FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION:

NADA No:	141-052
Sponsor:	Schering-Plough Animal Health P.O. Box 529 Kenilworth, New Jersey 07033
Generic Name:	0.2% cyclosporine USP ophthalmic ointment
Tradename:	OPTIMMUNE® Ophthalmic Ointment
Marketing Status:	Rx

II. INDICATIONS FOR USE:

OPTIMMUNE® Ophthalmic Ointment is indicated for the treatment of chronic keratoconjunctivitis sicca (KCS) in dogs.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE:

The ingredients of OPTIMMUNE® are formulated into a topical ophthalmic ointment. A 1/4 inch strip is to be administered every 12 hours to the affected eye(s). The ointment may be placed directly on the cornea or into the conjuctival sac.

IV. EFFECTIVENESS:

The new animal drug application for cyclosporine ophthalmic ointment contains adequate and well-controlled studies which demonstrate efficacy in the treatment of chronic keratoconjunctivitis sicca (KCS). KCS is a disease condition that occurs in animals that do not produce a normal amount of tears and consequently have an excessively dry ocular surface. This ocular dryness results in varying degrees of inflammation of the conjunctiva and cornea. Clinical manifestations of KCS include ocular discharge, conjunctivitis, keratitis, pain, and depending on the extent and duration of the condition may involve blindness. Though the mechanism of action is not completely known, cyclosporine when applied ophthalmically to dogs with chronic keratoconjunctivitis sicca (KCS) may increase lacrimation through local immunomodulation within lacrimal tissue. However, the clinical response to cyclosporine is not necessarily dependent upon an increase in lacrimation. Some dogs will improve clinically (i.e., exhibit a decrease in conjunctival and/or corneal pathology) despite a lack of increase in Schirmer Tear Test (test of tear production) values. This is thought to occur through suppression of inflammation by cyclosporine on the ocular surface.

A. Pivotal Studies

1. Cyclosporine Ophthalmic Ointment Clinical Dose Response

   a. Trial: Study #1330C-61-V89-032

   b. Objective: Dose determination study which was designed to compare the relative efficacy of four concentrations of topically applied cyclosporine ophthalmic ointment. The purpose of this comparison was to establish an optimal dose for the treatment of chronic keratoconjunctivitis sicca (KCS) in dogs.

   c. Investigators:

Six board certified veterinary ophthalmologists in three different states served as investigators in this blinded placebo-controlled clinical field study.

INVESTIGATOR	LOCATION	# OF CASES ANALYZED
Dr. R. Morgan	Boston, MA	11
Dr. R. Munger	Dallas, TX	26
Dr. J. Lavach	Garden Grove, CA	13
Dr. K. Boldy	Los Angeles, CA	10
Dr. J. Swanson	Houston, TX	14
Dr. C. Cook	San Mateo, CA	16
TOTAL		90

d. Animals: A total of 90 client owned animals of various breeds, ages, and sex were analyzed in the study. Only those animals with chronic KCS (greater than one month duration) that had a Schirmer Tear Test (STT) measurement of less than or equal to 5 mm/minute in one or both eyes were included. They also must have had conjunctivitis with or without keratitis in the affected eye(s).

e. Controls: One group of dogs received placebo ointment comprised of the formulation excipients without active ingredient.

f. Dosage Form: Cyclosporine ointment

g. Route of Administration: Ophthalmic

h. Doses Tested: 1/4 inch ribbon of 0.05%, 0.1%, 0.2%, 0.4% concentration ointments

i. Duration/Frequency of Treatment: Every 12 hours for 42 days

j. Study Design: Cases were enrolled upon satisfying the study entrance qualification criteria on Day -7. Prior to entering the study, all dogs received 7 days of topical ophthalmic antibiotic therapy (NEOBACIMYX® ointment - Schering-Plough). Cases were randomly assigned to dose groups and therapy was initiated on Day 0 and lasted for 6 weeks. The response to therapy with the test article was assessed by ophthalmic exams (Days 0, 7, 21, and 42) at which time the clinical appearance of the conjunctival, corneal, and internal ocular structures were numerically scored, and Schirmer Tear Test (STT) values were determined.

k. Results: The STT and associated improvement in conjunctival and corneal health were the pivotal parameters in the selection of optimal dose.

