Date of Approval: August 8, 2011

FREEDOM OF INFORMATION SUMMARY -

ORIGINAL NEW ANIMAL DRUG APPLICATION -

NADA 141-329 -

ATOPICA for Cats -

(cyclosporine oral solution, USP) MODIFIED
Cats -

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: -

Novartis Animal Health US, Inc. -

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-329
B. Sponsor:	Novartis Animal Health US, Inc. 3200 Northline Ave., suite 300 Greensboro, North Carolina 27408 - Drug Labeler Code: 058198
C. Proprietary Name:	ATOPICA for Cats
D. Established Name:	(cyclosporine oral solution, USP) MODIFIED
E. Pharmacological Category:	Immunosuppressant
F. Dosage Form:	Oral Solution
G. Amount of Active Ingredient:	100 mg/mL -
H. How Supplied:	Glass amber bottles of 5 and 17 mL, with a dispensing system dip tube and dosing syringe
I. How Dispensed:	Rx
J. Dosage:	The initial dose of ATOPICA 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 ATOPICA for Cats may be tapered by decreasing the frequency of dosing to every other day or twice weekly to maintain the desired therapeutic effect. ATOPICA for Cats should be administered directly on a small amount of food or orally just after feeding. Whenever possible, ATOPICA 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.
K. Route of Administration:	Oral
L. Species:	Cats

M. Indication: ATOPICA 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.

II. EFFECTIVENESS:

A. Dosage Characterization:

The targeted dose of 3.2 mg/lb (7.0 mg/kg) administered orally once a day during initial therapy was selected based on a review of published literature and the results from a pilot field study in client-owned cats. The ability to taper the dose for subsequent maintenance therapy was evaluated in a follow-up field study.

Cats identified with allergic dermatitis (miliary dermatitis, excoriations including facial or neck, self-induced alopecia, and/or eosinophilic plaques), along with non-seasonal localized or generalized pruritus were enrolled in a multi-site, controlled, masked, pilot field study. Cats presenting with clinical signs indicative of bacterial and/or fungal infections, or flea or food allergies, were excluded from the study. Cats received cyclosporine solution once daily for up to 42 days at a target dose of 0 mg/lb (excipient solution without cyclosporine, 35 cats), 1.1 mg/lb (2.5 mg/kg, 32 cats) or 3.2 mg/lb (7.0 mg/kg, 33 cats) which was administered mixed in food or directly in the mouth just after feeding. The Owner and the Investigator assessed clinical response to treatment.

The 3.2 mg/lb dose group demonstrated improvement over the control group. Results in the 1.1 mg/lb dose group were suboptimal.

In a multi-site, single arm, follow-up pilot study, the ability to taper the dosing frequency from daily to every other day to twice weekly was determined according to the clinical response of the cat as assessed by the Investigator. Cats from the previous study that qualified for continued treatment were included in this follow-up study. All qualified cats, whether they received active or the control in the initial study, were administered cyclosporine solution at 3.2 mg/lb daily for four weeks either mixed in food or directly in the mouth just after feeding. If a cat responded to treatment after four weeks, the dosing frequency was reduced to every other day. If, after an additional four weeks, the cat continued to respond to treatment, the dosing frequency was reduced to twice weekly. If at any time the cat's clinical response worsened, the dosing frequency was increased as appropriate to maintain an acceptable clinical response. The duration of treatment was up to 84 days.

Frequency of administration was reduced in 70% of the cats from daily to every other day dosing after an initial four weeks of daily treatment. After an additional four weeks, the dosing frequency in 57% of the cats was further reduced from every other day to twice weekly. This reduction in dose frequency was achieved without any clinically relevant loss of response to therapy.

Based on the results from these two pilot field studies, a target dose of 3.2 mg/lb/day was selected as the induction dose, with the option to taper to every other day and then to twice weekly dosing after four to six weeks at each dose level.

Cyclosporine blood level data from 97 cats (which included pilot field study data and data from a four-way crossover food effect study using 12 healthy cats) were used to generate population pharmacokinetic predictions using NONMEM based upon the First Order Conditional Estimation (FOCE) method (154 total observations, the input dataset). Using the data obtained from the healthy cats, the plasma concentration versus time data were determined to be best described by a three-compartment model (which included a central, peripheral, and a deep body compartment) and a multiple component absorption model with first order absorption kinetics. Standard errors of the population parameter estimates were determined from 100 bootstrap samples created from the original NONMEM dataset (estimates). The model parameters were re-estimated from the profiles created from each of the bootstrap datasets. The standard errors of the re-estimated parameters were calculated. The results of this analysis are provided below.

Table 1: Parameter estimates based upon a three-compartment model. Relative Standard error estimates obtained from 100 bootstrap samples from the original NONMEM dataset.

Parameter	Estimate	Standard Error	Relative standard error (%)
$ka_{\_fasted}$	2.98	1.76	51.3
$ka_{\_fed}$	0.261	0.14	50.3
$ka_{\_with\ food}$	0.786	0.19	23.2
$F_{fasted*with\ feed}$	0.264	0.037	13.8
F_{fed}	0.198	0.023	11.5
MTT (h)	0.353	0.049	13.9
N(-)	4.11	1.3	28.2
CL (L/h)	0.743	0.064	8.6
Vc (L)	2.43	0.2	8.2
V_{P1} (L)	9.52	0.76	7.9
V_{P2} (L)	6.09	0.46	7.7
Q_1 (L/h)	0.3	0.061	19.7
Q_2 (L/h)	2.99	0.43	14.4
$\omega_{ka\_fed}^2$	1.77	0.82	52.6
ω_{CL}^2,	0.057	0.031	53.2
ω_F^2	0.121	0.032	30.5
Prop. error (%)	30.1	0.031	10.4

Where $ka_{\_fasted}$ is the population estimate of the absorption rate constant under fasted condition

$ka_{\_fed}$ is the population estimate of the absorption rate constant when administered to cats after a meal

$ka_{\_with\ food}$ is the population absorption rate constant when administered to cats mixed into feed.

