Date of Approval: August 15, 2003

FREEDOM OF INFORMATION SUMMARY

NADA 141-218

ATOPICA

(Cyclosporine capsules, USP) Modified

"For the control of atopic dermatitis in dogs weighing at least four pounds body weight."

Sponsored by:

Novartis Animal Health US, Inc.

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1. GENERAL INFORMATION:

a. File Number:	NADA 141-218
b. Sponsor:	Novartis Animal Health US, Inc. 3200 Northline Ave., suite 300 Greensboro, North Carolina 27408 Drug Labeler Code: 058198
c. Established Name:	Cyclosporine capsules, USP Modified
d. Proprietary Name:	ATOPICA
e. Dosage Form:	Gelatin capsules
f. How Supplied:	Packages of 15 unit-dose blister packs
g. How Dispensed:	Prescription (Rx) – Federal law restricts this drug to use by or on the order of a licensed veterinarian
h. Amount of Active Ingredients:	10, 25, 50 and 100 mg capsules
i. Route of Administration:	Oral
j. Species/Class:	Dogs
k. Recommended Dosage:	The initial daily dose of ATOPICA is 5 mg/kg/day (3.3-6.7 mg/kg/day) as a single daily dose for 30 days. Following this initial daily treatment period, the dose of ATOPICA may be tapered by decreasing the frequency of dosing to every other day or two times a week until a minimum frequency is reached which will maintain the desired therapeutic effect.
l. Pharmacological Category:	Immunosuppressant
m. Indications:	For the control of atopic dermatitis in dogs weighing at least 4 lbs body weight.

2. EFFECTIVENESS:

a. Dosage Characterization:

Two studies were used for dosage characterization. In a dose titration study conducted in client-owned animals, dogs were enrolled after confirmation of uncomplicated canine atopic dermatitis and evaluation of prior disease. Nonsteroidal anti-inflammatory and antihistamine treatments were stopped and corticosteroid therapy was decreased until clinical signs reappeared. Drugs with the potential to interfere with cyclosporine therapy were discontinued. Immunological tests confirmed IgE-mediated allergy to environmental allergens. Dogs received placebo, 2.5 mg/kg or 5 mg/kg of cyclosporine in solution once daily for 6 weeks. Clinical response to treatment was assessed using a Canine Atopic Dermatitis Extent Severity Index (CADESI) to evaluate dermatologic lesions, as well as owner and veterinarian assessments of pruritus. Improvement compared to the placebo group was seen at 5 mg cyclosporine/kg/day from Day 10 to the end of the study. The 2.5 mg/kg/day dose did not demonstrate improvement compared to the placebo group.

A continuation of this study evaluated the effects of dose reduction by one of two mechanisms: either reducing the dose to 2.5 mg/kg/day given once daily for 4 weeks and then to 1.25 mg/kg/daily; or reducing the dose to 5 mg/kg/day given every other day for four weeks and then given every fourth day. Dogs were evaluated on CADESI and pruritus scores as in the initial phase of the study. Final results indicate that the treatment regimen using 5 mg/kg/day every other day provided better continuing control of atopic dermatitis signs than the other tapering regimen investigated in the study.

The dose was confirmed in a second study comparing the effect of an oral solution of cyclosporine at 5 mg/kg/day to prednisolone at 0.5 mg/kg/day. Dogs were selected and evaluated based on similar criteria to the first study. Results indicate that cyclosporine produced a reduction in clinical signs similar to prednisolone.

Based on the results of these studies, a dose of 5 mg/kg/day of ATOPICA was selected as the induction dose for the control of atopic dermatitis in dogs.

b. Substantial Evidence:

(1) Field Study: The efficacy of cyclosporine compared to a placebo for the treatment of atopic dermatitis in dogs.

(a) Type of Study: Phase 1 was a multicenter, placebo-controlled, randomized, double-masked, field study. Phase 2 was an open-label field study without a control group.

(b) Study Director: Craig Parks, MS, DVM

(c) Location(s) and Investigator(s):

Karin Beale, DVM, Dipl. ACVD Gulf Coast Dermatology & Allergy Houston, TX	Bernie Pukay, DVM Bayview Animal Hospital Animal Ottawa, Ontario, Canada
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Andrea Cannon, DVM, Dipl. ACVD College Veterinary Hospital Modesto, CA	Tiffany Tapp, DVM, Dipl. ACVD Veterinary Referral Center Little Falls, NJ
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(d) General Design:

1 Purpose of Study: To demonstrate the effectiveness and safety of cyclosporine for the treatment of atopic dermatitis in dogs. The objective of Phase 1 was to determine the effectiveness of ATOPICA compared to placebo for the control of atopic dermatitis in dogs. The objective of Phase 2 was to evaluate a proposed dose-tapering regimen.

2 Description of Test Animals: Two hundred and sixty-nine privately owned dogs were enrolled in the study. These were dogs of various ages (1 -10 years), weights (4 -121 lbs), and breeds. Mixed breed dogs, Labrador retrievers and Golden retrievers were the most common breeds, with 38, 33, and 27 dogs enrolled respectively. One hundred ninety-two dogs completed Phase 1 of the study. Seventy-three dogs were withdrawn from Phase 1 analysis for various reasons. One hundred forty-five dogs completed Phase 2. For the entire study, twenty-six dogs were withdrawn from the study due to no improvement in pruritus or skin lesion score, fourteen dogs withdrew due to adverse drug reactions, twenty dogs dropped out from the study due to various reasons, sixty dogs were withdrawn from Phase 2 analysis for various reasons, and four dogs were never formally enrolled in the study.