Use of the 0.4% cyclosporine ointment resulted in a very rapid STT response. A more gradual response was observed in the 0.2% cyclosporine group such that no statistically significant difference was found between the 0.2% and 0.4% cyclosporine groups on either Days 21 or 42. Use of cyclosporine

ointments below 0.2% produced no consistent improvement in STT.

The changes in the mean STT values from Day 0 were determined for each treatment group at each subsequent examination day. The 0.2% cyclosporine group had the greatest overall change in mean STT value (7.50 mm/min by Day 42) and the 0.4% cyclosporine had the most rapid response in mean STT change (5.67 mm/min by Day 7). A dose response was evident as indicated by significant linear trends on Days 7, 21, and 42. On Day 42 a significant quadratic trend was evident indicating a dose response plateau.

The increase in lacrimation was associated with improvement in conjunctival (character of discharge, volume of discharge, hyperemia, and hypertrophy) and corneal (edema, surface contour, vascularization) health. Clinical observation over the 6 week study period revealed statistically significant clinical improvements in only the 0.2% and 0.4% cyclosporine groups by Day 42. While the improvement over 6 weeks was slightly more evident in the 0.4% group, this was felt to be due to the earlier rise in STT in this group (thus exposure to an increased precorneal tear film for a greater part of the 6 week test period). As therapy for chronic KCS is expected to be for the rest of the animal's life, the more gradual clinical response seen with the cyclosporine 0.2% ointment is medically acceptable.

The results of this study demonstrate that both 0.2% and 0.4% cyclosporine ophthalmic ointment are significantly more effective than the lower cyclosporine concentrations and placebo ointments at increasing tear production and improving clinical signs associated with chronic KCS in dogs. Considering the overall clinical improvement in the 0.2% and 0.4% cyclosporine groups, and the dose response plateau in STT response at the 0.2% cyclosporine concentration, a 1/4 inch ribbon of 0.2% cyclosporine ophthalmic ointment applied to the eye at 12 hour intervals is the optimal dose in treating chronic keratoconjunctivitis sicca.

l. Adverse Reactions: There were no safety concerns recognized in any treatment group.

m. Conclusions: A 1/4 inch ribbon of cyclosporine ophthalmic ointment at a concentration of 0.2% administered every 12 hours is effective in the treatment of chronic keratoconjunctivitis sicca.

2. Cyclosporine Ophthalmic Ointment (0.2%) United States Controlled Clinical Field Efficacy Trial in the Treatment of Chronic Idiopathic Keratoconjunctivitis Sicca: Study #1330C-61-V91-092

a. Objective: Dose confirmation study

b. Investigators:

Eleven (11) board certified veterinary ophthalmologists in 9 states served as principal investigators in this blinded placebo-controlled clinical field study.

INVESTIGATOR	**LOCATION**	**# OF CASES ANALYZED**
Dr. K.P. Barrie	Tampa, FL	13
Dr. J. Eichenbaum	Charlotte, NC	7
Dr. K.L. Abrams	Warwick, RI	15
Dr. A. Bachrach, Jr.	Lincoln, MA	24
Dr. D.R. Priehs	Sanford, FL	19
Dr. K. Ketring	Cincinnati, OH	5
Dr. D. Lindley	W. Lafayette, IN	5
Dr. R. Morgan	Knoxville, TN	10
Dr. J. Swanson	Houston, TX	4
Dr. R.J. Munger	Dallas, TX	7
Dr. C.S. Cook	San Mateo, CA	15
TOTAL		124

c. Animals: A total of 132 client owned animals of various breeds, ages, and sex were enrolled and 124 cases were analyzed in this study. Only those animals with chronic KCS that had a Schirmer Tear Test (STT) measurement of less than or equal to 10 mm/minute in one or both eyes were included. They also must have had conjunctivitis with or without keratitis in the affected eye(s).

d. Controls: One group of dogs received placebo ointment comprised of the formulation excipients without active ingredient.

