Date of Approval: October 29, 2020

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-692

CYCLAVANCE™

(cyclosporine oral solution) USP MODIFIED

Dogs

CYCLAVANCE™ is indicated for the control of atopic dermatitis in dogs weighing at least 4 lbs (1.8 kg) body weight.

Sponsored by:

Virbac AH, Inc.

Executive Summary

CYCLAVANCE™ (cyclosporine oral solution) USP MODIFIED is approved to control atopic dermatitis in dogs weighing at least 4 lbs (1.8 kg). CYCLAVANCE™ is a generic version of Atopica™ and is the first generic cyclosporine oral solution for dogs.

	Proprietary Name	Established Name	Application Type and Number	Sponsor
Generic Animal Drug	CYCLAVANCE™	(cyclosporine oral solution) USP MODIFIED	ANADA[a] 200-692	Virbac AH, Inc.
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	Atopica™	(cyclosporine capsules) USP MODIFIED	NADA[b] 141-218	Elanco US Inc.
[a] Abbreviated New Animal Drug Application for a generic animal drug. [b] New Animal Drug Application for a brand name animal drug.				

Bioequivalence

The Federal Food, Drug, and Cosmetic (FD&C) Act allows an animal drug sponsor to submit an abbreviated new animal drug application (ANADA) for a generic version of an approved brand name animal drug (also called the reference listed new animal drug or RLNAD). This law typically requires the sponsor to show that the generic drug is bioequivalent to the approved RLNAD. Broadly, bioequivalence means the generic drug is absorbed by and performs the same way in the animal's body as the RLNAD, which has already been shown to be safe and effective when used according to the label. The FD&C Act doesn't require the sponsor to submit new effectiveness or target animal safety data in the ANADA for a generic animal drug.

For this approval, FDA approved a suitability petition to allow the sponsor to submit an ANADA for a generic animal drug that differs in dosage form from the RLNAD. CYCLAVANCE™ is an oral solution containing 100 mg/mL cyclosporine while the RLNAD, Atopica™, is a gelatin capsule containing cyclosporine solution in various strength capsule sizes. The sponsor conducted one *in vivo* blood-level study to show that 0.5 mL (50 mg) of CYCLAVANCE™ is bioequivalent to the 50 mg Atopica™ capsule. No serious adverse events were recorded during the study.

User Safety

CYCLAVANCE™ is an immunosuppressant and may be dangerous to people if ingested. Therefore, people who administer CYCLAVANCE™ to dogs should not eat, drink, smoke, or use smokeless tobacco while handling CYCLAVANCE™. They should also wear gloves when administering the drug and wash their hands afterward. In case a person accidentally ingests CYCLAVANCE™, he or she should seek medical advice immediately and provide the healthcare provider with the drug's package insert or label.

Conclusions

Based on the data submitted by the sponsor for the approval of CYCLAVANCE™, FDA determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-692

B. Sponsor

Virbac AH, Inc.
PO Box 162059
Fort Worth, TX 76161

Drug Labeler Code: 051311

C. Proprietary Name

CYCLAVANCE™

D. Drug Product Established Name

(cyclosporine oral solution) USP MODIFIED

E. Pharmacological Category

Immunosuppressant

F. Dosage Form

Solution

G. Amount of Active Ingredient

100 mg/mL

H. How Supplied

5, 15, 30, and 50 mL vials

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The initial dose of CYCLAVANCE™ is 5 mg/kg/day as a single daily dose for 30 days. Following this initial daily treatment period, the dose of CYCLAVANCE™ 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. CYCLAVANCE™ 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. The dispensing system for the 5 and 15 mL vial sizes includes a 1 mL oral dosing syringe graduated in 0.01 mL increments. To dose the dog, administer 0.05 mL of CYCLAVANCE™ per 2.2 lbs of body weight. The dispensing system for the 30 and 50 mL vial sizes includes both a 1 mL oral dosing syringe

graduated in 0.01 mL increments, and a 3 mL oral dosing syringe graduated in 0.1 mL increments. To dose the dog, administer 0.1 mL of CYCLAVANCE™ per 4.4 lbs of body weight.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

CYCLAVANCE™ is 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) USP MODIFIED; NADA 141-218; Elanco US Inc.