3 Control and Treatment Group(s):
Phase 1: Masked, placebo-controlled four week study. The dogs were randomized into two groups, half receiving placebo, the other half receiving 5 mg/kg/day cyclosporine.

Table 1. Phase 1 of the Field Study

Treatment Group	Dose	# and Sex of Animals
Cyclosporine	5 mg/kg/day	94 (45 M, 49 F)
Placebo	0 mg/kg/day	98 (40 M, 58 F)

Phase 2: Dogs completing Phase 1 continued into Phase 2. Phase 2 was an open-label study without a control group. All placebo dogs from Phase 1 initially received cyclosporine at a dose of 5 mg/kg/day. All dogs received cyclosporine for up to 16 weeks.

4 Inclusion Criteria: Dogs with a documented history of atopic dermatitis, at least 4 pounds and 1 year old. Since atopic dermatitis does not have a definite diagnosis, it is based upon exclusion and clinical signs.

- Dogs were to be free of fleas and using a long-lasting flea adulticide treatment at the time of enrollment.
- Dogs were to have had chronic or recurrent dermatitis (for more than one year).
- Dogs were to have been through a suitable diagnostic differential (food allergy, flea bite hypersensitivity, and external parasites) rule-out testing program.

- Dogs were to score greater than 25 on the Canine Atopic Dermatitis Extent Severity Index (CADESI) score at the first visit.
- Each case was to have documented either an *in vivo* or *in vitro* test (such as intradermal skin testing or allergen specific IgE determination), performed in the last 6 months, confirming the presence of immediate or late-phase hypersensitivity reactions, or reagin immunoglobulins, to environmental allergens such as flea saliva, house mites, pollens or molds.

A clinical diagnosis of atopic dermatitis was based on the clinical criteria of Willemse, modified by Prelaud as follows:

Presence of at least 3 major criteria
First signs between 6 months and 3 years of age
Corticosteroid responsive pruritus
Bilateral erythematous interdigital pododermatitis
Erythema of the concave aspect of the pinna
Cheilitis and/or facial inflammation

5 Exclusion Criteria: Specifically excluded from enrollment were pregnant or lactating bitches; dogs with malignant neoplasia; dogs on an established diet augmented with fatty acid supplements, where this therapy would not or could not be maintained throughout the trial; dogs treated, or on a diet with Vitamin E supplements in the week preceding enrollment, where the therapy would not or could not be maintained throughout the trial; dogs having received long acting steroids in the eight weeks or oral steroids in the two weeks preceding enrollment; dogs having received hyposensitization immunotherapy injected in the two weeks preceding enrollment.

6 Drug Administration: Phase 1 dogs were given placebo or 5 mg cyclosporine/kg/day orally for 28 days. During Phase 2, all dogs received cyclosporine at one of three dose levels: 5 mg/kg/day, 5 mg/kg every other day or 5 mg/kg twice a week (every 3-4 days). All dogs on placebo in Phase 1 were started at 5 mg cyclosporine/kg/day for 28 days.

Table 2. Field Study Drug Doses

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

At each month's visit, the veterinarian could taper the frequency of ATOPICA administration if the pruritus scores improved and CADESI scores showed ≥ 50% improvement (e.g. 50% decrease in CADESI score from the previous visit). After all dogs received 5 mg cyclosporine/kg/day for the initial 28 days, their CADESI score and pruritus score were evaluated. An algorithm was followed to determine if the dose should stay at 5 mg/kg/day or be reduced to 5 mg/kg every other day for the next 28 days. At the next visit, the dog's CADESI score and pruritus score were reevaluated. Again an algorithm was followed to determine if the dose should remain the same, be reduced or increased back to 5 mg/kg/day if reduced previously. Cyclosporine was given fasted, one hour before a meal or two hours after a meal.

7 Variables Measured: Pruritus, skin lesions (CADESI score), dog owners' global assessment and clinical investigators' global assessment were assessed. CBC, serum chemistry and urinalyses were performed pre-study, after eight weeks on drug, and when the dog left the study. Cyclosporine blood levels were assessed after 4 weeks on drug.

(e) Results:

1 CADESI scores: Only results from Visits 1 and 2 were used in the statistical analyses of effectiveness. Both placebo and cyclosporine groups showed similar CADESI scores at Visit 1. At Visit 2 after 28 days of treatment, the cyclosporine-treated group showed improvement with the average CADESI score decreasing by 45%. The placebo group worsened over the same period with the average CADESI score increasing by 9% (see tables below). There was a significant difference in CADESI score between the treated and the control group at the end of study Visit 2 ($p<0.000l$) using an analysis of variance.