$F_{fasted*with\ feed}$ is the oral bioavailability of the drug when administered to either fasted cats or mixed in feed

F_{fed} is the cyclosporine oral bioavailability when administered to cats that have been fed

MTT is the mean transit time in the absorption compartment

N is the number of absorption components

CL is the systemic clearance

Vc is the volume of the central compartment

V_{P1} is the volume of the peripheral compartment 1

V_{P2} is the volume of the peripheral compartment 2 (the "deep compartment" Q1 and Q2 is the, respectively

Q_1 and Q_2 are the intercompartmental clearances

$\omega_{ka\_fed}^2$, ω_{CL}^2, and ω_F^2 are the intersubject variances associated with ka_fed, CL and F, respectively.

Prop. error is the residual (within-subject) error.

Possible covariate relationships were evaluated by inclusion of the covariate effects in the model. Four covariates were tested on CL/F: weight, hematocrit, alanine aminotransferase, and alkaline phosphatase. No relationship between these covariates and CL/F was observed. The conclusions derived from this population analysis are as follows:

- Administration of the drug as an oral bolus to fed cats will decrease peak concentrations and may result in a slight decrease in absolute bioavailability as compared to that observed when administered mixed in feed or administered as an oral bolus to fasted cats. Therefore, the drug should be administered using a consistent manner of dosing.
- There does not appear to be a quantifiable correlation between drug pharmacokinetics and age, weight, gender or liver function.
- Marked inter-subject variability in the relationship between exposure and clinical response renders it difficult to draw any conclusions regarding that relationship.
- There was no observed inter-subject relationship between the magnitude of drug exposure and the likelihood of vomiting or diarrhea.

B. Substantial Evidence:

The effectiveness of ATOPICA for Cats for the control of feline allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia along with non-seasonal localized or generalized pruritus was evaluated in a field study of client-owned cats. The ability to taper the frequency of dose administration from daily to every other day and then to twice weekly was evaluated in a follow-up study. The two studies were conducted at 24 veterinary clinics throughout various geographic regions within the U.S. and included one site in Canada.

1. Randomized, masked, controlled, multi-center field study: Study NAH-07-0028

a. - Study Title: "A randomized, blinded, placebo-controlled, multi-center, confirmatory efficacy field trial for the evaluation of cyclosporine A at a target dose of 3.2 mg/lb (7 mg/kg) administered orally for six weeks in the control of allergic dermatitis in cats" (Study NAH-07-0028)

b. - Investigators: See table below

Table 2: Investigators for NAH-07-0028

Dr. Karen Beale, DACVD* Houston, TX	Dr. Paul Bloom, DACVD Livonia, MI
Dr. Glen Burkett, DACVD Estero, FL	Dr. Kevin Byrne, DACVD Bensalem, PA
Dr. Andrea Cannon, DACVD Rocklin, CA	Dr. Jenise Daigle, DACVD Round Rock,TX
Dr. Terese DeManuelle, DACVD Milwaukie, OR	Dr. Cecilia Friberg, DACVD Chicago, IL
Dr. Terry Grieshaber, DACVD Carmel, IN	Dr. Craig Griffin, DACVD San Diego, CA
Dr. Patrick McKeever, DACVD Eden Prairie, MN	Dr. Linda Messinger, DACVD Englewood, CO
Dr. Millie Rosales, DACVD Homestead, FL	Dr. Mary Schick, DACVD Roswell, GA
Dr. Ian Spiegel, DACVD Tinton Falls, NJ	Dr. Laura Stokking, DACVD San Diego, CA
Dr. Tiffany Tapp, DACVD East Greenwich, RI	Dr. Kathy Tater, DACVD Boston, MA
Dr. Randall Thomas, DACVD Mt. Pleasant, SC	Dr. Ann Trimmer, DACVD Las Vegas, NV
Dr. Carlo Vitale, DACVD San Francisco, CA	Dr. Stephen Waisglass, DACVD Thornhill, ON, Canada
Dr. Patricia White, DACVD Atlanta, GA	Dr. Nicola Williamson, DACVD Richmond, VA

* Diplomate of the American College of Veterinary Dermatology

c. - Study Design: This was a masked, randomized, multi-center field study comparing ATOPICA for Cats to an excipient control (ATOPICA for Cats minus cyclosporine).

1) - Objectives: The objective of the study was to demonstrate the safety and effectiveness of ATOPICA for Cats for the control of feline allergic dermatitis administered at a target dose of 3.2 mg/lb (7 mg/kg) body weight once daily for 42 days.

2) - Study Animals: The study enrolled 217 cats (92 males and 125 females) of various breeds, 1 to 16 years of age, and weighing 4.3 to 21.8 lbs (1.95 to 9.91 kg).

3) - Treatment Groups: The cats were randomized into two treatment groups in a 2:1 ratio of ATOPICA for Cats to control, resulting in 144 cats in the ATOPICA for Cats group and 73 cats in the control group.

4) Drug Administration: The ATOPICA for Cats group received the final market formulation, an oral solution with 100 mg/mL of cyclosporine. The control group received the same formulation without cyclosporine. Owners administered the products mixed in a small amount of food or directly in the cat's mouth just after feeding.

5) - Measurements and Observations: A clinical (including body weight determination) and dermatological examination was conducted prior to inclusion and at each study visit. Cats with allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia along with a non-seasonal localized or generalized pruritus were included. Cats presenting with clinical signs indicative of primary bacterial and/or fungal infections, or flea or food allergies, were excluded from the study along with feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV) positive cats. No additional therapy with antihistamines, corticosteroids, or medicated shampoos was permitted. Scheduled evaluations were conducted on Days 0, 21 and 42. Variables assessed at each visit included total lesion score (sum of scores for excoriations, miliary dermatitis, eosinophilic plaques and self-induced alopecia), Investigator and Owner assessment of overall clinical improvement (categorical scales with ratings of excellent, good, fair, poor, or worse), Owner assessment of pruritus (visual analog scale), Investigator assessment of pruritus (categorical scale), and number of regions with lesions (maximum of 10 body regions per cat). Samples for hematology, serum chemistry, and *Toxoplasma gondii* titers were obtained and evaluated prior to study and at study exit. Cyclosporine levels were measured at study exit.

6) - Statistical Methods: All effectiveness and safety hypothesis tests were evaluated at a 2-sided 0.05 level of significance. Due to convergence issues, final models used for analysis often included fewer effects, with denominator degrees of freedom imputed to test the treatment main effect. Where p-values are not reported, no appropriate statistical model could be fit.