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, allows for an abbreviated new animal drug application (ANADA) to be submitted for a generic version of an approved new animal drug (RLNAD). The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. Effectiveness, target animal safety and human food safety data (other than tissue residue data) are not required for approval of an ANADA. If bioequivalence is demonstrated through a clinical endpoint study in a food-producing animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

The sponsor submitted a suitability petition (FDA-2013-P-0426) requesting permission to submit an ANADA for a generic new animal drug that differed in dosage form from the RLNAD. The proposed generic drug product is an oral solution containing 100 mg/mL cyclosporine. The RLNAD is a gelatin capsule containing cyclosporine solution in 10 mg, 25 mg, 50 mg, and 100 mg capsule sizes. This petition was approved on August 1, 2013, under 512(n)(3)(C) of the FD&C Act.

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic (cyclosporine oral solution) USP MODIFIED 100 mg/mL solution and RLNAD (cyclosporine capsules) USP MODIFIED 50 mg capsule. The RLNAD is available in 10 mg, 25 mg, 50 mg, and 100 mg capsule sizes. The *in vivo* blood-level study was conducted in 26 healthy, fasted dogs. The pivotal parameters to evaluate bioequivalence are the observed maximum plasma drug concentration (C_{MAX}) and area under the concentration-time curve (AUC) from time 0 to the last sampling time before the first unquantifiable concentration after C_{MAX}. Bioequivalence was demonstrated between the 50 mg RLNAD cyclosporine capsule and the 100 mg/mL generic cyclosporine oral solution by the average bioequivalence approach as described in the Statistical Methods section below. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic cyclosporine oral solution (100 mg/mL) and the RLNAD cyclosporine capsules (50 mg).

Title: Bioequivalence Study Between Two Formulations Of Cyclosporine Following A Single Oral Administration To Healthy Dogs (Study No. A144625, CL13015).

Study Dates: May 9, 2014 to September 3, 2014

Study Locations:

In-life phase:	Fontenilles, France
Bioanalytical testing:	Fontenilles, France

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 100 mg/mL CYCLAVANCE™ (cyclosporine oral solution) USP MODIFIED and the RLNAD 50 mg Atopica™ (cyclosporine capsules) USP MODIFIED in fasted dogs. The study was conducted according to Good Laboratory Practice regulations.

Study Animals: 26 intact male beagle dogs, approximately 1-3 years old and weighing 9-11 kg at selection.

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study.

Drug Administration: Each animal received 50 mg of either the generic or RLNAD cyclosporine (50 mg RLNAD cyclosporine capsule or the 0.5 mL generic cyclosporine oral solution [100 mg/mL]) according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: 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.

Statistical Methods:

The laboratory study was conducted as a randomized, masked, two-period, two-sequence, two-treatment, single-dose crossover design using 26 beagle dogs with a 7-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. Time to maximum concentration (T_{MAX}) was summarized and evaluated clinically.

A mixed-effect model was used to evaluate bioequivalence. The model included fixed effects of treatment, sequence and period, and random effects of room and subject nested within room by sequence interaction. Prior to the analysis, C_{MAX} and AUC were natural logarithm transformed. Bioequivalence is established because the back-transformed estimated upper and lower bounds of the 90% confidence interval for geometric mean ratios (generic:RLNAD) of both C_{MAX} and AUC are contained within the acceptance limits of 0.80 to 1.25.

Results:

As seen in the table below, C_{MAX} and AUC fall within the prescribed bounds (Table II.1). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.1 Bioequivalence Evaluation in Dogs

Parameter	Generic Mean	RLNAD Mean	Ratio*	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	3676.4†	3804.7†	0.97	0.91	1.03
C_{MAX} (ng/mL)	800.9†	772.1†	1.04	0.99	1.09
T_{MAX} (hours)	1.0‡	1.25‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
* Ratio = Generic/Reference
CI = confidence interval
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 100 mg/mL CYCLAVANCE™ (cyclosporine oral solution) USP MODIFIED and the RLNAD 50 mg Atopica™ (cyclosporine capsules) USP MODIFIED are bioequivalent in dogs.

III. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this ANADA.

IV. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to CYCLAVANCE™:

Not for human use. Keep this and all drugs out of reach of children. **For use only in dogs. Special precautions to be taken when administering CYCLAVANCE™ in dogs**: Do not eat, drink, smoke, or use smokeless tobacco while handling CYCLAVANCE™. 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.

People with known hypersensitivity to cyclosporine should avoid contact with CYCLAVANCE™.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that CYCLAVANCE™, when used according to the label, is safe and effective for the indications listed in Section I.M. above.