Table 3. Means and Standard Deviations of Field Study CADESI Scores

Treatment	Visit	N	Mean	SD	Min	Max
Cyclosporine	1	94	76.94	51.56	26	290
	2	94	42.18	38.75	0	214
Placebo	1	98	75.02	42.98	25	263
	2	98	82.18	50.86	7	246

Minimum score of 25 for enrollment, maximum score 360.

2 Pruritus scores: No statistical difference existed between the two treatment groups at Visit 1. At Visit 2 after 28 days of treatment, 74% of cyclosporine-treated dogs showed improvement in their pruritus scores while only 24% of placebo-treated dogs showed an improvement. There was a statistically significant difference in pruritus score between the treated and control group at the end of study Visit 2 ($p<0.000l$) in the generalized linear model analysis.

Table 4. Means and Standard Deviations of Field Study Pruritus Score

Treatment	Visit	N	Mean	SD	Min	Max
Cyclosporine	1	94	4.15	0.87	1	5
	2	94	2.78	1.12	1	5
Placebo	1	98	4.31	0.74	2	5
	2	98	4.08	0.92	1	5

3 Global Assessments

Owner Global Assessment: There was a significant difference in the owner's global assessment score ($p<0.000l$) using Fisher's Exact test, in the cyclosporine-treated group at Visit 2 after 28 days of treatment. At the end of Visit 2, the cyclosporine-treated dogs had scores that showed approximately twice the improvement as placebo-treated dogs. At study end, both groups showed similar responses. Therefore, once dogs were switched from placebo to cyclosporine treatment, dogs responded similarly to dogs originally started on cyclosporine treatment.

Investigator Global Assessment: The investigator's global assessment showed similar results to the owner's global assessment. There was a significant difference in the investigator global assessment score ($p<0.000l$) using Fisher's Exact test, in the cyclosporine-treated group at Visit 2. At Visit 2, the cyclosporine-treated dogs had scores that showed over twice as much improvement as the placebo-treated dogs. At the end of the study, a similar response to cyclosporine treatment was seen in the two groups.

4 Cyclosporine blood levels: Analysis of blood levels of cyclosporine drawn during the study demonstrated no correlation between CADESI score or pruritus and blood cyclosporine levels.

5 Dosing in Phase 2: All dogs started at 5 mg cyclosporine/kg/day for 28 days. Of all the dogs enrolled in the study, 4% of the dogs responded to the drug treatment with the greatest effectiveness by decreasing the drug dosage at each visit from 5 mg/kg/day for 28 days to 5 mg/kg every other day for 28 days to 5 mg/kg two times per week until the end of the study (SID-EOD-2x/wk-2x/wk). Conversely 2% of the dogs were unable to change their dose during the study (SID-SID-SID-SID). These dogs did not meet the criteria for reduction of dose frequency, but were kept in the study for various reasons.

Table 5. Dosage Changes in Field Study for All dogs and All Visits

# of Dogs	% Out of 265	Dosage Scheme
11	4.15	SID-EOD-2x/wk-2x/wk
12	4.53	SID-EOD-2x/wk-EOD
12	4.53	SID-EOD-EOD-2x/wk
15	5.66	SID-EOD-EOD-EOD
6	2.26	SID-EOD-EOD-SID
10	3.77	SID-EOD-SID-EOD
8	3.02	SID-EOD-SID-SID
22	8.30	SID-SID-EOD-2x/wk
16	6.04	SID-SID-EOD-EOD
22	8.30	SID-SID-EOD-SID
6	2.26	SID-SID-SID-EOD
5	1.89	SID-SID-SID-SID
26	9.81	No improvement
14	5.28	Drop out due to ADR
20	7.55	Drop out other
60	22.64	Excluded from analysis
4		Did not start study
Total # 269		

***SID** – once a day; **EOD** – every other day, **ADR** – adverse drug reaction.

Four-Week Evaluation for Dosage Adjustment, Irrespective of Initial Treatment Group: Of the 265 dogs in the study, 201 received 5 mg cyclosporine/kg/day for 28 days and were reevaluated for dosage adjustment. Of these 201 dogs, 41.3% were able to have their dose of cyclosporine reduced from 5 mg/kg/day to 5 mg/kg every other day, and 58.7% of the dogs remained at the induction dose of 5 mg/kg/day (see table below). Seven dogs dropped out of the study due to adverse drug events prior to completing the initial 28-day treatment period. Adverse events included vomiting, diarrhea, lethargy, seizure, and skin erythema, with vomiting being the most common reason. Thirteen dogs dropped out for various reasons, and 44 dogs were excluded from the analysis due to protocol deviations.

Table 6. Dosage Change after Four Weeks on Cyclosporine

# of Dogs	% out of 201	Dosage Scheme
118	58.7	SID-SID
83	41.3	SID-EOD

6 Clinical Pathology

Hematology: No drug-related changes were observed during the study.

Serum Chemistry: The following changes were found in clinical chemistry values during the study.

Table 7. Field Study Clinical Chemistry Changes

Clinical Chemistry	**% Affected (out of 265)**
Elevated Creatinine	7.8 %
Hyperglobulinemia	6.4%
Hyperphosphatemia	5.3%
Hyperproteinemia	3.4%
Hypercholesterolemia	2.6%
Hypoalbuminemia	2.3%
Hypocalcemia	2.3%
Elevated BUN	2.3%

In addition, the following changes in clinical chemistry variables were noted in less than 2% of dogs: hypernatremia, hyperkalemia, elevated ALT, elevated ALP, hypercalcemia and hyperchloremia.

