

Date of Approval: March 29, 2023

**FREEDOM OF INFORMATION SUMMARY**  
**ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION**

ANADA 200-744

Modulis® for Cats

(cyclosporine oral solution) USP MODIFIED

Cats

Modulis® for Cats is indicated for the control of feline allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia in cats at least 6 months of age and at least 3 lbs (1.4 kg) in body weight.

Sponsored by:

Provetica LLC

## Executive Summary

Modulis® for Cats (cyclosporine oral solution) USP MODIFIED is approved for the control of feline allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia in cats at least 6 months of age and at least 3 lbs (1.4 kg) in body weight. The reference listed new animal drug (RLNAD) is Atopica™ for Cats (cyclosporine oral solution) USP MODIFIED. This is the first generic cyclosporine oral solution for cats.

### Bioequivalence

The sponsor conducted one *in vivo* blood-level study in cats to show that the 100 mg/mL Modulis® for Cats is bioequivalent to the 100 mg/mL Atopica™ for Cats. No serious adverse events were reported during the study.

### Conclusions

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

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**I. GENERAL INFORMATION**

**A. File Number**

ANADA 200-744

**B. Sponsor**

Provetica LLC  
8735 Rosehill Road  
Suite 300  
Lenexa, KS 66215

Drug Labeler Code: 086097

**C. Proprietary Name**

Modulis® for Cats

**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, 15, and 30 mL glass amber bottles

**I. Dispensing Status**

Prescription (Rx)

**J. Dosage Regimen**

The initial dose of Modulis® for Cats is 3.2 mg/lb/day (7 mg/kg/day) as a single daily dose for a minimum of 4 to 6 weeks or until resolution of clinical signs. Following this initial daily treatment period, the dose of Modulis® for Cats may be tapered by decreasing the frequency of dosing to every other day or twice weekly to maintain the desired therapeutic effect. Modulis® for Cats should be administered directly on a small amount of food or orally just after feeding. Whenever possible, Modulis® for Cats should be administered on a consistent schedule with regard to meals and time of day. 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 an oral

dosing syringe graduated in 1 lb increments. To dose the cat, the syringe should be filled to the nearest 1 lb corresponding to the cat's body weight (round down if 0.1 to 0.4 lb, round up if 0.5 to 0.9 lb). Each pound graduation on the syringe delivers a volume of 0.032 mL providing 3.2 mg/lb.

**K. Route of Administration**

Oral

**L. Species/Class**

Cats

**M. Indication**

Modulis® for Cats is indicated for the control of feline allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia in cats at least 6 months of age and at least 3 lbs (1.4 kg) in body weight.

**N. Reference Listed New Animal Drug**

Atopica™ for Cats; (cyclosporine oral solution) USP MODIFIED; NADA 141-329; 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.

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD cyclosporine oral solution 100 mg/mL. The RLNAD is available in a 100 mg/mL oral solution. The *in vivo* blood-level study was conducted in 30 healthy, fed cats. 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 100 mg/mL RLNAD and 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 Cats**

**Title:** Pivotal Bioequivalence Study of Atopica™ for Cats (Cyclosporine Oral Solution) and a Generic Cyclosporine Oral Solution when Administered Orally to Cats. (Study No. 04-BQ-F-2008)

**Study Dates:** March 1, 2021, to September 30, 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 Cats (cyclosporine oral solution) USP MODIFIED and the RLNAD 100 mg/mL Atopica™ for Cats (cyclosporine oral solution) USP MODIFIED in fed cats.

Study Animals: 30 non-pregnant intact female and neutered male cats, approximately between 15 months to 4 years of age and weighing 3.4 to 5.0 kg.

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 3.2 mg per lb of body weight of either the generic or RLNAD cyclosporine oral solution 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 30 cats with a 21-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C<sub>MAX</sub> and AUC. Time to maximum concentration (T<sub>MAX</sub>) 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<sub>MAX</sub> 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<sub>MAX</sub> 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 <sup>◇</sup>	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	14013 <sup>†</sup>	13525 <sup>†</sup>	1.04	0.96	1.12
$C_{MAX}$ (µg/mL)	1680 <sup>†</sup>	1712 <sup>†</sup>	0.98	0.87	1.10
$T_{MAX}$ (hours) (SD) <sup>‡</sup>	1.75 (0.76) <sup>‡</sup>	1.54 (0.59) <sup>‡</sup>	NE	NE	NE

<sup>†</sup> Geometric mean

<sup>‡</sup> Arithmetic mean and standard deviation (SD)

<sup>◇</sup> Ratio = Test/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 Modulis<sup>®</sup> for Cats (cyclosporine oral solution) USP MODIFIED and the RLNAD Atopica<sup>™</sup> for Cats (cyclosporine oral solution) USP MODIFIED are bioequivalent in cats.

## III. HUMAN FOOD SAFETY

This drug is intended for use in cats. 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<sup>®</sup> for Cats:

### Human Warnings:

Not for human use. Keep this and all drugs out of reach of children. **For use only in cats.**

### Special precautions to be taken when administering Modulis<sup>®</sup> for Cats:

Do not eat, drink, smoke, or use smokeless tobacco while handling Modulis<sup>®</sup> for Cats. 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<sup>®</sup> for Cats.

**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 Cats, when used according to the label, is safe and effective for the indications listed in Section I.M. above.