Date of Approval: March 21, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-743

MODULIS® for Dogs

(cyclosporine oral solution) USP MODIFIED

Dogs

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

Sponsored by:

Provetica LLC

Executive Summary

MODULIS® for Dogs (cyclosporine oral solution) USP MODIFIED is approved for the control of atopic dermatitis in dogs weighing at least 4 lbs. (1.8 kg) body weight. The reference listed new animal drug (RLNAD) is ATOPICA™ (cyclosporine capsules) USP MODIFIED, sponsored by Elanco US Inc., under NADA 141-218.

Bioequivalence

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. MODULIS® for Dogs 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 in dogs to show that 50 mg of 100 mg/mL of MODULIS® for Dogs is bioequivalent to the 50 mg ATOPICA™ capsule. No serious adverse events were reported during the study.

Conclusions

Based on the data submitted by the sponsor for the approval of MODULIS® for Dogs, 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 200-743

B. Sponsor

Provetica LLC
8735 Rosehill Road
Suite 300
Lenexa, KS 66215

Drug Labeler Code: 086097

C. Proprietary Name

MODULIS® for Dogs

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

4.7 mL, 15 mL, 30 mL, and 50 mL glass amber bottles

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The initial dose of MODULIS® for Dogs is 5 mg/kg/day as a single daily dose for 30 days. Following this initial daily treatment period, the dose of MODULIS® for Dogs 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. MODULIS® for Dogs 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 includes oral dosing syringes to accompany MODULIS® for Dogs:

- For dogs 4 lbs to 40 lbs, use the 1 mL syringe: The 1 mL syringe is graduated in 1 pound (lb) increments. To dose the dog, the syringe should be filled to the nearest 1 lb graduation corresponding to the dog's body weight in lbs (round down to the nearest whole lb if 0.1 to 0.4 lb, or round up to the nearest whole lb if 0.5 to 0.9 lb). Each 1-lb graduation on the 1 mL syringe delivers a volume of 0.023 mL, providing 2.3 mg/lb (5 mg/kg) dose.

- For dogs 41 lbs to 125 lbs, use the 3 mL syringe: The 3 mL syringe is graduated in 5 pound (lb) increments. To dose the dog, the syringe should be filled to the nearest 5 lb graduation corresponding to the dog's body weight in lbs (round down to the nearest whole lb if 0.1 to 0.4 lb, or round up to the nearest whole lb if 0.5 to 0.9 lb). Each 5-lb graduation on the 3 mL syringe delivers a volume of 0.115 mL, providing 2.3 mg/lb (5 mg/kg) dose.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

MODULIS® for Dogs 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-2018-P-4642) requesting permission to submit an ANADA for a generic new animal drug that differed in dosage form from the RLNAD. The proposed generic 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 February 21, 2019, 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 50 mg of 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, 25, 50, and 100 mg capsule sizes. The *in vivo* blood-level study was conducted in 30 healthy, fasted dogs. The pivotal parameters to evaluate bioequivalence are the observed maximum blood 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 50 mg of the 100 mg/mL generic cyclosporine oral solution by the average bioequivalence approach as described in the Statistical Methods section below.

A. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of ATOPICA™ (cyclosporine capsules) and a Generic Oral Cyclosporine Solution when Administered Orally to Beagle Dogs

Study Dates: November 17, 2020 to June 7, 2021

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Middleton, WI

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 MODULIS® for Dogs (cyclosporine oral solution) USP MODIFIED and the RLNAD 50 mg ATOPICA™ (cyclosporine capsules) USP MODIFIED in fasted dogs.

Study Animals: 30 intact male beagle dogs, approximately 19 months to 3 years of age and weighing 9.8 to 13.0 kg at the time of inclusion.

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 50 mg of either the generic cyclosporine oral solution USP MODIFIED or RLNAD cyclosporine capsules USP MODIFIED according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The whole blood 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 30 dogs with a 14-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 a random effect of subject nested within sequence. 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

Parameter	**Generic Mean**	**RLNAD Mean**	**Ratio◇**	**Lower 90% CI**	**Upper 90% CI**
AUC (ng/mL)*hour	3949†	3990†	0.99	0.94	1.04
C_{MAX} (ng/mL)	740†	732†	1.01	0.95	1.08
T_{MAX} (hours) (SD)±	1.31 (0.53) ±	1.34 (0.48) ±	NE	NE	NE

†Geometric mean
± Arithmetic mean and standard deviation (SD)
◇ Ratio = Generic/RLNAD
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 MODULIS® for Dogs (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 MODULIS® for Dogs:

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

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that MODULIS® for Dogs, when used according to the label, is safe and effective for the indications listed in Section I.M. above.