Urinalysis: Many of the dogs entered the study with bacteruria, proteinuria or both. The incidence increased slightly through the course of the study (see table below). Ten dogs developed urinary tract infections during the study. Many of these were asymptomatic and found during routine urinalysis.

Table 8. Field Study Urinalyses

	Week 0	**Week 8**	**Week 16**
# of dogs with Bacteruria (# of dogs checked)	46 (27%) (171)	47 (33%) (142)	43 (30%) (141)
# of dogs with Proteinuria (# of dogs checked)	87 (46%) (190)	78 (50%) (155)	86 (56%) (153)
# of dogs with both (# of dogs checked)	28 (16%) (175)	32 (23%) (139)	32 (23%) (139)

7 Adverse Reactions: Fourteen dogs withdrew from the study due to adverse reactions (see Table 9). Vomiting and diarrhea were the most common adverse reactions occurring during the study. Other adverse reactions observed during the course of the study are shown in Table 10 as the percent of dogs affected.

Table 9. Field Study Adverse Drug Reaction Withdrawals

Adverse Reaction	Number of Animals Affected	% Affected (out of 265)
Vomiting	4	1.5%
Diarrhea	1	0.4%
Vomiting, Diarrhea and Pruritus	1	0.4%
Vomiting, depression and lethargy	1	0.4%
Lethargy, anorexia, hepatitis	1	0.4%
Gingival hyperplasia, lethargy, PU/PD, soft stool	1	0.4%
Seizure	1	0.4%
Sebaceous cyst	1	0.4%
Pruritus	1	0.4%
Skin erythema	1	0.4%
Otitis externa	1	0.4%

Table 10. Clinical Observations in Field Study

Clinical Sign	% Affected (out of 265)
Vomiting	30.9%
Diarrhea	20.0%
Persistent Otitis Externa	6.8%
Urinary Tract Infection	3.8%
Anorexia	3.0%
Gingival Hyperplasia	2.3%
Lethargy	2.3%
Lymphadenopathy	2.3%

The following clinical signs were reported in less than 2% of dogs treated with ATOPICA in the field study: constipation, flatulence, Clostridial organisms in the feces, nausea, regurgitation, polyuria/polydipsia, strong urine odor, proteinuria, pruritus, erythema/flushed appearance, pyoderma, sebaceous adenitis, crusty dermatitis, excessive shedding, coarse coat, alopecia, papillomas, histiocytoma, granulomatous mass or lesion, cutaneous cyst, epulis, benign epithelial tumor, multiple hemangioma, raised nodule on pinna, seizure, shaking/trembling, hind limb twitch, panting, depression, irritability, hyperactivity, quieter, increased light sensitivity, reluctance to go outside, weight loss, hepatitis.

Otitis externa, allergic otitis, or pinna erythema with or without exudate, occurred in this study, as it is frequently seen in conjunction with atopic dermatitis. Most of the dogs had a history of chronic otitis externa due to atopy. Many dogs entered the study with otitis externa, which did not resolve without otic treatment. Of the 265 dogs, 6.8% had persistent otitis externa. New cases (56.2% of 265) of otitis externa, allergic otitis or pinna erythema developed while dogs were receiving ATOPICA. However, the incidence rate was lower with ATOPICA compared to placebo. A change in the dose frequency was not necessary when new cases occurred.

Lymphadenopathy was seen in six dogs. Three dogs had enlarged popliteal lymph nodes, two dogs had peripheral lymphadenopathy, and one dog had enlarged submandibular lymph nodes.

(f) Conclusions: ATOPICA at 5 mg/kg/day for 28 days is effective in the control of atopic dermatitis in dogs with the most common adverse reactions being vomiting, diarrhea and otitis. Effectiveness of treatment was maintained in most dogs by dosing with 5 mg/kg every other day. Monitoring cyclosporine blood levels is not an appropriate predictor of effectiveness.

3. TARGET ANIMAL SAFETY:

a. 90-Day Target Animal Safety Study

(1) Type of Study: GLP Target Animal Safety

(2) Investigator: Joseph Siglin PhD, DABT
Springborn Labs, Inc.
Ohio Research Center
Spencerville, OH

(3) General Design:

(a) Purpose of Study: To evaluate the margin of safety of an oral cyclosporine A formulation administered via capsules to Beagle dogs over the course of 90 days.

(c) Description of Test Animals: Twenty two male and 22 female Beagle dogs approximately 6 months of age.

(d) Control and Treatment Groups: Groups 2, 4, and 6 received a constant dose of 5 mg cyclosporine/kg/day while Groups 3, 5 and 7 had their dose tapered throughout the study, as shown in the table below.