Total lesion score and Owner assessment of overall clinical improvement were evaluated using an analysis of variance (ANOVA). The model included the fixed effect treatment and the random effects site and interaction treatment-by-site.

Change in total lesion score was calculated as the change in the sum of the excoriation, miliary dermatitis, eosinophilic plaques, and self induced alopecia scores from Day 0 to Day 42 (or final visit) and was analyzed using a mixed model. Based on arithmetic means, the difference between the mean total lesion score of the cats at Day 0 and the mean total lesion score of the cats at Day 42 (or final visit) was also calculated.

Owner assessment of overall clinical improvement on Day 42 (or final visit) was categorized as a 'Success' (score = 0 [excellent] or 1 [good]); or a 'Failure' (score = 2 [fair], 3 [poor], or 4 [worse], or withdrew due to reasons potentially related to treatment) and analyzed using a generalized linear mixed model.

Number of regions with lesions as well as Owner and Investigator assessment of pruritus were evaluated using a repeated measures analysis of covariance with the pre-treatment value (Day 0) used as the covariate. Investigator assessment of overall clinical improvement was analyzed using a repeated measures analysis of variance. All models included the fixed effects treatment, time (Day 21, Day 42 or Final Visit)

and interaction treatment-by-time and the random effects site, and interactions treatment-by-site and treatment-by-site-by-time.

Hematology and serum chemistry variables were analyzed using an analysis of covariance with the pre-treatment value (Day 0) used as the covariate. The mixed model included the fixed effect treatment and the random effects site and interaction treatment-by-site. The variables were also compared to a laboratory-provided normal range and assigned a value of 'Low', 'Normal', or 'High'. Shift tables were created to show the tendency of animals to move from 'Low' or 'Normal' at pre-treatment to 'High' at study exit, and to move from 'High' or 'Normal' at pre-treatment to 'Low' at study exit.

Change in body weight was calculated from baseline to Day 42 (or final visit), and analyzed using an ANOVA with the main effect treatment and random effects site and treatment-by-site.

d. - Results: Safety was evaluated in the 217 cats (144 ATOPICA for Cats, 73 control) that received at least one dose of study drug. Cases with protocol deviations that could have compromised results were excluded from the effectiveness data set. Effectiveness was evaluated in 181 cats (120 ATOPICA for Cats, 61 control). Protocol-compliant cases that withdrew from the study prior to Day 42 were included in the effectiveness data set and effectiveness was evaluated at their final visit. The major reason for early withdraw was lack of effectiveness. See Table 3 below:

Table 3: Cats that Withdrew from NAH-07-0028, by Cause and Group

Reason for Withdrawal	Number of Cases (Percent)	
	ATOPICA for Cats n = 144	Control Group n = 73
Lack of Effectiveness	12 (8.3%)	29 (39.7%)
Owner unable to medicate cat	3 (2.1%)	1 (1.4%)
Adverse Events	2 (1.4%)	1 (1.4%)
Other (Owner non-compliance, lost to follow-up)	2 (1.4%)	3 (4.1%)

There was a significant difference ($p < 0.0001$) in the change in total lesion score from study entry to final visit between treatment groups. The ATOPICA for Cats group had greater reduction (improvement) in mean total lesion scores (65.1% versus 9.2%) compared to the control group. See Table 4 below:

Table 4: Total Lesion Score (TLS) Results[a] in NAH-07-0028

Group	Variable	Mean	SD[c]	Individual Cat TLS	
				Minimum	Maximum
ATOPICA for Cats n = 120	Entry TLS	7.27	3.04	2	15
	Final TLS[b]	2.54	2.84	0	12
	Change	-4.73	3.54	--	--
Control n = 61	Entry TLS	7.48	2.96	2	15
	Final TLS[b]	6.79	3.39	0	15
	Change	-0.69	2.83	--	--

[a] A lower score indicates less severe and/or fewer lesions
[b] TLS at Day 42 or final visit if earlier withdraw
[c] SD = standard deviation

There was a significant difference ($p < 0.0001$) in the Owner assessment of overall clinical improvement at final visit between treatment groups. The ATOPICA for Cats group had a greater percentage of cats classified as successes (78.6% versus 26.2%) compared to the control group. See Table 5 below:

Table 5: Final Visit Owner Assessment of Overall Clinical Improvement

Group	Successes	Failures
ATOPICA for Cats n = 117[a]	92 cats (**78.6%**)	25 cats (21.4%)
Control n = 61	16 cats (**26.2%**)	45 cats (73.8%)

[a] Three results were not available.

There was a significant difference ($p < 0.0001$) in the Investigator assessment of overall clinical improvement at final visit between groups, in favor of the ATOPICA for Cats group.

The ATOPICA for Cats group had lower (improved) mean Owner and Investigator assessment of pruritus scores at Day 21 and Day 42 (or final visit) than the control group.

There was a significant difference in the number of body regions with lesions on both Day 21 ($p = 0.0011$) and the final visit ($p < 0.0001$) between groups, in favor of the ATOPICA for Cats group.

Owners initially administered ATOPICA for Cats in their cats' food. In cats with a visit on Day 42, 35% still accepted ATOPICA for Cats solution in their food. For the other 65%, Owners administered ATOPICA for Cats solution orally by syringe.

Cats treated with ATOPICA for Cats tended to lose weight during this study. There was a significant ($p = 0.0063$) difference in body weight change from study entry to study exit between the two treatment groups, with the ATOPICA for Cats group having a greater negative weight change than the control group.

There were significant ($p < 0.05$) differences between groups for certain clinical pathology variables. Mean alkaline phosphatase, calcium, cholesterol, creatinine, glucose, total bilirubin, and urea nitrogen were higher in the ATOPICA for Cats group compared to the control group. Mean aspartate aminotransferase, magnesium, eosinophil count, and white blood cell count were lower in the ATOPICA for Cats group compared to the control group. All means remained within the normal ranges for cats.