e. Dosage Form: Cyclosporine ointment

f. Route of Administration: Ophthalmic

g. Doses Tested: 1/4 inch ribbon of 0.2% concentration ointment

h. Frequency of Treatment: Every 12 hours

i. Study Design: Cases were enrolled upon satisfying the study entrance qualification criteria on Day 0. Therapy was initiated on Day 0 and continued for 12 weeks. The response to therapy with the test article was assessed by ophthalmic exams (Day 7, 21, 42 and 84) at which time the clinical appearance of the conjunctival, corneal, and internal ocular structures were scored, and Schirmer Tear Test (STT) values were determined. After completion of the 84 day treatment period, therapy was withheld for up to 6 weeks depending on the clinical response of the animal. If the animal's eyes

met the criteria for a worsened condition, then therapy was re-instituted at that time.

The retreatment phase lasted up to 4 weeks with exams scheduled for 7, 14 and 28 days following re-institution of treatment to evaluate the animal's response to re-institution of therapy.

j. Results:

(1) Assessment of initial 84 days of therapy:

The response to therapy with the test article was assessed by ophthalmic examinations (Days 7, 21, 42 and 84 post-treatment initiation) at which time the clinical appearance of the conjunctiva, cornea and internal ocular structures were numerically scored, and Schirmer Tear Test (STT) values were determined.

The lacrimomimetic effect of 0.2% cyclosporine ointment was clearly evident in this study. Statistical evaluation of the differences between treatment groups on each examination day was performed using the mixed model analysis of variance/covariance methodology. Regardless of which test eyes are considered, the treatment groups differed in mean STT response in favor of cyclosporine therapy.

The increase in STT was associated with improvement in clinical signs of KCS. Blepharitis, blepharospasm and "other signs of ocular discomfort" (e.g. pawing at eyes) were markedly reduced. Improvement in conjuctival health as manifested by reduced conjunctival hypertrophy, reduced hyperemia, reduced conjunctival discharge volume, and improved character of discharge was clearly evident. Improvement in corneal health as manifested by improved corneal surface contour, reduced corneal edema and corneal neovascularization was also noted.

An overall investigator assessment on Day 84 showed overall improvement (vast or some improvement) in 81% of left eyes (versus 46% for placebo vehicle) and 81% of right eyes (versus 48% for placebo vehicle). A 1/4 inch ribbon of cyclosporine ophthalmic ointment at a concentration of 0.2% administered every 12 hours significantly improves tear production and is effective in the treatment of chronic keratoconjunctivitis sicca.

(2) Assessment of Treatment Withdrawal:

For the test eyes demonstrating an improvement on either the placebo or test article by Day 84, treatment was withheld after this point until the eye(s) began to regress clinically. Referencing the clinical baseline established by Day 84, the investigator assessed the clinical regression without therapy. In all but 1 cyclosporine test eye, clinical regression occurred when treatment was stopped. This overall assessment clearly demonstrated in both groups that withdrawal of therapy resulted in a worsening of the clinical status of the test eye(s).

(3) Assessment of Retreatment Response:

Once the test eye(s) in the treatment withdrawal phase exhibited signs of clinical regression, treatment was re-instituted and clinical progress was monitored. This third phase of the study was designed to show that after a hiatus of no therapy, if treatment was re-instituted, dogs treated with the test article would again begin to improve clinically. All but two cyclosporine treated dogs improved once treatment was re-instituted.

k. Adverse Reactions: There were 20 reported adverse reactions of the cases enrolled: 13 of these were in cyclosporine treated dogs and 7 were in placebo treated dogs. The incidence rate of adverse reaction reports in the cyclosporine group was 12.9% (13 of 101), while the incidence rate in the placebo group was 22.6% (7 of 31). The descriptions of the apparent reactions indicate that most were mild to moderate local inflammatory reactions involving the conjunctiva and periocular structures. Some cases exhibited transient increases in conjunctival discharge, hyperemia, periocular alopecia, and associated signs of local discomfort. Only one of the adverse reactions reported in the cyclosporine treated dogs was deemed to be drug related by the investigator.

l. Conclusions: The results of this controlled, and blinded clinical trial confirmed the efficacy and safety of 0.2% cyclosporine ophthalmic ointment in treating chronic keratoconjunctivitis sicca (KCS) in dogs. This study has also shown that in KCS, continual therapy is essential for maintaining any beneficial effects achieved and that there was no evidence the drug became less effective with time or after a period of drug withdrawal.