Table 11. 90-Day Safety Study Drug Dosages

Group	Dosage	Minimum Exposure Level (mg/kg/day)		
		Days 0-29	Days 30-59	Days 60-89
1	0X	0	0	0
2	1X	6.7	6.7	6.7
3	1X	6.7	3.3	2.5
4	3X	20	20	20
5	3X	20	10	7.5
6	5X	33.3	33.3	33.3
7	5X	33.3	16.7	12.5

(e) Dosage Form: ATOPICA final formulation (gelatin capsules)
Placebo Control: empty gelatin capsules

(f) Route of Administration: orally in fasted dogs
Frequency: Once daily
Treatment Duration: 90 days

(g) Variables Measured: Clinical observations, physical examinations, ophthalmoscopic examinations, body weights, food consumption, hematology, clinical chemistry, urinalysis, ECG and blood pressure, gross necropsy and histopathology were performed on all animals.

(4) Results:

(a) Clinical Observations and Exams: Test article-related clinical signs were observed in all treated groups and included diarrhea, vomiting, callus-like lesions on the footpads (Groups 2 and 4-7); raised lesions on the body (Groups 4-7); red/swollen pinnae (Groups 2-7); and abnormal excreta suggestive of gastrointestinal disturbance (Groups 2-7).

(b) Physical Examinations: Test-article related physical examination findings consisted of verruciform areas in the integument in Groups 4-7, gingival proliferation and hyperkeratotic areas on the integument (limbs, pinna, and vaginal area) in Groups 2-7. The gingival proliferation, which was first observed on Day 45, followed a dose-related pattern in its progression and severity during the last six weeks of the study. Whereas most of the dogs in Groups 2 and 3 had minimal to mild gingival proliferation at study termination, the majority of dogs in Groups 4-7 had moderate gingival proliferation, and one dog each in Groups 6 and 7 had severe gingival proliferation by study conclusion.

Enlarged popliteal lymph nodes were noted during physical examination in three of eight dogs in Group 4, four of eight dogs in Group 6, and two of four dogs in Group 7. These were usually first noted on Day 58 or 76 and persisted to the end of the study.

Hair loss was noted in one dog each in Groups 4 and 6, and two dogs in Group 2. It is not clear if these findings are drug related.

(c) Body Weights and Weight Gain: Groups 2 and 6 had significantly lower mean body weight than that of the control group ($p=0.0324$, $p=0.0291$, respectively).

(d) Clinical Pathology:

1 Hematology: Erythrocyte Sedimentation Rate (ESR) was increased in Group 6 compared to control overall ($p<0.004$) and on Day 70 ($p<0.01$).

2 Serum Chemistry: Test-article related effects in clinical chemistry variables were observed in all groups. In the constant dose groups, all groups (2, 4 and 6) had a significant decrease in phosphorus ($p<0.0001$). Groups 4 and 6 had the most changes including hyperproteinemia ($p<0.01$), hyperglobulinemia ($p<0.01$), and hypoalbuminemia ($p<0.05$). A corresponding hypocalcemia was seen in Groups 4 and 6 ($p<0.01$). Hypomagnesemia was seen in Groups 4 and 6 ($p<0.01$). In Group 6 only, a decrease in potassium ($p < 0.05$) and an increase in GGT ($p<0.05$) were seen. See the summary table on the next page.

3 Similar findings were seen in the taper groups 3, 5, and 7. Hyperproteinemia, hyperglobulinemia, hypoalbuminemia, hypophosphatemia, and hypokalemia were seen at Day 14, after the dogs had received the highest doses for the study and resolved as the dose was tapered to lower levels.

Table 12. Summary of Results for the 90-Day Safety Study Constant Dose Groups

	Group 2 (1X)	Group 4 (3X)	Group 6 (5X)
Observations/ Exam	Callus-like lesions on footpads (1/8) Red/swollen pinna (8/8) Diarrhea/abnormal stool (8/8) Salivation (1/8) Vomiting (4/8)	Raised lesions (2/8) Callus-like lesions on footpads (5/8) Red/swollen pinna (7/8) Diarrhea/abnormal stool (8/8) Salivation (1/8) Vomiting (3/8)	Raised lesions (5/8) Callus-like lesions on footpads (5/8) Red/swollen pinna (7/8) Diarrhea/abnormal stool (8/8) Dehydration (1/8) Vomiting (5/8)
Physical Exam	Gingival Proliferation (mild – moderate) 8/8 Hyperkeratotic areas (footpads, limbs, pinna, vagina) (1/8) Hairloss (2/8)	Verruciform areas (2/8) Gingival Proliferation (moderate) 8/8 Hyperkeratotic areas (footpads, limbs, pinna, vagina) (2/8) Hairloss (1/8) Increased popliteal lymph node (3/8)	Verruciform areas (5/8) Gingival Proliferation (moderate – severe) 8/8 Hyperkeratotic areas (footpads, limbs, pinna, vagina) (4/8) Hairloss (1/8) Increased popliteal lymph node (4/8)
Body Weight	Decreased		Decreased
Food Consumption		Decreased	Decreased
Hematology			↑ ESR
Clinical Chemistry		↑ Protein	↑ Protein
		↓ Albumin	↓ Albumin
		↑ Globulin	↑ Globulin
	↓ Phosphorus	↓ Phosphorus	↓ Phosphorus
		↓ Calcium	↓ Calcium
		↓ Magnesium	↓ Magnesium
			↓ Potassium
			↑ GGT

(e) Pathology:

1 Gross Post-Mortem Exam: Gross necropsy findings were generally unremarkable with the exception of those observations that confirmed antemortem findings of gingival proliferation, hyperkeratosis, and verruciform lesions.

