Date of Approval: December 14, 2012

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-543

Cefpodoxime Proxetil

(cefpodoxime proxetil)

Tablets

Dogs

For the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius*, *Staphylococcus aureus*, *Streptococcus canis* (group G, β hemolytic), *Escherichia coli*, *Pasteurella multocida*, and *Proteus mirabilis*.

Sponsored by:

Putney, Inc.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-543

B. Sponsor

Putney, Inc.
400 Congress St., suite 200
Portland, ME 04101

Drug Labeler Code: 026637

C. Proprietary Name

Cefpodoxime Proxetil Tablets

D. Established Name

cefpodoxime proxetil

E. Pharmacological Category

Antimicrobial

F. Dosage Form:

Oral tablet

G. Amount of Active Ingredient

100 mg, 200 mg

H. How Supplied

Bottles containing 100 mg x 100 count or 200 mg x 100 count tablets

I. Dispensing Status

Rx

J. Dosage Regimen

5-10 mg/kg (2.3-4.5 mg/lb) body weight once a day for 5-7 days or 2-3 days beyond the cessation of clinical signs, up to a maximum of 28 days. Treatment of acute infections should not be continued for more than 3-4 days if no response to therapy is seen.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

For the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius*, *Staphylococcus aureus*, *Streptococcus canis* (group G, β hemolytic), *Escherichia coli*, *Pasteurella multocida*, and *Proteus mirabilis*.

N. Reference Listed New Animal Drug

SIMPLICEF Tablets; cefpodoxime proxetil; NADA 141-232; Pharmacia & Upjohn Co., a Division of Pfizer, Inc.

II. BIOEQUIVALENCE:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act of 1988, an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (reference listed new animal drug or RLNAD). 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. Information to show that the generic version is bioequivalent to the approved RLNAD is required for approval.

For this ANADA, an *in vivo* blood-level study was conducted using the test and reference cefpodoxime proxetil 100 mg tablets to demonstrate product bioequivalence. Additionally, an in vitro dissolution study comparison of the test and reference products was conducted to meet the criteria for a waiver of the requirements to demonstrate in vivo bioequivalence for the 200 mg generic cefpodoxime proxetil tablets.

A. Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and reference formulations of cefpodoxime proxetil (100 mg) tablets.

1. Protocol:
   A randomized, four-way crossover, single dose, replicate design bioequivalence study to evaluate the relative bioavailability of a test tablet formulation of cefpodoxime proxetil (100 mg) compared to an equivalent dose of a commercially available reference drug product SIMPLICEF (cefpodoxime proxetil) Tablets (100 mg, Pfizer, Inc.) in 40 fasted, healthy beagle dogs.

2. Testing Facility:
   Kingfisher International Inc., 165 Mostar St., Unit 8, Stouffville, Ontario, CANADA L4A 0Y2

3. Study Number:
   KFI-048-BC-2510
4. Objective:
   The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of Putney, Inc.'s 100 mg generic cefpodoxime proxetil tablets and Pfizer, Inc.'s 100 mg SIMPLICEF (cefpodoxime proxetil) Tablets, in a 4-period, 2-treatment, 2-sequence crossover study in dogs.

5. Study Summary:
The study was conducted as a 4-period, 2-treatment, 2-sequence crossover design with 7 day washout between periods using forty intact male beagle dogs. Variables evaluated are area under the concentration curve (AUC) from time 0 to the first value below the limit of quantitation, the observed maximum concentration (C_{MAX}), and time to maximum concentration (T_{MAX}). CDER's Draft Guidance on Progesterone (April 2010) outlines a method to evaluate a highly variable drug. The method is used when a within-subject standard deviation of the reference product (S_{WR}) ≥ 0.294. The S_{WR} for the AUC is < 0.294 and was therefore evaluated using the average bioequivalence method detailed in CVM's Guidance for Industry #35. Because S_{WR} for C_{MAX} is ≥ 0.294, C_{MAX} was evaluated using the reference scale bioequivalence method outlined in CDER's Draft Guidance on Progesterone (April 2010).

For the products to be bioequivalent, the following conditions must be met:

- For the $AUC_{t\text{-}last}$, the calculated 90% confidence bioequivalence bounds must fall within the acceptance bounds of 80.0% to 125.0%.
- For the C_{MAX} point estimate the geometric mean ratio of the test to the reference product must be between 0.80 and 1.25; and the 95% upper confidence bound for $[(Yt - Yr)^2 - 0.7967 * S_{WR}]$ must be ≤ 0, where (Yt – Yr) is the difference between LC_{MAX} (natural log C_{MAX}) for the test and reference products, respectively.
- Each animal receiving test product treatment must demonstrate a concentration of at least 2 mg/mL for at least 8 hours (T2-8).