3. Cyclosporine Ophthalmic Ointment Formulations Bridging Study: Study #1330C-61-V93-141

a. Objective: Clinical field study which was designed to demonstrate that the 0.2% cyclosporine ointment formulation (without the preservative, chlorobutanol) intended for commercial use is comparable in clinical efficacy and field safety to the formulation (with the preservative, chlorobutanol) used in the clinical/safety studies.

This minor change in formulation was made as a result of Antimicrobial Preservative Effectiveness (USP, BP) testing which demonstrated that the product inhibited growth of a microbial challenge equally well, with or without the preservative. Because the studies demonstrated that the ointment is bacteriostatic, no preservative is needed in this product.

b. Investigators:

Three (3) board certified veterinary ophthalmologists served as principal investigators in this open (unblinded) clinical field trial.

INVESTIGATOR	**LOCATION**	**# OF CASES ANALYZED**
Dr. K.P. Barrie	Tampa, FL	8
Dr. A. Bachrach, Jr.	Lincoln, MA	7
Dr. D.R. Priehs	Sanford, FL	8
TOTAL		23

c. Animals: A total of 23 client owned animals of various breeds, ages, and sex, participating in the studies as described earlier, were included in the data analysis. The dogs with KCS eligible for inclusion in this study were responsive to the 0.2% cyclosporine formulation containing chlorobutanol and had been receiving it for a minimum of 3 weeks.

d. Controls: No controls were used.

e. Dosage Form: Cyclosporine ointment

f. Route of Administration: Ophthalmic

g. Doses Tested: 1/4 inch ribbon of 0.2%, concentration ointment without the preservative, chlorobutanol

h. Duration/Frequency of Treatment: Every 12 hours for 12 weeks

i. Study Design: Clients were asked to change treatment of their dog from the original preserved ointment at Day 0 of this study to the new unpreserved ointment formulation. Following the initial Day 0 evaluation, the response to therapy with the test article was assessed by ophthalmic exams (Days 42 and 84) at which time the clinical appearance of the conjunctiva, cornea, and Schirmer Tear Test (STT) values were determined.

j. Results: The following table contains a summary of the mean STT results (in mm/min) of the left and right eye comparing Day 0, DAY 42, and Day 84:

Day	**Left eye**	**Right eye**
0	13.7	12.7
42	14.4	12.8
84	15.9	15.8

The slight increase in the STT values in each eye throughout the course of the study is not statistically significant.

k. Adverse reactions: Three adverse reactions were reported. The reactions were local inflammatory changes involving the ocular and periocular structures of the eye. Investigators felt the reaction to be drug related in two of the three cases. Since these observations are consistent with the clinical

signs associated with KCS, they can be viewed as poor therapeutic responses or a lack of product efficacy.

Accordingly, it is difficult to determine an association of obviously drug-related adverse reactions with the ophthalmic administration of cyclosporine ophthalmic ointment. This is supported by the target animal safety study in beagle dogs (Batelle laboratories) in which no significant gross ocular abnormalities were reported.

l. Conclusions: The fact that there is no significant change in the STT measurement from Day 0 to Day 84 is indicative that this change in formulation (i.e., removing the chlorobutanol) does not alter its safety or efficacy profile. This study demonstrates that the minor modification in formulation made to the 0.2% cyclosporine ophthalmic ointment does not alter its safety or efficacy profile.

B. CORROBORATIVE STUDY

1. Cyclosporine Ophthalmic Ointment (0.2%) United States Open Clinical Field Efficacy Trial in the Treatment of Chronic Idiopathic Keratoconjunctivitis Sicca: Study #1330C-61-V92-110:

   a. Objective: Clinical field study to confirm the efficacy and safety of cyclosporine ophthalmic ointment under field conditions.

   b. Investigators: Twelve licensed veterinarians, with or without specialty training in ophthalmology, in eight states served as principal investigators in this open (unblinded) clinical field study.