2 Histopathology: Histopathological examinations revealed a number of test article-related changes involving gingival epithelium and the epithelium of toe pads and other skin sites, principally the pinna. These changes were of a proliferative nature and were characterized in the gingiva by minimal to moderate hyperplasia that was frequently associated with minimal to moderate chronic inflammation of the underlying connective tissue.

The gingival lesions were of greater incidence and severity in the three constant dose groups (Groups 2, 4, and 6) compared to the three taper dose groups (Groups 3, 5, and 7). In addition, a positive dose response in severity and incidence was apparent in the constant dose groups but was not seen in the taper dose groups.

The toe-pad lesion consisted of mild to moderate epidermal hyperplasia, minimal to marked hyperkeratosis, and mild to moderate chronic dermatitis, which was sometimes accompanied by minimal to mild parakeratosis. As in the gingiva, the toe pad lesions were of greater incidence and severity in the constant dose groups, where a positive dose response in incidence and severity was evident for most of the lesions.

Skin lesions at other sites, principally the pinna, were observed in the mid-and high dose groups of the constant and taper-dose regimens (Groups 4-7). These lesions were characterized by mild to moderate epidermal hyperplasia, mild to marked chronic dermatitis, and mild to moderate hyperkeratosis. Occasionally, minimal to moderate parakeratosis was also observed. Like at the gingival and toe pad sites, these lesions tended to have a greater incidence and severity in the constant dose groups.

(5) Conclusions: Oral administration of ATOPICA capsules at the maximum recommended dose, when administered for 90 days causes callus-like lesions on the footpads, red/swollen pinnae, mild to moderate gingival proliferation, hyperkeratotic areas on the integument, hair loss, salivation, vomiting and diarrhea/abnormal stools. These clinical signs either lessen in severity or resolve as the drug is tapered to a lower dose. Increased erythrocyte sedimentation rate, hyperproteinemia, hyperglobulinemia, hypoalbuminemia, hypocalcemia, hypophosphatemia, and hypomagnesemia were observed at three and five times the recommended dose. These resolved as the dose was tapered.

When the drug was administered at higher than the maximum recommended dose, raised lesions, verruciform areas on the integument, popliteal lymph node enlargement, and weight loss were also seen.

b. 52-Week Target Animal Safety Study

(1) Type of Study: GLP Target Animal Safety

(2) Investigator: B.P. Richardson, Dr. Med. Vet.
Study Location: Sandoz Ltd.
Basel, Switzerland

(3) General Design:

(a) Purpose: To determine the safety of cyclosporine when administered to dogs at 1, 3, and 9X the target induction dose of 5 mg/kg/day.

(b) Animals: 32 beagles (16 males and 16 females) approximately 8-10 months old, 8 dogs per group (4 males and 4 females).

(c) Control and Treatment Groups:

Table 13. 52-Week Safety Study Groups

Group	Dose mg/kg	Number and Sex of Animals
K	0 mg/kg (0X)	4 M, 4 F
A	5 mg/kg (1X)	4 M, 4 F
B	15 mg/kg (3X)	4 M, 4 F
C	45 mg/kg (9X)	4 M, 4F

(d) Dosage Form: Cyclosporine in solution
Placebo Control: Olive oil

(e) Route of Administration: Orally in fasted dogs
Frequency: Once daily
Duration of Study: 52 weeks (1 male and 1 female per group were retained as recovery animals for 12 weeks at the end of the study).

(f) Variables Measured: General health, physical examination, hematology and blood chemistry, urinalysis, ECG and ophthalmoscopic examination, body weight, food intake, gross necropsy and histopathology were performed.

(4) Results: Changes in the 5 mg/kg treated group were minimal. They included vomiting, an increased erythrocyte sedimentation rate, and weight loss. The 15 and 45 mg/kg treated groups had vomiting, papillomatosis, and skin lesions. Vomiting, diarrhea and weight loss were seen in all cyclosporine-treated groups with increasing frequency as the dose increased. Multilocular papilloma-like lesions of the skin were observed in 5 out of 8 high dose animals between weeks 20 and 40. Other findings in the mid and high dose animals included swollen

gums due to chronic gingivitis and periodontitis, lower serum albumin and higher cholesterol, triglyceride, IgA and IgG. Hematological findings consisted of anemia and decreased leukocyte counts in a few high-dose animals. Erythrocyte sedimentation rates were increased at all dose levels in a dose-dependent manner. Notable histopathological findings were limited to lymphoid atrophy, hypertrophic gums (from gingivitis) and slight regenerative changes of the renal tubular epithelium in high dose animals. The findings were shown to be reversible during a 12-week recovery phase of the study.

(5) Conclusions: Cyclosporine administered at 1, 3, and 9 times the recommended dosage caused dose-dependent vomiting, diarrhea, weight loss, swollen gums, papilloma growths, periodontitis, and gingivitis. These signs were reversible with drug withdrawal.

c. Impact of Cyclosporine Administration on the Vaccination of Dogs

(1) Type of Study: GLP Target Animal Safety

(2) Location and Investigator:
Joseph Siglin PhD, DABT
Springborn Labs, Inc.
Ohio Research Center
Spencerville, OH

(3) General Design:
(a) Purpose of Study: The purpose of this study was to evaluate the safety of oral cyclosporine when administered prior to and following revaccination of Beagle dogs.

