Date of Approval: November 1, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-627

Cyclosporine Capsules, USP MODIFIED

(cyclosporine capsules)

Dogs

For the control of atopic dermatitis in dogs weighing at least 4 lbs. (1.8 kg) body weight

Sponsored by:

Putney, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-627

B. Sponsor

Putney, Inc.
One Monument Sq.
Suite 400
Portland, ME 04101

Drug Labeler Code: 026637

C. Proprietary Name

Cyclosporine Capsules, USP MODIFIED

D. Drug Product Established Name

cyclosporine capsules

E. Pharmacological Category

Immunosuppressant

F. Dosage Form

Capsules

G. Amount of Active Ingredient

10 mg, 25 mg, 50 mg, or 100 mg per capsule

H. How Supplied

Each capsule strength is supplied in packages of 15 single-dose blisters.

I. Dispensing Status

Rx

J. Dosage Regimen

The initial dose of Cyclosporine Capsules, USP MODIFIED is 5 mg/kg/day (3.3-6.7 mg/kg/day) as a single daily dose for 30 days. Following the initial daily treatment period, the dose of Cyclosporine Capsules, USP MODIFIED may be tapered by decreasing the frequency of dosing to every other day or twice weekly, until a minimum frequency is reached which will maintain the desired therapeutic effect. Cyclosporine Capsules, USP MODIFIED should be given at least one hour before or two hours after a meal. If a dose is missed, the next dose should be administered (without doubling) as soon as possible, but dosing should be no more frequent than once daily.

Table I.1. Dose Administration

Dog body weight (lbs)	Dog body weight (kg)	Dose 5 mg/kg
4-6.5 lbs	2.-2.9 kg	10 mg capsule
6.6-9 lbs	3-3.9 kg	2 x 10 mg capsules
9.1-16 lbs	4-7.9 kg	25 mg capsule
16.1-33 lbs	8-14.9 kg	50 mg capsule
33.1-64 lbs	15-28.9 kg	100 mg capsule
64.1-79 lbs	29-35.9 kg	100 mg capsule + 50 mg capsule
79.1-121 lbs	36-55.9 kg	2 x 100 mg capsules

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

Cyclosporine Capsules, USP MODIFIED are indicated for the control of atopic dermatitis in dogs weighing at least 4 lbs. (1.8 kg) body weight.

N. Reference Listed New Animal Drug

Atopica™; cyclosporine capsules; NADA 141-218; Elanco US 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 (GADPTRA) 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 (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.

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD (cyclosporine capsules) 50 mg capsules. The RLNAD is available in 10, 25, 50, and 100 mg capsule sizes. The *in vivo* blood-level study was conducted in 32 healthy, fasted beagle dogs. Bioequivalence was demonstrated between the 50 mg RLNAD cyclosporine capsule and the 50 mg generic cyclosporine capsule by demonstrating that the confidence limits for the difference between the pivotal parameters C_{MAX} and AUC are contained within the equivalence limits of 80.00% and 125.00%. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 10 mg, 25 mg, and 100 mg capsules was

requested. Capsule rupture data was used to demonstrate that the generic 10 mg, 25 mg, and 100 mg cyclosporine capsules are comparable to the generic 50 mg capsule strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 10 mg, 25 mg, and 100 mg cyclosporine capsules was granted. The study information is summarized below.

A. Canine Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of cyclosporine capsules (50 mg).

1. Study Title:
   "Pivotal Bioequivalence Study of Putney's Generic Cyclosporine A Capsules vs. ATOPICA® (Cyclosporine Capsules, USP) MODIFIED in Beagle Dogs"

2. Protocol:
   A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of a generic 50 mg capsule formulation of Cyclosporine Capsules, USP MODIFIED compared to an equivalent dose of the RLNAD Atopica™ (cyclosporine capsules) USP MODIFIED (Elanco US Inc., NADA 141-218) in 32 healthy, fasted beagle dogs.

3. Testing Facilities:
   In-life phase: Kingfisher International Inc.
   Stouffville, ON, Canada

   Bioanalytical testing: Agilux Laboratories
   Worcester, MA

4. Study Number:
   Kingfisher International Inc. study number: KFI-048-BC-0513
   Agilux Laboratories study number: GT-0006-RB-AS

5. Objective:
   The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence of Putney, Inc.'s 50 mg generic Cyclosporine Capsules, USP MODIFIED and the RLNAD 50 mg Atopica™ (cyclosporine capsules) USP MODIFIED in a randomized, two-period, two-sequence, single-dose crossover study in dogs.