INVESTIGATOR	**LOCATION**	**# OF CASES ANALYZED**
Dr. E. L. Kuhns	Wyoming, MI	12
Dr. H. J. Schadler	Columbus, OH	11
Dr. S. A. Gardner	Albany, CA	5
Dr. A. D. Kay	Oakland, CA	2
Dr. A. G. Shriro	Berkeley, CA	2
Dr. C. O. Bright	Columbus, SC	5
Dr. J. M. Empel	Atlanta, GA	3
Dr. R. B. Garrett	Roswell, GA	4
Dr. D. E. Harling	Greensboro, NC	8
Dr. V. Pentlarge	Athens, GA	14
Dr. D. F. Thompson	Asheville, NC	5
Dr. W. H. Van Hooser	Montgomery, AL	9
TOTAL		80

   c. Animals: A total of 80 client owned animals of various breeds, ages, and sex were included in the data analysis. Only those animals with chronic KCS that

had a Schirmer Tear Test (STT) measurement of less than or equal to 10 mm/minute in one or both eyes were included. They also must have had conjunctivitis with or without keratitis in the affected eye(s).

d. Controls: No control group was included in the study.

e. Dosage Form: Cyclosporine ointment

f. Route of Administration: Ophthalmic

g. Doses Tested: 1/4 inch ribbon of 0.2% concentration ointment

h. Duration/Frequency of Treatment: Every 12 hours for 12 weeks

i. Study Design: Cases were enrolled upon satisfying the study entrance qualification criteria on Day 0. Therapy was initiated on Day 0 and lasted for 12 weeks. The response to therapy with the test article was assessed by ophthalmic exams (Day 7, 21, 42 and 84) at which time the clinical appearance was numerically scored, and Schirmer Tear Test (STT) values were determined.

j. Results: The STT and associated improvement in conjunctival and corneal health were the pivotal parameters in the selection of optimal dose.

The results indicated that 84 days of 0.2% cyclosporine therapy was effective in treating chronic KCS in dogs, which was demonstrated through significant improvements or alleviation of clinical signs by Day 84 of therapy. Because of low incidence of epiphora and third eyelid gland prolapse on Day 0, Day 84 responses in these clinical parameters were not clearly apparent. Even so, numerical decreases in both of these conditions occurred throughout the course of therapy. Lid masses were few initially and static throughout the study.

Schirmer Tear Test values were highly statistically significantly improved with increases in STT values (in mm/min) of 8.4 (left eye) and 9.1 (right eye) by Day 84 of the study.

All conjunctival parameters were highly statistically significantly improved by Day 84 of cyclosporine therapy. Corneal parameters of edema, surface contour, vascularization and pigmented opacity were also highly significantly improved by cyclosporine treatment (left eye and right eye). Corneal ulceration was observed rarely in the study and, therefore, was insufficiently frequent to demonstrate a therapeutic response.

The investigators' overall assessment of therapeutic response after 84 days of cyclosporine is consistent with the improvements seen in the clinical parameters measured in this study. Eighty-eight percent (left eye) and 94% (right eye) of the treated eyes showed improvement by Day 84 of treatment. Client assessments indicated little change in tolerability and general attitude over the course of therapy.

k. Adverse Reactions: Only one adverse reaction was deemed by the investigator to be drug related. In this case, the irritation was not noted when a new tube of ointment was started.

l. Conclusions: The results of this trial indicate that 0.2% cyclosporine ophthalmic ointment is effective and safe under field conditions in treating chronic KCS.

