Approval Date: November 25, 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-498

NOROCARP Caplets
(carprofen)
Caplets

Indicated for relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs

Sponsored by:

Norbrook Laboratories, Ltd.

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number:	ANADA 200-498
b. Sponsor:	Norbrook Laboratories, Ltd. Station Works Newry BT35 6JP Northern Ireland Drug Labeler Code: 055529
U.S. Agent:	Bill Zollers, Ph.D Norbrook, Inc. 9733 Loiret Boulevard Lenexa, KS 66219
c. Established Name:	Carprofen
d. Proprietary Name:	NOROCARP Caplets
e. Dosage Form:	Caplets
f. How Supplied:	25 mg caplets in bottles of 30, 60 and 180 caplets 75 mg caplets in bottles of 30, 60 and 180 caplets 100 mg caplets in bottles of 30, 60 and 180 caplets
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	25 mg, 75 mg, and 100 mg
i. Route of Administration:	Oral
j. Species/Class:	Dogs
k. Recommended Dosage:	2 mg/lb (4.4 mg/kg) of body weight. 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. For the control of postoperative pain, administer approximately 2 hours before the procedure. Caplets are scored and dosage should be calculated in half-caplet increments.
l. Pharmacological Category:	Non-steroidal, anti-inflammatory drug (NSAID)

m. Indications:	NOROCARP Caplets is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.
n. Pioneer Product:	RIMADYL Caplets; carprofen; NADA 141-053; Pfizer, Inc.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

A. Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic caplet formulation and pioneer caplet formulation of carprofen.

Testing Facility: Norbrook Laboratories Limited,
Research Division
105, Armagh Road
Newry,
Co. Down,
Northern Ireland, BT35 6PU

Objective: The objective of this study was to determine the comparative blood-levels of Norbrook Laboratories Limited's 25 mg carprofen caplet (generic) and Pfizer Animal Health's 25 mg RIMADYL caplet (reference) in a two period crossover study in dogs.

Summary: The design of this study is a comparative bioavailability study using healthy adult dogs in a single-dose, two-period, two sequence, crossover design with randomization of experimental units to two sequences. Fourteen dogs (7 males and 7 females) were blocked by weight without regard to sex and, within block, randomly assigned to either of two treatment sequences where the treatment sequences were reference followed by generic or vice versa. A 35-day washout interval separated the two periods. Blood samples were collected at approximately 17 hours before dose administration, and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.66, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0, 48.0 and 72.0 hours following dose administration for the measurement of carprofen in plasma.

Results: The area under the curve was compared using the trapezoidal rule from time 0 out to the last sampling time associated with quantifiable drug concentrations (AUC). The natural logarithm of AUC was computed and used as the variable for analysis. The maximum concentration measured for all time periods (C_{MAX}) was determined and the natural logarithm of C_{MAX} was computed and used as the variable for analysis.

The criteria for determining bioequivalence, as described in CVM's Bioequivalence Guidance is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the log scale of AUC and C_{MAX} and then take the anti-log of the confidence limits multiplied by 100. The resulting bounds should be between 80.00% and 125.00%. As seen in the table below both AUC and C_{MAX} fall within those bounds.

Variable	Norbrook Mean	Pfizer Mean	Lower Bound	Upper Bound
AUC (µg/mL*hr)	403.2*	375.7*	100.38%	114.74%
C_{MAX} (µg/mL)	37.7*	37.1*	86.34%	119.85%
T_{MAX} (hr)	3.43†	2.62†	NA	NA

* Geometric Mean
† Arithmetic Mean

The variable time to maximum concentration (T_{MAX}) is permitted to be interpreted by clinical judgment. In this case, there is no reason to expect the difference in T_{MAX} will affect the efficacy of the drug, since both AUC and C_{MAX} are bioequivalent and the product is administered as a single dose. Therefore, the study objective to determine the bioequivalence of the generic and pioneer carprofen caplets was achieved**.**

B. Dissolution Study

Objective: *In vitro* dissolution data were submitted in support of a request for waiver of *in vivo* bioequivalence study requirements for the 75 mg and 100 mg strength caplets.

Testing Facility: Norbrook Laboratories Limited,
Research Division
105, Armagh Road
Newry,
Co. Down,
Northern Ireland, BT35 6PU

Study Design: Twelve tablets of each product strength were examined using USP 26, dissolution apparatus 2 (paddle) at 50 rpm. The dissolution medium was USP simulated intestinal fluids without enzyme, pH 7.5. This is the same method that has been used for quality control purposes for RIMADYL caplets. Samples were taken at 5, 10, 15, 20, and 30 minutes of testing and the carprofen concentrations were determined by HPLC with UV

detection. The percent drug released from each strength and for each formulation was calculated at each time point.

Similarity of profiles was based upon the model-free approach defined in CDER's 8/97 guidance for industry titled "Dissolution Testing of Immediate Release Dosage Forms". In brief, the similarity factor (f_2) used for confirming comparability is defined as follows:

$$f_2 = 50*\log\{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} * 100\}$$

where n = the number of time points, R_t is the mean dissolution value of the reference product at time t, and T_t is the mean dissolution value of the test product at time t. Comparability is defined by f_2 values are equal to or greater than 50.

Results: The relative dissolution profiles for the test and reference products are provided in Figures 1 – 3.