6. Measurement and Observation:
   The plasma concentrations of cyclosporine were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events. No significant adverse events were recorded.

7. Statistical Methods:
   The study was conducted as a randomized, two-period, two-treatment, single-dose crossover design using 32 dogs with a 7-day washout between periods. The randomization to sequence and pen number/treatment order assignments were generated using a Statistical Analysis System (SAS) program. Primary

variables evaluated are area under the curve from time 0 to the first observed concentration below the limit of quantitation (AUC) and the observed maximum concentration (C_{MAX}). Time to maximum concentration (T_{MAX}) is also evaluated.

The criteria for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the natural log scale of AUC and C_{MAX} and then take the anti-log of the confidence limits multiplied by 100. To demonstrate bioequivalence, the resulting bounds should be between 80.00% and 125.00% for both AUC and C_{MAX}. As seen in the table below, AUC and C_{MAX} fall within the prescribed bounds (Table II.1). T_{MAX} values obtained for the test product and reference product indicate that these drugs will provide equivalent therapeutic results.

Table II.1. Bioequivalence Evaluation

Parameter	Test Mean	Reference Mean	Ratio[◇]	Lower Bound (%)	Upper Bound (%)
AUC (ng/mL)*hour	3614[†]	3791[†]	0.95	85.95	105.77
C_{MAX} (ng/mL)	753[†]	798[†]	0.94	80.44	110.69
T_{MAX} (hours)	1.5[‡]	1.5[‡]	NE	NE	NE

[†] Geometric mean
[‡] Arithmetic mean
[◇] Ratio = Test/Reference
NE = not estimated

B. Bioequivalence Waiver

A pivotal *in vivo* blood-level bioequivalence study was conducted using the 50 mg cyclosporine capsule strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 10 mg, 25 mg, and 100 mg cyclosporine capsules was requested. To qualify for a biowaiver for each of these product strengths, *in vitro* dissolution testing was performed to compare the generic capsule strengths in terms of product availability. Specifically, a capsule rupture time test was performed, according to the USP monograph, for cyclosporine capsules containing liquid formulation. The objective was to demonstrate uniformity of rupture times between the generic 50 mg capsule strength and three other generic capsule strengths: 10 mg, 25 mg, and 100 mg.

A total of 12 capsules (12 vessels) were evaluated for each of the following generic capsule strengths: 10 mg, 25 mg, and 100 mg. For the generic 50 mg capsule strength, 48 capsules (12 vessels with 4 replicates) were evaluated. The USP requirements are met if all the capsules tested rupture in less than 15 minutes.

Test conditions were as follows:

- Dissolution medium: Deionized (DI) water
- Volume of DI water in each vessel: 500 mL
- Dissolution apparatus: Apparatus II (paddles)
- Paddle speed: 50 rpm
- Temperature: 37.0 °C ± 0.5 °C

The minimum rupture time, maximum rupture time, mean rupture time, and one-sided 90% tolerance limit for each of the different generic capsule strengths are presented in the table below (Table II.2).

Table II.2. Rupture Study Results

Generic Capsule Strength (mg)	Minimum Rupture Time (minutes)	Maximum Rupture Time (minutes)	Mean Rupture Time (minutes)	Upper 90% Tolerance Limit (minutes)
50	0.33	7.60	2.66	7.43
10	0.33	8.85	3.01	8.48
25	0.70	5.83	1.99	4.7
100	0.33	4.00	2.24	4.3

As shown in Table II.2, all capsules tested ruptured within 15 minutes. The upper tolerance limits for the generic 25 mg and 100 mg capsule strengths are less than the upper tolerance limit for the generic 50 mg capsule strength that was used in the *in vivo* blood-level bioequivalence study.

The slightly higher upper tolerance limit for the 10 mg capsule strength is not expected to impact bioavailability of the 10 mg capsule strength in the dog, as the maximum rupture time for the 10 mg capsules is much less than the gastric emptying time in the dog (approximately 30 minutes).

This demonstrates that the rupture times for the 10 mg, 25 mg, and 100 mg strengths of the generic formulation are comparable to the generic 50 mg capsule strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 10 mg, 25 mg, and 100 mg cyclosporine capsules 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

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Cyclosporine Capsules, USP MODIFIED:

Not for human use. Keep this and all drugs out of the reach of children. For use only in dogs. Capsules should not be broken or opened. Wear gloves during

administration. Wash hands after administration. In case of accidental ingestion, seek medical advice immediately and provide the package insert or the label to the physician.

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 Cyclosporine Capsules, USP MODIFIED, when used according to the label, are safe and effective.