V. ANIMAL SAFETY:

A. PIVOTAL STUDY

1. SCH 36547: Twenty-Six Week Safety Study of Cyclosporin A Ophthalmic Ointment Administered Epicorneally (Topically) to Dogs. (Schering-Plough Study #92501[1]) Battelle Laboratories, Columbus, Ohio.

   a. Type: A blinded chronic (26 week) laboratory safety study during which cyclosporine ophthalmic ointment was administered twice daily at 0, 1X, and 10X the daily use concentration of 0.2%.

   b. Animals: Twenty-four young adult Beagle dogs (12 male, 12 female)

   c. Controls: One group of 8 dogs received placebo ointment comprised of the formulation excipients without active ingredient.

   d. Dosage Form: Cyclosporine ointment

   e. Route of administration: Ophthalmic

   f. Dosage and Frequency of Treatment: The dogs were randomly divided into three test groups and were dosed as follows:

Test Group	**Description of Test Article**	**Number /Sex**	**Details of Dosing**
Control	0% ophthalmic ointment (placebo vehicle)	4M, 4F	1/4 inch ribbon BID, 7 days/week, 26 consecutive weeks, applied onto cornea or into lower conjunctival sac of each eye
1X	0.2% cyclosporine ophthalmic ointment	4M, 4F	1/4 inch ribbon BID, 7 days/week, 26 consecutive weeks, applied onto cornea or into lower conjunctival sac of each eye
10X	2% cyclosporine ophthalmic ointment	4M, 4F	1/4 inch ribbon BID, 7 days/week, 26 consecutive weeks, applied onto cornea or into lower conjunctival sac of each eye

[1] This pivotal study was conducted in compliance with the Food and Drug Administration's Good Laboratory Practice Regulations (21 CFR 58).

g. Evaluation: The following parameters were used to assess toxicity:

Parameter	**Timing**
Food Consumption	Daily
Body Weights	Predosing and at Monthly Intervals
Clinical Observations	Twice Daily
Physical Examinations	Every Monday, Wednesday, Friday
ECG	Predosing and at Monthly Intervals
Clinical Pathology (hematology, clinical chemistry, urinalysis)	Predosing and at Monthly Intervals
Ophthalmic Examinations	Predosing and at Monthly Intervals
Immunological Response to Vaccination	CDV titer - prevaccination and at 2, 8, 20 weeks post-vaccination RV titer - prevaccination and at 2, 12 weeks post-vaccination
Gross Pathology/Histopathology	After 26 weeks of dosing

h. Results:

Administration of cyclosporine ophthalmic ointment had no effect on food consumption, body weight, body temperature, heart rate, respiration rate, or ECG. There were no abnormalities noted in regards to the general ocular assessment, conjunctival, corneal and internal ocular structure assessments, and intraocular pressure measurement.

Epiphora was exhibited by dogs in both placebo control and cyclosporine test groups of both sexes. The dogs did not exhibit any signs of ocular discomfort, i.e., ocular swelling, squinting, blepharospasm, rubbing of the eyes, or sensitivity to touch. Ophthalmic examination did not reveal any sign of inflammation. The incidence of epiphora was greater for the cyclosporine 0.2% and 2% test groups compared to the placebo controls. There was no apparent change in the incidence of epiphora when the male 0.2% group was compared to the male 2% group. However, for the female dogs, the incidence was generally greater for the 2% group than the 0.2% group.

Hematology, clinical chemistry, and urinalysis group mean data for the 0.2% and 2% cyclosporine test groups were similar to placebo control group values for both sexes and at all time periods. There were no trends in the data to suggest a cyclosporine effect.

i. Immunological Response Evaluation:

Parenteral and oral forms of cyclosporine are used to immunosuppress humans receiving organ transplants. Potential for immunosuppression via topical application in dogs was addressed. Immunological responsiveness of

dogs was evaluated by measuring antibody titers to specific antigens. The antigens, canine distemper virus (CDV) and rabies virus (RV), were used to assess the dogs' ability to elicit an immunological response.

(1) Canine Distemper Virus Antibody (CDVAb):

The CDVAb test involved collecting baseline serum specimens from all study dogs 30 days after initiation of dosing, after which all study dogs were vaccinated with a commercial modified live virus (MLV) CDV vaccine. At 2, 8 and 20 weeks after vaccination (which corresponded to 6, 12, and 24 weeks after initiation of dosing), a single serum sample per dog per collection period was collected for determination of CDVAb titer.