Compared to the control group, the ATOPICA for Cats group had a greater percentage of cases with shifts in lymphocyte count and magnesium from a high or normal value pre-study to a low value at study exit. The ATOPICA for Cats group also had a greater percentage of cases with shifts in cholesterol and glucose from a low or normal value pre-study to a high value at study exit.

Ten cats treated with ATOPICA for Cats (6.9% of 144 cats) and four control group cats (5.5% of 73 cats) developed positive *Toxoplasma gondii* titers (IgM, IgG, or both IgM and IgG) during NAH-07-0028. Three cats treated with ATOPICA for Cats (2.1%) and three control group cats (4.1%) that entered the study with positive *Toxoplasma gondii* titers had negative titers at the end of NAH-07-0028. Cats with positive *Toxoplasma gondii* titers did not have clinical signs of toxoplasmosis during NAH-07-0028.

Blood levels of cyclosporine were highly variable, even among cats with similar clinical response, suggesting no generalizable correlations can be made with regard to blood cyclosporine levels and clinical response.

ATOPICA for Cats was used in conjunction with various medications including a macrocyclic lactone and other antiparasitic agents, systemic antimicrobials, nutritional supplements, and topical skin and otic cleansers and antimicrobials. Of the 144 cats treated with ATOPICA for Cats, 26 (18.0%) were on concurrent systemic antimicrobials and 6 (4.2%) were on concurrent topical otic products (ear cleaners, antimicrobials). Of the 73 cats in the control group, 12 (16.4%) were on concurrent systemic antimicrobials and 4 (5.5%) were on concurrent topical otic products. Sixty-seven (46.5%) of the cats treated with ATOPICA for Cats received a macrocyclic lactone.

e. - Adverse Reactions: Three cats withdrew from NAH-07-0028 because of adverse reactions. These three cats included an ATOPICA for Cats group cat that had hypersalivation, vomiting, and diarrhea; another ATOPICA for Cats group cat that had a convulsion, ataxia, vomiting, inappetance, weight loss, and lethargy; and a control group cat that had vomiting and inappetance. Adverse reactions that occurred in at least two ATOPICA for Cats cases are shown in Table 6 below.

Table 6: Adverse Reactions in NAH-07-0028

Adverse Reaction	Number (Percent) of Cases	
	ATOPICA for Cats Group, n = 144	Control Group, n = 73
Vomiting/ Retching/ Regurgitation	40 (27.8%)	12 (16.4%)
Anorexia/ Decreased Appetite	14 (9.7%)	4 (5.5%)
Diarrhea	12 (8.3%)	4 (5.5%)
Behavioral Changes (hiding, hyperactivity, aggression, inappropriate elimination)	12 (8.3%)	5 (6.8%)
Lethargy/ Malaise	11 (7.6%)	3 (4.1%)
Hypersalivation	11 (7.6%)	2 (2.7%)
Weight Loss	10 (6.9%)	0
Ocular Discharge/ Epiphora/ Conjunctivitis	7 (4.9%)	1 (1.4%)
Sneezing/ Rhinitis	3 (2.1%)	0
Gingivitis/ Gingival Hyperplasia	2 (1.4%)	0
Polydipsia	2 (1.4%)	0
Constipation	2 (1.4%)	0

The following adverse reactions occurred in single cats in the ATOPICA for Cats group: lymphopenia, muscle wasting, choking sounds, ataxia, convulsion, and urinary tract infection.

No cats died or were euthanized during NAH-07-0028.

f. - Conclusions: Study NAH-07-0028 demonstrated that administration of ATOPICA for Cats once daily for 6 weeks, either mixed in a small amount of food or administered directly in the mouth, at a target dose of 3.2 mg/lb (7 mg/kg) was effective in the control of feline allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia. The most common adverse reactions were vomiting, anorexia, diarrhea, behavioral changes, lethargy, weight loss, hypersalivation, ocular discharge, and sneezing.

2. **Open-labeled, multi-center, dose-tapering field study: Study NAH-07-0029**

a. - Study Title: "A multi-center, single arm field trial to evaluate dose tapering of cyclosporine A administered orally in the control of allergic dermatitis in cats" (Study NAH-07-0029)

b. - Investigators: NAH-07-0029 was a follow-up study to NAH-07-0028 and had the same investigators as in NAH-07-0028.

c. - Study Design: This was an unmasked, multi-center field study.

1) - Objectives: The objectives of the study were to evaluate safety of ATOPICA for Cats for the control of feline allergic dermatitis and the ability to taper the frequency of dose administration from daily to every other day or twice weekly according to the clinical response of the cat.

2) - Study Animals: NAH-07-0029 enrolled 191 cats (82 males and 109 females) of various breeds, 1 to 16 years of age, and weighing 5.0 to 21.6 lbs (2.3 to 9.8 kg). All cats had completed at least ten days in NAH-07-0028.

Of the 217 cats (144 ATOPICA for Cats group and 73 control group) that enrolled in NAH-07-0028, 191 cats (130 from the ATOPICA for Cats group and 61 from the control group) enrolled in NAH-07-0029, and 26 cats (14 ATOPICA for Cats group and 12 control group) did not enroll in NAH-07-0029.

3) - Treatment Groups: All cats received ATOPICA for Cats, including the 61 cats that had been in the control group in NAH-07-0028.

4) Drug Administration: All cats received the final market formulation ATOPICA for Cats solution with 100 mg/mL cyclosporine. Owners administered ATOPICA for Cats mixed in a small amount of food or directly in the cat's mouth just after feeding.

5) - Measurements and Observations: A clinical (including body weight determination) and dermatological examination was conducted at each study visit. Scheduled evaluations were conducted on Days 28, 56, and 84. The study assessed the ability to taper the administration of ATOPICA for Cats from daily for the first 28 days, to every other day, and then to twice weekly at subsequent visits according to the cat's individual clinical response. In addition, variables assessed at each visit included total lesion score (sum of excoriations, miliary dermatitis, eosinophilic plaques, and self-induced alopecia), Investigator and Owner assessment of overall clinical improvement compared to baseline in NAH-07-0028, Owner and Investigator assessments of pruritus, and number of regions with lesions. Samples for hematology, serum chemistry, and *Toxoplasma gondii* titers were obtained and evaluated prior to study and at study exit. Cyclosporine levels were measured on Day 28. No additional therapy with antihistamines, corticosteroids, or medicated shampoos was permitted.