Figure 1: Comparative mean dissolution profiles: 25 mg caplet

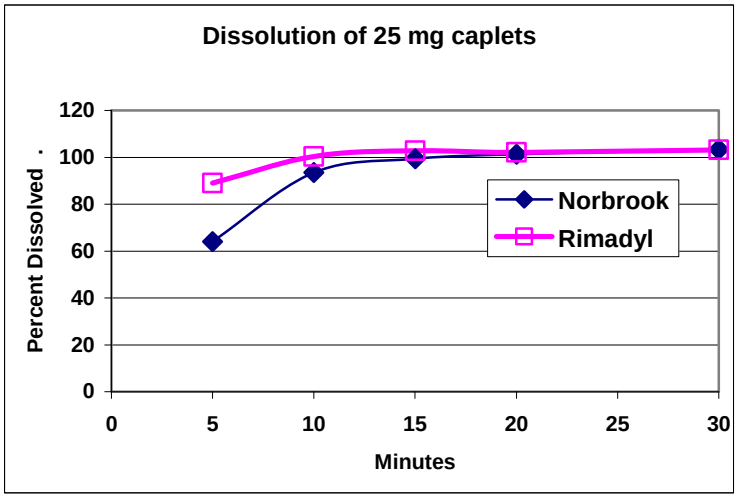


Figure 2: Comparative mean dissolution profiles: 75 mg caplet

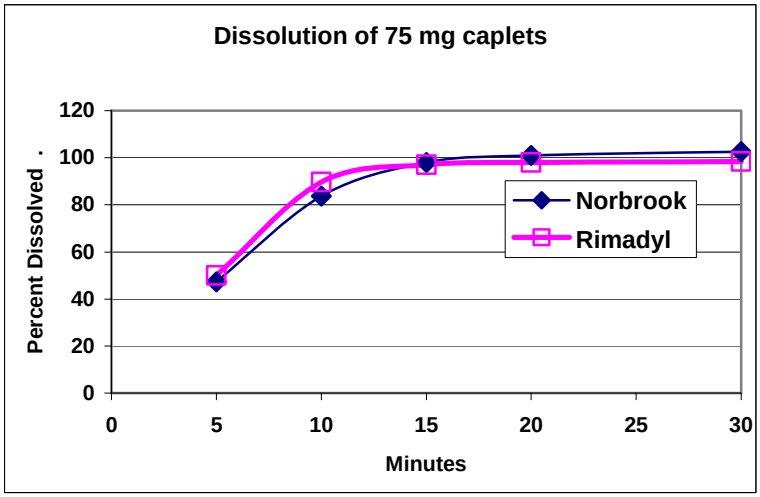
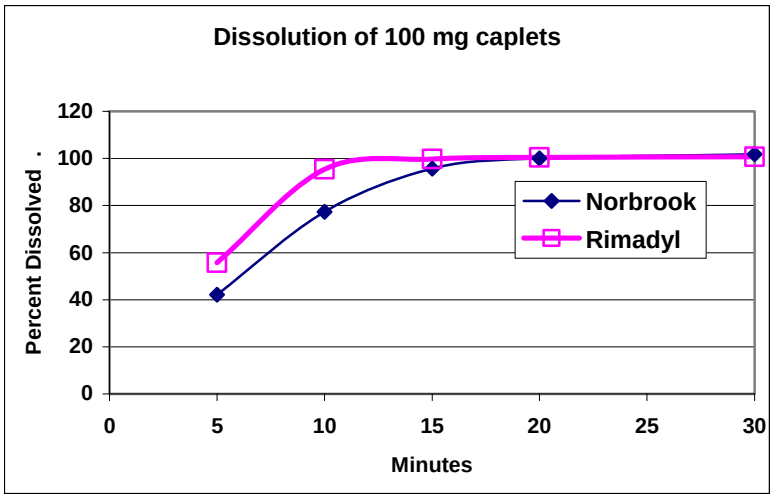


Figure 3: Comparative mean dissolution profiles: 100 mg caplet



Conclusions: As seen in these figures, although the Norbrook product had a slightly slower initial dissolution rate than Rimadyl, by 15 minutes of testing, both products and all strengths were >90% dissolved. Furthermore, since the 25 mg test and reference products are bioequivalent, we see that the slight initial differences in percent dissolved does not influence product relative bioavailability. Accordingly, we conclude that this difference in the initial *in vitro* dissolution results will not influence product relative bioavailability.

In addition, the formulations of the Norbrook product demonstrated dose proportionality. Consequently, considering these findings along with the determination of product bioequivalence, CVM concludes that Norbrook has submitted the information needed to support the granting of a biowaiver for their 75 mg and 100 mg strength caplets.

3. 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 ANADA.

Human Warnings are provided on the product label as follows:

Keep out of the reach of children.
Not for human use.
Consult a physician in cases of accidental ingestion by humans.

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that NOROCARP Caplets, when used under its proposed conditions of use, is safe and effective for its labeled indications.

5. ATTACHMENTS:

Facsimile Generic Labeling and Currently Approved Pioneer Labeling are attached as indicated below:

<u>Generic Labeling for ANADA 200-498:</u>
Package Insert
Dog Owner Information Sheet
Bottle label and carton for the following:
25 mg caplets in bottles of 30, 60 and 180 caplets
75 mg caplets in bottles of 30, 60 and 180 caplets
100 mg caplets in bottles of 30, 60 and 180 caplets

<u>Pioneer Labeling for NADA 141-053:</u>
Package Insert
Dog Owner Information Sheet
Bottle label for the following:
25 mg caplets in bottles of 30, 60 and 180 caplets
75 mg caplets in bottles of 30, 60 and 180 caplets
100 mg caplets in bottles of 30, 60 and 180 caplets