The estimated geometric means for the test and reference $AUC_{t\text{-}last}$ are 146.65 and 150.85 (mg/mL)*hr, respectively. The calculated bioequivalence bounds for AUC (90.73%, 104.17%) fall within the acceptance bounds of 80.0% to 125.0%. For C_{MAX}, the geometric mean ratio of the test to reference product (0.9704) is between 0.80 and 1.25, and the 95% upper confidence bound for $[(Yt - Yr)^2 - 0.7967 * S_{WR}]$ is −0.09308, which is ≤ 0. Each animal receiving test treatment demonstrated a concentration of at least 2 mg/mL for 8 hours (T2-8). Therefore, bioequivalence criteria are met for C_{MAX}. Based on the pivotal metrics of AUC and C_{MAX} falling within acceptable limits, product bioequivalence can be concluded between Putney's Cefpodoxime Proxetil Tablets and Pfizer Inc.'s SIMPLICEF Tablets.

Table 1. Summary statistics for T_{MAX} (hours)

Treatment	Arithmetic Mean	Standard Deviation	Minimum	Maximum
Test	3.45	3.420	1.5	16.0
Reference	2.86	1.932	1.5	16.0

T_{MAX} values obtained for the test and reference product indicate that these drugs will provide equivalent therapeutic results.

B. Bioequivalence Waiver

A waiver of the requirement to demonstrate *in vivo* bioequivalence for the generic 200 mg cefpodoxime proxetil tablet was requested. Comparative dissolution

studies were conducted to determine the dissolution profiles of the generic and reference 100 mg and 200 mg cefpodoxime proxetil tablets at various pH values in glycine buffer. The dissolution studies compared the following tablets in the indicated media:

- Generic 100 mg and RLNAD 100 mg tablet in glycine buffered solutions at pH 1.5, 3.5, and 6.8.
- Generic 100 mg and generic 200 mg in glycine buffered solution at a pH of 3.0.
- Generic 200 mg and RLNAD 200 mg tablet in glycine buffer at a pH of 3.0

Dissolution parameters:

Apparatus:	USP/EP apparatus II (paddle)
Medium:	Glycine/NaCl/H_2O/HCl pH adjusted
Volume:	900 mL vacuum degassed medium
RPM:	75
Temperature:	37°C ± 0.5°C
Data points:	12
Time:	Up to 45 Min, with 3 minute intervals
Analysis:	UV spectrophotometer (λ= 259 nm)

Table 2. Dissolution comparison of Generic and RLNAD 100 mg at varying pH:

pH	Time (min)	*Mean % Release 100 mg tablet (Generic)	*Mean % Release 100 mg tablet (RLNAD)
1.5	0	0	0
1.5	15	96	98
1.5	30	96	98
3.5	0	0	0
3.5	15	93	90
3.5	30	94	95
6.8	0	0	0
6.8	15	88	94
6.8	30	87	95

*Mean value of 12 dissolution tests

Table 3. Dissolution comparison of the generic 100 mg and 200 mg tablets at pH 3.0:

pH	Time (min)	*Mean % Release 100 mg tablet (Generic)	*Mean % Release 200 mg tablet (Generic)
3.0	0	0	0
3.0	15	91	88.5
3.0	30	97.2	94.5

*Mean value of 12 dissolution tests

Table 4. Dissolution comparison of the 200 mg generic and reference products at pH 3.0:

pH	Time (min)	*Mean % Release 200 mg tablet (Generic)	*Mean % Release 200 mg tablet (RLNAD)
3.0	0	0	0
3.0	15	88.5	88.7
3.0	30	94.5	93.5

*Mean value of 12 dissolution tests

In all the dissolution media, both the test and reference tablets were greater than 85% dissolved in less than 15 minutes. For tablets that meet these fully soluble criteria, dissolution profile comparison using a similarity factor (f2) test is unnecessary.

Study results demonstrate similar dissolution profiles for the 100 mg test and reference tablets at varying pH values, coupled with comparable dissolution data at pH 3.0 for the 100 mg and 200 mg generic tablets and for the 200 mg tablets of the test and reference products. Therefore, a waiver of the requirement to demonstrate *in vivo* bioequivalence for the 200 mg generic Cefpodoxime Proxetil Tablet was granted.

III. EFFECTIVENESS:

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY:

Data on human food safety, pertaining to drug residues in food, were not required for approval of this application. This drug is approved for use in dogs, which are not food producing animals.

VI. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Cefpodoxime Proxetil Tablets:

- Not for human use.
- Keep this and all drugs out of reach of children. Antimicrobial drugs, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals.
- To minimize the possibility of allergic reactions, those handling such antimicrobials, including cefpodoxime, are advised to avoid direct contact of the product with the skin and mucous membranes.

VII. AGENCY CONCLUSIONS:

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that Cefpodoxime Proxetil Tablets, when used according to the label, are safe and effective.