(b) Description of Test Animals: Sixteen Beagle dogs (8 male and 8 female) were used for the study. Dogs were approximately 6 months old.

(c) Control and Treatment groups:

Table 14: Vaccine Study Groups

Treatment Group	Treatment	Number and Sex of Animals
1	Placebo capsules + vaccinations on Day 27	4M, 4F
2	20 mg cyclosporine/kg/day + vaccinations on Day 27	4M, 4F

The cyclosporine dosage of 20 mg/kg/day represents 3X the proposed maximum exposure of 6.7 mg/kg/day (or 4X the proposed target dose of 5 mg/kg/day).

(d) Dosage Form: ATOPICA Final Formulation (gelatin capsules)
Killed rabies vaccine (Prorab-1, Intervet Inc., Millsboro, DE)

Multivalent vaccine (Galaxy: Canine Distemper, Canine Adenovirus Type-2, Canine Parainfluenza, Canine Parvovirus (modified live virus), *Leptospira canicola*, *Leptospira icterohemorrhagiae*) Fort Dodge Laboratories, Ft. Dodge, IA

(e) Dosage Amount, Frequency, and Duration: 20 mg/kg/day for 56 days
Route of administration: Orally in fasted dogs
Vaccines administered subcutaneously on Day 27

(f) Variables Measured: Clinical observations, physical examinations, body weights, food consumption, hematology and clinical chemistry were performed. Antibody titer analyses were conducted on Study Days 0, 27, 42 and 56, serum samples were obtained from each dog for antibody titer analyses (CDV, CPV, PI3, CAV-2, Lepto CAN, Lepto ICT, and Rabies). Quantification of CD4, CD8 and CD3 T-lymphocytes were conducted on Days -8, -2, 6, 13, 20, 26, 34, 41, 48 and 55.

(4) Results

(a) Clinical Observations and Physical Examinations: Treatment with cyclosporine resulted in an increased incidence of abnormal excreta signs (primarily mucoid stools and mucoid material in the cage/tray) in the Group 2 dogs. The excreta was typically yellow or green in appearance. Other clinical observations which occurred with an increased frequency in the cyclosporine-treated dogs included vomiting, salivation, reddening of the nose, mouth, pinna and urogenital areas, hair loss, and scab formation on the forelimbs, paws, ventral thoracic region and urogenital areas. Drug-related physical examination findings consisted of minimal to moderate gingival proliferation and minimal to mild hyperkeratosis of the footpads. The gingival proliferation occurred in all 8 cyclosporine-treated dogs, beginning in most animals on Day 21. The footpad changes occurred in 4/4 male and 2/4 female cyclosporine-treated dogs, beginning in most animals between Days 27 and 49. The following physical examination findings were noted in cyclosporine-treated dogs; however, these were not regarded as toxicologically significant due to their low incidence and transient occurrence. Two dogs treated with cyclosporine had extreme miosis with minimal retinal reflex on Day 27. One dog treated with cyclosporine had enlarged popliteal lymph nodes on Day 35.

(b) Clinical Pathology

1 Hematology: The only toxicologically meaningful difference in hematology data consisted of a higher erythrocyte sedimentation rate in cyclosporine-treated males on Day 56.

2 Clinical chemistry: Occasional statistical differences in clinical chemistry data were observed on Day 56, including hyperglobulinemia ($p<0.09$), decreased potassium ($p<0.04$), and increased triglycerides ($p<0.008$).

(c) Antibody Titer Analyses: Antibody titer analyses did not reveal an effect on existing antibody levels or on antibody titers following administration of cyclosporine and re-vaccination on Day 27. Both the placebo and cyclosporine-treated dogs exhibited a marked increase in rabies titers on Day 42, which

remained well above baseline levels on Day 56. In contrast, results of Lepto CAN and Lepto ICT testing showed only modest increases in titers in a few placebo and cyclosporine group dogs on Day 42. CAV-2 titers were generally low. With regard to PI3, all samples had a titer of less than 1:2, which was considered negative. Evaluation of CDV and CPV also did not reveal any change in antibody titer.

(d) Quantification of CD4, CD8 and CD3 T-lymphocytes: Quantification of T-lymphocyte populations revealed an increase (39%) in the ratio of CD4/CD8 cells in the cyclosporine-treated dogs. The increase was a consequence of a higher proportion of CD4 cells (T-helper cells) and a lower proportion of CD8 cells (cytotoxic/suppressor T-cells). Although the biological significance of this shift, if any, was not clear, it was not considered indicative of an immunosuppressive effect since the absolute number of CD8 cells remained unchanged in the cyclosporine-treated dogs.

