable tablets and 25 mg and 100 mg chewable tablets at 5 minutes. There were significant differences ($P \leq 0.05$) at all other sampling times (15, 30, 45, 60, 90 and 120 minutes). There were no significant differences ($P > 0.05$) between the 75 mg and 100 mg chewable tablet at any sampling time.

Table 7. Mean Percent Carprofen Release - Chewable Tablets

	Time (minutes)						
Dose Strength	5	15	30	45	60	90	120
25 mg							
75 mg	12.9	34.3	53.2	64.3	73.5	84.8	87.1
100 mg	12.7	35.3	54.2	64.6	73.0	86.3	88.3
Contrast							
25 mg vs. 75	ns	*	*	*	*	*	*
25 mg vs 100	ns	*	*	*	*	*	*
75 mg vs 100	ns	ns	ns	ns	ns	ns	ns

* = significant difference ($P \leq 0.05$) ns = no significant difference ($P > 0.05$)

* = significant difference ($P \leq 0.05$) ns = no significant difference ($P > 0.05$)

In addition, the f2 factor, based upon the comparative profiles of the 75 mg and 100 mg chewable tablets, was 97. This value is contained within the limits of 50 to 100, indicating that the two dissolution profiles are comparable.

e. Statistical Methods:

The data were analyzed with a mixed model procedure (SAS/STAT User's Guide, SAS Institute, Cary, North Carolina). The response variable (percent carprofen released) was analyzed using a multivariate, repeated measures approach to assess the effect of dosage strength and sampling time (the fixed effects). The variability attributable to block (day during which the dissolution was conducted) was treated as a random variable. One degree of freedom contrasts between treatments (dose strengths) at each time period were made. The analysis was carried out separately for the two formulations.

Since the 75 mg chewable tablets was shown to be bioequivalent to the 75 mg caplet formulation, additional support of the waiver request for the 100 mg chewable tablets was obtained by estimating the f2 factor, thereby confirming the similarity in the profiles for the 75 mg and 100

mg chewable tablets. This model-independent metric is estimated as follows:

$$f2 = 50 * \log\{[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)]^{-0.5} * 100\}$$

where n = number of time points
R_t = dissolution value of the reference batch at time t
T_t = the dissolution value of the test batch at time t.

For curves to be considered similar, f2 values should range between 50-100.

f. Conclusions:

Waiver of *in vivo* bioequivalence study requirements for the 100 mg chewable tablets is granted on the basis of the following information: the lack of significant differences between the percent carprofen dissolved from the 75 mg and 100 mg caplet formulations, the similarity in the *in vitro* dissolution profiles of the 75 mg and 100 mg chewable tablets, and the successful demonstration of *in vivo* product bioequivalence for the 75 mg chewable tablet and the 75 mg caplet formulation. Accordingly, the 100 mg chewable tablets and 100 mg caplets are determined to be bioequivalent.

V. Animal Safety:

Studies demonstrating the safety of Rimadyl® chewable tablets for use in dogs is contained in the FOI Summary for the approval for Rimadyl® caplets under NADA 141-053. No further studies were conducted with Rimadyl® chewable tablets.

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 NADA. Rimadyl® chewable tablets are approved for use in dogs only.

Human Safety Relative to Possession, Handling and Administration:

Labeling contains adequate caution/warning statements.

VII. Agency Conclusions:

Data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. Its demonstrates that Rimadyl® chewable tablets (carprofen), when used under labeled conditions of use, are safe and effective.

Rimadyl® chewable tablets are restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine when a dog has osteoarthritis which is clinically severe enough to warrant treatment with such a non-steroidal anti-inflammatory drug.

Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval for non food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the 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.

Labeling:

Package Insert
Carton Label
Bottle Label