6) - Statistical Methods: Dose tapering assignments at each visit were tabulated.

Descriptive statistics (number of observations, mean, standard deviation, minimum and maximum values) for the Investigator and Owner assessments of overall clinical improvement score, Owner and Investigator assessment of pruritus scores, total lesion score, and number of regions with lesions were calculated at each visit.

Descriptive statistics were also calculated for body weight, hematology, and clinical chemistry variables. Values at the entry visit of NAH-07-0028 were compared with values at the exit visit of NAH-07-0029 using paired t-tests.

d. - Results: Safety was evaluated in all 191 cats. Cases and data points with protocol deviations that could have compromised results were excluded from the evaluation of effectiveness. Effectiveness and the ability to taper the dose were evaluated in 157 cats. Protocol-compliant cases that withdrew from the study prior to Day 84 were included in the effectiveness data set and effectiveness was evaluated on available data.

Of the 191 enrolled cats, 12 cats (6.3%) withdrew early for adverse reactions, 15 cats (7.8%) withdrew for lack of effectiveness, and 9 cats (4.7%) withdrew for other reasons (reasons unrelated to cyclosporine).

Based on response to treatment, the potential for dose tapering was evaluated at Day 28 and Day 56. Upon entry in NAH-07-0029, all cats were assigned daily doses. At Day 28, 80.1% of the 136 evaluable cats were assigned every other day doses. At Day 56, 15.0%, 22.0%, and 63.0% of the remaining 100 evaluable cats were assigned daily, every other day, or twice weekly doses, respectively. See Table 7 below:

Table 7: Dose Tapering Assignments Beginning at Each Monthly Study Visit

Dose Assignments	Monthly Study Visits [a]		
	Entry Visit to Day 28 n = 157	Day 28 to Day 56 n = 136	Day 56 to Day 84 n = 100
Daily	157 cats (100.0%)	27 cats (19.9%)	15 cats [b] (15.0%)
Every Other Day (EOD)	0	109 cats (80.1%)	22 cats [c] (22.0%)
Twice Weekly	0	0	63 cats (63.0%)

[a] Per protocol, at Days 28 and 56, cats that had been on daily dosing and had Investigator assessment ratings of 'poor' or 'worse' exited the study and were not assigned the next month's dosing regimen.
[b] Includes cats with daily-daily-daily and daily-EOD-daily monthly dose assignments
[c] Includes cats with daily-daily-EOD and daily-EOD-EOD monthly dose assignments

Of the 97 remaining cats with evaluable data for the Day 84 visit, 62.9% were on twice weekly, 21.6% were on every other day, and 15.5% were on daily dosing regimens.

Mean values for Investigator and Owner assessments of overall clinical improvement were the lowest (most improved) at Day 28. Values increased slightly at each subsequent visit but remained as a good to excellent improvement in the clinical signs as compared to the cat at the initial enrollment into study NAH-07-0028.

Table 8: Investigator Assessment of Overall Clinical Improvement Score Results[a] at each Visit in NAH-07-0029

Visit	N	Mean	SD	Individual Cat Score	
				Minimum	Maximum
Day 28	150	0.75	0.80	0	4
Day 56	127	0.84	0.90	0	4
Day 84[b]	115	0.98	1.08	0	4

[a] 0 = excellent, 1 = good, 2 = fair, 3 = poor, 4 = worse
[b] Day 84 or final visit if exited early

Owner and Investigator assessments of overall clinical improvement were similar. On Day 28, both the Investigator and Owner assessment of pruritus mean scores decreased (improved) with a slight increase in means on Days 56 and 84.

Between NAH-07-0029 entry and Days 28, 56, and 84 (or final visit), mean total lesion scores decreased (improved) by 45.8%, 44.5%, and 33.0%, respectively. The mean number of regions with lesions decreased on Day 28 and remained relatively consistent on Days 56 and 84.

ATOPICA for Cats was used in conjunction with various medications including a macrocyclic lactone and other antiparasitic agents, systemic antimicrobials, nutritional supplements, and topical skin and otic cleansers and antimicrobials. Of the 191 cats in NAH-07-0029, 32 (16.8%) were on concurrent systemic antimicrobials, and 9 (4.7%) were on concurrent topical otic products (ear cleaners, antimicrobials). Eighty-three (43.4%) of the cats were treated with a macrocyclic lactone.

e. - Adverse Reactions: Twelve of the 191 cats (6.3%) withdrew from NAH-07-0029 because of adverse reactions. Adverse reactions in these 12 cats included weight loss, anorexia, vomiting, diarrhea, hypersalivation, lethargy, hepatic lipidosis, upper respiratory signs, ocular discharge, toxoplasmosis, lymphopenia, anemia, bacterial dermatitis, and small cell gastrointestinal lymphoma.

f. - Conclusions: Study NAH-07-0029 demonstrated that administration of ATOPICA for Cats for the control of feline allergic dermatitis at a target dose of 3.2 mg/lb (7.0 mg/kg), either mixed in a small amount of food or directly in the mouth, can be effectively tapered according to clinical response to every other day or twice weekly dosing in most cats. Adverse reactions leading to discontinuation of treatment occurred in 6.3% of the cats and included weight loss, anorexia, vomiting, diarrhea, hypersalivation, lethargy, hepatic lipidosis, upper respiratory signs, ocular discharge, toxoplasmosis, lymphopenia, anemia, bacterial dermatitis, and small cell gastrointestinal lymphoma.

3. **Combined Safety Results for ATOPICA for Cats from Studies NAH-07-0028 and NAH-07-0029**

a. - Study Animals: Between NAH-07-0028 and NAH-07-0029, 205 cats received ATOPICA for Cats (144 from the ATOPICA for Cats group in NAH-07-0028

and 61 from the control group in NAH-07-0028 that enrolled in NAH-07-0029). Cats received ATOPICA for Cats for up to 18 weeks (6 weeks in NAH-07-0028 and 12 weeks in NAH-07-0029). There were 130 cats that received ATOPICA for Cats in both NAH-07-0028 and NAH-07-0029.

b. - Deaths: Two cats died or were euthanized within 2 weeks following their final visit in NAH-07-0029. A two-year old cat was diagnosed with the effusive form of feline infectious peritonitis (FIP) and subsequently died following normal study exit. A nine-year old cat with pre-existing anemia that worsened during the study was diagnosed with aplastic anemia and euthanized due to a poor prognosis for recovery.

c. - Withdraws for Safety Reasons: Fourteen of the 205 cats (6.8%) treated with ATOPICA for Cats were withdrawn from NAH-07-0028 or NAH-07-0029 due to the occurrence of an adverse reaction.