Long term ophthalmic administration of 0.2% and 2% cyclosporine ophthalmic ointment had no effect on antibody titer responses to canine distemper virus and no gender differences were noted. In addition, there was no evidence of MLV vaccine reversion to virulence which further supports the conclusion that the dogs' immune responses to vaccinations were not compromised by cyclosporine treatment.

(2) Rabies Virus Antibody (RVAb):

The RVAb test involved collecting baseline serum specimens from all study dogs at 12 weeks after initiation of dosing, after which all study dogs were vaccinated with a commercial rabies vaccine. At 2 and 12 weeks after vaccination (which corresponds to 14 and 24 weeks after initiation of dosing), a serum sample was collected from each dog. All RVAb titer assays were conducted in the Rapid Fluorescent Focus Inhibition Test (RFFIT) laboratory at the Department of Veterinary Diagnostic Investigation (VDI), College of Veterinary Medicine, Kansas State University.

Antibody titers after rabies virus vaccinations for the 0.2% and 2% cyclosporine test groups were similar to placebo control titers for both sexes. There was a statistically significant increase in antibody titer responses following vaccination in all test groups. This is indicative of a normal humoral immune response to an antigen following vaccination. Cyclosporine administration had no effect on the immune responses to RV and no gender differences were noted.

j. Gross Pathology:

At the end of the 26 weeks, a necropsy was performed on all study dogs under the direct supervision of a veterinary pathologist.

There were no significant lesions seen in any dogs. The few isolated findings were considered to be incidental in nature since they lacked any specificity or dose-related trends suggestive of cyclosporine-related effects and are findings commonly observed as background in laboratory dogs.

k. Histopathology:

Four slides containing (1) left upper palpebral conjunctiva, (2) left lower palpebral conjunctiva, (3) right upper palpebral conjunctiva, (4) right lower

palpebral conjunctiva, (5) full length left third eyelid and (6) full length right third eyelid were prepared for subsequent microscopic examination. Besides the externa adnexal structures, slides of the left and right eyes sectioned in a dorsal-ventral direction on either side of the optic nerve, left and right lacrimal glands, and the left and right orbital glands were prepared. Additional slides contained lymph nodes, spleen, kidneys, liver and all gross lesions. All of the tissues and gross lesions processed to slides were examined by light microscopy.

No significant treatment related findings were noted.

l. Adverse Reactions: No observable adverse effects were induced by 0.2% or 2% cyclosporine ophthalmic ointment when administered twice daily for 6 months.

m. Conclusions: Cyclosporine ophthalmic ointment, administered to male and female Beagle dogs epicorneally (topically) twice daily at doses of 0.2% and 2%, showed a wide margin of safety. No apparent toxicity or adverse reactions were observed in the treated or control groups. The epiphora noted in all dose groups was not associated with any inflammatory change, nor was there any correlation to gross and histopathology changes.

VI. Human Safety:

A. Human Safety Relative to Food Consumption:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This product is labeled as a prescription drug for use only in dogs, which are non-food animals.

B. Human Safety Relative to Possession, Handling, and Administration:

There is a bolded statement on the front panel of all labeling components "Keep out of reach of children," except for the product information sheet (package insert) which contains the bolded statement "Keep this and all drugs out of the reach of children."

VII. Agency Conclusions:

The data submitted in support of this original NADA satisfy the requirements of Section 512 of the Act and 21 CFR 514.111 of the regulations. The data demonstrate that OPTIMMUNE® Ophthalmic Ointment (0.2% cyclosporine USP), when used under the labeled conditions of use, is safe and effective.

OPTIMMUNE® Ophthalmic Ointment is restricted to use by or on the order of a licensed veterinarian because professional expertise, specifically knowledge of veterinary ophthalmology and a correct diagnosis of keratoconjunctivitis sicca, are needed for safe use and treatment success. A veterinarian is required to monitor the results of treatment and determine the importance of adverse reactions. Therefore, the drug is a prescription product.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for 5 years of marketing exclusivity beginning on the date of approval because no active ingredient has been approved in any other application.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.