(5) Conclusion: Cyclosporine administered at three times the maximum recommended dose for 56 days did not affect the immune response to killed rabies vaccination. All dogs demonstrated an increase in rabies antibody titer by 15 days post-vaccination. In contrast, all components of a multivalent vaccine containing modified live parvovirus (DHLPP) failed to increase antibody titers in either ATOPICA or placebo dogs. Clinical signs noted with an increased frequency in the cyclosporine-treated dogs included diarrhea, vomiting, salivation, reddening of the nose, mouth, pinna, and urogenital areas, hair loss, scab formation in the forelimbs, paws, ventral thoracic region and urogenital areas, gingival proliferation, and footpad changes. Clinical chemistry findings on Day 56 included hyperglobulinemia ($p<0.09$), decreased potassium ($p< 0.04$) and increased triglycerides ($p<0.008$).

d. Safety of Concomitant Medications in the Dog: Cyclosporine and an Intermediate Duration Glucocorticoid (Methylprednisolone)

(1) Type of Study: GLP Target Animal Safety

(2) Location and Investigator:
Joseph Siglin PhD, DABT
Springborn Labs, Inc.
Ohio Research Center
Spencerville, OH

(3) General Design:
(a) Purpose of Study: To evaluate the safety of short-term concomitant use of oral cyclosporine and an oral, intermediate duration glucocorticoid, methylprednisolone (MP) in Beagle dogs

(b) Description of Test Animals: 24 Beagle dogs (12 male and 12 female) approximately 6 months old.

(c) Control and treatment groups:

Table 15. Concomitant Methylprednisolone Study Treatment Groups

		Treatment Phase	
Group	**No. of Animals**	**Phase A (Days 0-13)**	**Phase B (Days 14-27)**
1	4M, 4F	1 mg MP/kg/day	placebo capsules
2	4M, 4F	1 mg MP/kg/day	1 mg MP/kg/day + 20 mg cyclosporine/kg/day*
3	4M, 4F	1 mg MP/kg/day	20 mg cyclosporine/kg/day*

*The cyclosporine dosage of 20 mg/kg/day represents 3X the proposed maximum exposure of 6.7 mg/kg/day (or 4X the proposed target dose of 5 mg/kg/day).

(d) Dosage Form: Cyclosporine, final formulation (gelatin capsules);
Methylprednisolone tablets in a gelatin capsule;
Placebo: Empty gelatin capsules

(e) Dosage Amount, Frequency and Duration: Cyclosporine 20 mg/kg, administered once a day for 14 days
Route of Administration: Orally to fasted dogs

(f) Variables Measured: Experimental endpoints included survival, clinical observations, physical examinations, body weights, food consumption, and clinical pathology determinations.

(4) Results:

(a) Clinical Observations and Exams: All dogs survived to study conclusion. Phase A: Clinical signs were unremarkable. Phase B: Groups 2 and 3 exhibited increased occurrences of abnormal excreta, gingival proliferation, and raised skin lesions. One dog in Group 2 had a decreased pupillary light response on Days 7, 14 and 21. Groups 2 and 3 had lower mean body weights than the control group. Group 3 dogs had decreased food consumption in Phase B.

(b) Clinical Pathology:
Serum Chemistry: Hyperproteinemia ($p<0.01$), hyperalbuminemia ($p<0.01$) hyperglobulinemia ($p<0.01$) and hypophosphatemia ($p<0.01$) were reported in group 2 dogs on day 27. Hypophosphatemia ($p<0.01$), hypomagnesemia ($p<0.01$) and hypokalemia ($p<0.10$) were reported in Group 3 dogs on Day 27.

(5) Conclusions: Cyclosporine, administered at three times the maximum recommended induction dose for 14 days, either concurrently or directly following administration of 1 mg/kg methylprednisolone, did not show additional adverse effects beyond those expected. No convulsions or seizures were reported in this study. Clinical signs of gastrointestinal disturbance, reductions in mean body weights in the Groups 2 and 3 dogs, and decreased food consumption in the Group

3 dogs were observed. Other effects of cyclosporine included slight to mild gingival proliferation, raised skin lesions, decreased pupillary light response, and hyperproteinemia, hyperalbuminemia, hyperglobulinemia, and hypophosphatemia.

4. HUMAN SAFETY:

This drug is intended for use in dogs which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Not for human use. Keep this and all drugs out of reach of children. Contact a physician if human ingestion occurs. For use in dogs only."

5. 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 of the implementing regulations. The data demonstrate that ATOPICA (cyclosporine capsules, USP) Modified, when administered under labeled conditions of use, is safe and effective for the control of atopic dermatitis in dogs weighing at least 4 lbs body weight.

The drug is restricted to use by or on the order of a licensed veterinarian due to the complexity of the disease and dosing required to control atopic dermatitis in dogs and to monitor for adverse reactions.

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 approval. This NADA contains a field study for substantial evidence of effectiveness and reports from four target animal safety studies.

ATOPICA is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
5,342,625	August 30, 2011
5,741,512	April 27, 2015
5,866,159	August 30, 2011
5,916,589	March 6, 2017
5,962,014	March 6, 2017
5,962,017	April 27, 2015
6,024,978	September 13, 2009
6,007,840	March 6, 2017
6,262,022	June 25, 2012
6,258,808	June 26, 2012
5,985,321	September 26, 2014

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below.

Package Insert
Blister Foil (10 mg, 25 mg, 50 mg, 100 mg)
Unit Dose Carton (10 mg, 25 mg, 50 mg, 100 mg)