Adverse reactions in these 14 cats included weight loss, anorexia, vomiting, diarrhea, hypersalivation, lethargy, hepatic lipidosis and jaundice, upper respiratory signs, ocular discharge, cough, toxoplasmosis, lymphopenia, anemia, bacterial dermatitis, convulsion, ataxia, and small cell gastrointestinal lymphoma.

d. - Adverse Reactions: See Table 9 for Adverse Reactions reported in greater than 2% of the cats on ATOPICA for Cats in NAH-07-0028 or NAH-07-0029.

Table 9: Adverse Reactions with ATOPICA for Cats in NAH-07-0028 or NAH-07-0029

Adverse Reaction	Number (Percent) of Cases n = 205
Vomiting/ Retching/ Regurgitation	72 (35.1%)
Weight Loss	42 (20.5%)
Diarrhea	31 (15.1%)
Anorexia/ Decreased Appetite	29 (14.1%)
Lethargy/ Malaise	28 (13.6%)
Hypersalivation	23 (11.2%)
Behavioral Disorder (hiding, hyperactivity, aggression)	18 (8.8%)
Ocular Discharge/ Epiphora/ Conjunctivitis	14 (6.8%)
Sneezing/ Rhinitis	11 (5.4%)
Gingivitis/ Gingival Hyperplasia	9 (4.4%)
Polydipsia	6 (2.9%)

The following adverse reactions were reported in less than or equal to 2% of cats treated with ATOPICA for Cats in NAH-07-0028 or NAH-07-0029: bacterial dermatitis, hepatic lipidosis and jaundice, gastrointestinal small cell lymphoma, constipation, cough, toxoplasmosis, muscle wasting, muscle tremors, ataxia, convulsion, polyuria, urinary tract infection, inappropriate urination or defection, seborrhea, worsening otitis externa, papilloma, leukotrichia (whitening of hair) and excessive hair growth, anemia, lymphopenia, worsening monocytosis, worsening neutrophilia, hyperglobulinemia, increased serum creatinine and urea nitrogen, and increased alanine aminotransferase.

Of the 205 cats that received ATOPICA for Cats in NAH-07-0028 or NAH-07-0029:

- 25 (12.2%) had *Toxoplasma gondii* titers go from negative to positive (20 of these developed IgM titers only)
- 9 (4.4%) had *Toxoplasma gondii* titers go from positive to negative
- 5 (2.4%) had *Toxoplasma gondii* titers go from negative to positive and return to negative while on ATOPICA for Cats
- 3 (1.4%) that began with positive *Toxoplasma gondii* titers had greater than 2-fold increases in IgG titers

One cat that developed a positive titer was diagnosed with clinical toxoplasmosis and subsequently recovered following discontinuation of ATOPICA for Cats and appropriate treatment.

In the subgroup of cats (n = 130) that received ATOPICA for Cats in both studies, mean alkaline phosphatase, amylase, cholesterol, creatinine, glucose, and urea nitrogen were higher at NAH-07-0029 exit compared to NAH-07-0028 entry. Mean magnesium, chloride, and eosinophil count were lower at the final visit. All means remained within the normal ranges for cats.

In the subgroup of cats (n = 130) that received ATOPICA for Cats in both studies, mean body weight was similar at NAH-07-0029 exit compared to NAH-07-0028 entry. However, two cats that experienced anorexia and weight loss developed hepatic lipidosis during treatment with ATOPICA for Cats.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety Study: Study NAH-07-0019

1. - Study Title: "A six-month repeat dose toxicity study of cyclosporine oral microemulsion formulation in cats" (Study NAH-07-0019)

2. - Study Director: Joyce K. Heward, MS, DABT, Mattawan, Michigan

3. - Study Design:

   a. - Objective: The objective of this Good Laboratory Practice (GLP) study was to evaluate the safety of ATOPICA for Cats (cyclosporine oral microemulsion formulation), in its final formulation, when administered orally for 6 months to adult cats.

   b. - Study Animals: Six-month-old healthy male and female domestic short hair cats

   c. - Treatment Groups: The cats were randomized to five treatment groups (4/sex/group).

   d. - Drug Administration: Cats were administered ATOPICA for Cats at 8, 16, 24, or 40 mg/kg/day orally for 6 months. The doses represent 1X, 2X, 3X, and 5X the maximum therapeutic dose, respectively. The control group cats were sham dosed with an empty syringe.

e. - Measurements and Observations: Fecal analysis, body weight, food consumption, clinical observations, physical/neurologic examinations, ophthalmic examinations, electrocardiographic examinations, blood pressure measurements, clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis), pharmacokinetics, organ weights, and anatomic pathology (macroscopic and microscopic) results were recorded.

f. - Statistical Methods: The individual cat was the experimental unit. Continuous variables measured only once (e.g., organ weights) during the study were analyzed using the analysis of variance. The model included treatment, sex and the sex-by-treatment interaction as fixed effects. Continuous outcomes measured multiple times during the study (e.g., clinical pathology variables) were analyzed using repeated measures analysis of covariance, with treatment, sex, day, and treatment-by-sex, sex-by-day, treatment-by-day, and treatment-by-sex-by-day terms in the model as fixed effects. The pretreatment value was used as a covariate. All main effects and interaction terms were tested at alpha=0.10, except for the treatment-by-sex and treatment-by-sex-by-day interactions which were tested at alpha=0.05. For all variables, appropriate mean contrasts between each dosed group and the control group were performed at an unadjusted alpha=0.10 to follow up on significant treatment effects in two-way interactions or main effects.

4. - Results: There was an increase in the frequency and number of cats with observations of 'soft feces' during the study. Body weight and food intake were increased in cats administered cyclosporine when compared to control cats. Activated partial thromboplastin time (APTT) was prolonged in cats administered cyclosporine when compared to control cats. An intermittent interventricular conduction disturbance was noted on electrocardiogram in one 3X and one 5X treatment group cat following 6 months of dosing.

A 5X cat was euthanized on Day 14 of the study following a rapidly-declining clinical condition including recumbency, inappetance, dehydration, and decreased body weight (~18%). A terminal blood draw revealed a trough cyclosporine concentration of 4,858.8 ng/mL, nearly five-fold higher than any other cat in this treatment group. A post-mortem examination showed a healing rib fracture and bone marrow hypocellularity characterized by a moderate reduction in the number of bone marrow cells from multiple lineages. Hematology parameters drawn prior to euthanasia for this cat did not reveal abnormalities indicative of bone marrow hypocellularity.

At necropsy, a 5X male cat had lymphoma of the kidneys and a mesenteric lymph node, and a 5X female cat had abdominal fibroadenomatous nodules.

Dose-normalized peak plasma concentrations and plasma drug concentration-time curves were not dose proportional at dose levels greater than 1X (8 mg/kg/day). The bioaccumulation factor (R) was calculated for the 1X group to compare trough levels across the duration of the study. Relative to Day 7 (when drug blood levels are expected to be at steady state), bioaccumulation factors were generally not different than 1 (except on Day 154; R = 1.72), indicating a low potential for bioaccumulation with long term dosing of cyclosporine.

5. - Conclusions: Study NAH-07-0019 evaluated the safety of ATOPICA for Cats when administered at 1X, 2X, 3X, and 5X the maximum therapeutic dose for 6 months. Cats administered cyclosporine had prolonged APTT. Bone marrow hypocellularity and lymphoma occurred in the 5X group.

B. Vaccine Response Study: Study NAH-07-0031

1. - Study Title: "The effect of cyclosporine oral microemulsion formulation (CsA) on vaccine titers in cats" (Study NAH-07-0031)

2. - Study Director: Elizabeth L. Reagan, Waverly, NY

3. - Study Design:

   a. - Objective: The objective of this GLP study was to evaluate the effect of cyclosporine oral microemulsion formulation on vaccine titers in adult cats.

   b. - Study Animals: Seven-month-old healthy male and female domestic short hair cats

   c. - Treatment Groups: The cats were randomized into two treatment groups (8/sex/group).

   d. - Drug and Vaccine Administration: Cats were administered ATOPICA for Cats at 24 mg/kg/day orally for 56 days. This dose represents 3X the maximum therapeutic dose. The control group cats were sham dosed with an empty syringe.

      Cats were vaccinated prior to enrollment in the study. FVRCP vaccine, containing feline rhinotracheitis/herpevirus type 1 (FHV-1), feline calicivirus (FCV), and feline panleukopenia virus (FPV) components, was administered at 8, 12, and 16 weeks of age. Feline leukemia virus (FeLV) vaccine was administered at 9 and 12 weeks of age. Rabies vaccine was administered at 16 weeks of age. The last pre-enrollment vaccines (FVRCP and rabies) were administered approximately 16 weeks prior to the first administration of ATOPICA for Cats. In order to determine the impact of the administration of cyclosporine on titer response to vaccinations, on Day 28 of ATOPICA for Cats administration, all cats received booster vaccines for FVRCP, FeLV, and rabies, and were vaccinated for the first time with feline immunodeficiency virus (FIV) vaccine.

   e. - Measurements and Observations: Fecal analysis, body weight, food consumption, clinical observations, physical/neurological examinations, clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis), and vaccine titer results were recorded.

   f. - Statistical Methods: The individual cat was the experimental unit. Continuous variables measured only once (e.g., body weight change) during the study were analyzed using the analysis of variance. The model included treatment, sex and the sex-by-treatment interaction as fixed effects. Continuous outcomes measured multiple times during the study (e.g., clinical pathology variables) were analyzed using repeated measures analysis of covariance, with treatment, sex, day, and treatment-by-sex, sex-by-day, treatment-by-day, and treatment-by-sex-by-day terms in the model as

fixed effects. The pretreatment value was used as a covariate. Using logarithmic transformations, titer values were transformed for analysis. The day -1 pretreatment value was used as a covariate. All main effects and interaction terms were tested at alpha=0.10, except for the treatment-by-sex and treatment-by-sex-by-day interactions which were tested at alpha=0.05. For all variables, appropriate mean contrasts between each dosed group and the control group were performed at an unadjusted alpha=0.10 to follow up on significant treatment effects in two-way interactions or main effects.

4. - Results: All cats survived until the end of the study. In the ATOPICA for Cats group, there was a decrease in mean body weight in males (14% less than controls) and an increase in mean body weight in females (5.4% more than controls) over the course of the study. Pooled food consumption in the ATOPICA for Cats group was decreased (Weeks 0 and 1) and then increased (Weeks 4, 5, 6 and 7), relative to controls. An increase in incidence and frequency of diarrhea, vomiting, and salivation were noted in cats in the ATOPICA for Cats group. One female cat in the ATOPICA for Cats group was observed to be in estrus during the study compared to five of the female cats in the control group. One cat in the ATOPICA for Cats group was noted as having a slow or absent startle reflex, ataxia, small lymph nodes, thin body condition, and gas and fluid filled loops of intestine. Lymphocyte counts were lower in the ATOPICA for Cats group than the control group. APTT was prolonged (up to 30-40 sec) in the ATOPICA for Cats group compared to the control group. Cholesterol, glucose, and total protein values were elevated just above normal reference ranges in the ATOPICA for Cats group. Blood urea nitrogen and creatinine values were elevated just above normal reference ranges in some cats in the ATOPICA for Cats group. Glucosuria was noted in three cats in the ATOPICA for Cats group that had hyperglycemia.

   Vaccine titers for previously administered vaccinations (FCV, FPV, FeLV, FHV-1 and rabies) were decreased in the ATOPICA for Cats group compared to the control group. However, titers for these vaccines remained adequate in both treatment groups after booster vaccinations at Day 28. In contrast, cats in the ATOPICA for Cats group failed to develop titers to the novel vaccine (FIV).

5. - Adverse Reactions: An increased incidence of diarrhea, vomiting, and salivation were noted in cats in the ATOPICA for Cats group compared to the control group. Observed lymphopenia is consistent with chronic immunosuppression and likely related to administration of 3X ATOPICA for Cats. Prolonged APTT and elevations in cholesterol, glucose, and total protein were likely related to administration of 3X ATOPICA for Cats.

6. - Conclusions: Study NAH-07-0031 evaluated the effect of ATOPICA for Cats on vaccine titers in adult cats. The study findings suggest that titer response to vaccination during repeated 3X ATOPICA for Cats administration depends upon the vaccination status prior to treatment. Vaccine naïve cats failed to develop titers when they were vaccinated while receiving ATOPICA for Cats.

C. Cyclosporine and *Toxoplasma gondii* Infection Study: Study NAH-06-0013

1. - Study Title: "The effect of cyclosporine (oral) treatment on the *Toxoplasma gondii* status of cats" (Study NAH-06-0013)

2. - Study Director: Elizabeth L. Reagan, AAS, Waverly, NY

3. - Study Design:

a. - Objective: The objective of this GLP study was to evaluate the effect of cyclosporine treatment on the *Toxoplasma gondii* (*T. gondii*) status of cats when administered prior to and after infection with *T. gondii* or only after infection with *T. gondii*.

b. - Study Animals: One to two-year-old healthy male and female domestic short hair cats

c. - Treatment Groups: The cats were randomized to three treatment groups (5/sex/group).

d. - Drug Administration and *T. gondii* Infection: -
Group 1 cats were administered placebo for 126 days.
Group 2 cats were administered placebo for 84 days followed by administration of 7.5 mg/kg/day ATOPICA for Cats for 42 days.
Group 3 cats were administered 7.5 mg/kg/day ATOPICA for Cats for 126 days.

All cats were infected with *T. gondii* (approximately 100 cysts per cat) orally on Day 42.

e. - Measurements and Observations: Results were recorded for body weight, food consumption, clinical observations, physical/neurological examinations, clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis), ophthalmic examinations, and organ weights and anatomic pathology (macroscopic and microscopic). Results were also recorded for clinical scoring for signs typical of *T. gondii* infection, fecal analysis for *T. gondii* oocysts, *T. gondii* titers, *T. gondii* PCR analysis of blood samples, and detailed histopathology evaluation of selected central nervous system and lung tissues for *T. gondii* lesions.

f. - Statistical Methods: The individual cat was the experimental unit. Continuous variables measured only once (e.g., organ weights) during the study were analyzed using the analysis of variance. The model included treatment, sex and the sex-by-treatment interaction as fixed effects. Continuous outcomes measured multiple times during the study (e.g., clinical pathology variables) were analyzed using repeated measures analysis of covariance, with treatment, sex, day, and treatment-by-sex, sex-by-day, treatment-by-day, and treatment-by-sex-by-day terms in the model as fixed effects. The pretreatment value was used as a covariate. All main effects and interaction terms were tested at alpha=0.10, except for the treatment-by-sex and treatment-by-sex-by-day interactions which were tested at alpha=0.05. For all variables, appropriate mean contrasts between each dosed group and the control group were performed at an unadjusted alpha=0.10 to follow up on significant treatment effects in two-way interactions or main effects.

4. - Results: One Group 3 male cat was found dead and another was euthanized within 42 days following infection. Both cats had signs of toxoplasmosis prior to death and histopathologic lesions consistent with toxoplasmosis, including *T.*

gondii organisms in tissues. Clinical signs typical of *T. gondii* infection, including bloody feces, lethargy, and vomiting/regurgitation, were also seen in most of the remaining cats, but resolved within six weeks following infection. Clinical signs were more severe and lasted the longest in Group 3 cats. There were no differences in mean body weight between groups, however, several cats in each group lost weight following *T. gondii* infection. The majority of these cats returned to their pre-infection body weights by Day 70 (i.e., within 28 days post infection). Although several cats had decreased food consumption following infection, their appetites returned to pre-infection levels by Day 56.

All inoculated cats developed *T. gondii* IgG antibodies. IgM titers were detected in only three cats (one Group 1 and two Group 3 cats).

The oocyst shedding period and the number of oocysts shed for cats in Groups 1 and 2 was greater than that of cats in Group 3, and the shedding period in Group 2 was greater than that of Group 1. *T. gondii* oocyst shedding was not detected in Group 2 during the 42 days of cyclosporine administration (which began 42 days after *T. gondii* infection), suggesting that cyclosporine did not reactivate oocyst shedding.

On Day 57, ophthalmic examinations revealed one Group 2 cat with punctate tapetal scars and one Group 1 cat with punctate nontapetal scars. Examinations on Day 122 revealed three additional cats with ophthalmic lesions consistent with *T. gondii* infection. One Group 2 cat and one Group 1 cat had punctate tapetal scars, and a Group 3 cat had retinal edema of the left eye and a nontapetal retinal scar in the right eye.

Group 3 had the highest incidence and severity of central nervous system and pulmonary histopathological findings typical of *T. gondii* infection, followed by Group 2. Lesions typical of *T. gondii* infection were more prevalent in male cats than in female cats. No *T. gondii* organisms were observed in the tissues of cats that survived to Day 126.

5. - Adverse Reactions: APTT was prolonged (40-60 sec) in the ATOPICA for Cats group compared to the control group. Cholesterol, glucose, and total protein/globulin values were elevated just above normal reference ranges in the ATOPICA for Cats group.

6. - Conclusions: Study NAH-06-0013 evaluated the effect of ATOPICA for Cats on the *T. gondii* status in cats. ATOPICA for Cats increased the severity of *T. gondii* infection in naïve (seronegative) cats, but not in cats previously exposed to *T. gondii* infection (seropositive) cats. In this study, the administration of ATOPICA for Cats did not reactivate oocyst shedding in cats previously exposed to *T. gondii* infection (seropositive) cats.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in cats, which are non-food animals. 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 NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ATOPICA 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 ATOPICA for Cats:
Do not eat, drink, smoke, or use smokeless tobacco while handling ATOPICA 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 ATOPICA for Cats. -

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that ATOPICA for Cats, when used according to the label, is safe and effective 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.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to assess the risk in case selection and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.