ANTIROBE AQUADROPS Liquid
(clindamycin hydrochloride)
Supplement to NADA 135-940

For Treatment of Feline Infected Wounds, Abscesses and Dental Infections

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I. GENERAL INFORMATION

NADA Number: 135-940

Sponsor: Pharmacia and Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001

Generic Name: Clindamycin hydrochloride oral liquid

Trade Name: ANTIROBE AQUADROPS Liquid

Marketing Status: This is a prescription product and will include the caution statement as follows: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Supplement Effect: This supplement provides for the use of clindamycin HCl (ANTIROBE AQUADROPS Liquid) in cats for new indications.

II. INDICATIONS FOR USE

ANTIROBE AQUADROPS Liquid (clindamycin hydrochloride) is for use in cats for the following indications:

- **Aerobic Bacteria:** ANTIROBE AQUADROPS Liquid is indicated for the treatment of soft tissue infections (wounds and abscesses) and dental infections caused by susceptible strains of *Staphylococcus aureus, Staphylococcus intermedius* and *Streptococcus* spp.

- **Anaerobic Bacteria:** ANTIROBE AQUADROPS Liquid is indicated for the treatment of soft tissue infections (deep wounds and abscesses) and dental infections caused by susceptible strains of *Bacteroides fragilis* and *Clostridium perfringens.*

III. PRODUCT INFORMATION

A. Dosage Form: ANTIROBE AQUADROPS Liquid (brand of clindamycin hydrochloride liquid) is available as 20 mL filled in 30 mL bottles (25 mg/mL) supplied in packers containing 12 cartoned bottles and calibrated dosing droppers.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

B. Route of Administration: ANTIROBE AQUADROPS Liquid is to be orally administered to cats.

C. Recommended Dosage: ANTIROBE AQUADROPS Liquid is to be orally administered to cats at the dosage range of 5.0 to 10.0 mg/lb body weight once every 24 hours depending on the severity of the condition.

Duration: Treatment with ANTIROBE AQUADROPS Liquid may be continued up to a maximum of 14 days if clinical judgment indicates. Treatment of acute infections

should not be continued for more than three to four days if no clinical response to therapy is seen.

Dosage Schedule: ANTIROBE AQUADROPS Liquid, to provide 5.0 mg/lb, administer 1 mL/5 lb body weight once every 24 hours; to provide 10.0 mg/lb, administer 2 mL/5 lb body weight once every 24 hours.

IV. EFFECTIVENESS

Pivotal Studies (4): Four separate studies (3 efficacy studies and 1 pharmacokinetic study) were conducted which demonstrate that clindamycin hydrochloride is an effective antibacterial therapy for feline infected wounds/abscesses and dental infections as follows:

- For the treatment of soft tissue infections (wounds and abscesses) and dental infections caused by susceptible strains of *Staphylococcus aureus, Staphylococcus intermedius* and *Streptococcus* spp.

- For the treatment of soft tissue infections (deep wounds and abscesses) and dental infections caused by susceptible strains of *Bacteroides fragilis* and *Clostridium perfringens.*

- The following clinical data support the effectiveness of 5.0 to 10.0 mg of clindamycin/lb BW orally administered once every 24 hours as antibacterial therapy for feline infected wounds/abscesses and dental infections.

A. Pivotal Dose Determination Study - Infected Wounds and Abscesses (US Study)

1. Type of Study: This well-controlled pivotal dose determination study was conducted using an established model for inducing infected wounds and abscesses in cats by subcutaneous inoculation of a mixture of *Staphylococcus aureus, Bacteroides fragilis*, and *Clostridium perfringens.* This study was conducted according to Guidelines for Good Clinical Practices.

2. Investigator: John N. Berg, DVM, PhD, Professor, Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri, Columbia, MO 65211.

3. General Design

a. Purpose of Study: The purpose of the study was to determine a clindamycin dosage regimen that is efficacious for therapy of feline infected wounds and abscesses.

b. Test Animals: Forty-one (41) closed-colony bred adult short-haired domestic cats of both sexes were utilized for the study. Prior to administration of treatments, the cats were randomly divided into four treatment groups (1, 2, 3, 4) in four replicates as described in Table 4.1.

Table 4.1 Treatment groups evaluated. All treatments were administered once orally at 24 hour intervals for 10 days.

Study Group	1		2		3		4	
Dosage	2 mL Sterile Percent (Placebo)		2.5 mg Clindamycin/lb BW*		5.0 mg Clindamycin/lb BW		10.0 mg Clindamycin/lb BW	
Sex (M,F)	M	F	M	F	M	F	M	F
No. of Test Cats	5	5	6	4	6	5	6	4

*BW=Body weight.

c. Controls: A placebo (sterile water) control group was included in the study.

d. Diagnosis: To induce infected wounds and abscesses, the cats were challenged by subcutaneous inoculations of a mixture of *Staphylococcus aureus, Bacteroides fragilis* and *Clostridium perfringens* at two sites; the lateral cervical and thoracic wall. Treatments were administered one day after inoculation of the cats. The study veterinarian monitored each cat once daily for general clinical appearance, appetite, weight, rectal temperature and the clinical appearance of the lesion sites.

e. Dosage Form: Each mL of the clindamycin hydrochloride liquid contained clindamycin hydrochloride equivalent to 25 mg clindamycin.

f. Route of Administration: Orally.

g. Doses: Two mL sterile water (placebo), 2.5, 5.0 and 10.0 mg clindamycin/lb body weight at 24 hour intervals for 10 consecutive days.

h. Pertinent Parameters Measured: The variable of primary importance (identified prior to initiation of the study) for determining the effective dosage range of clindamycin was the bacterial culture results obtained by sampling the neck lesions 6 days post inoculation. The sum of the clinical evaluation scores from day 2 to day 10 post initial treatment was identified (prior to study initiation) as a secondary variable. The lesion sites and each cat's general appearance were scored daily by the study veterinarian using an established scoring system with 0 = normal to 4 = most severe for lesions and 0 = normal to 3 = depressed for clinical appearance. The veterinarians evaluating the clinical response were not aware of which treatments the cats were administered.

4. Post-Treatment Microbiology: The neck sites were used for bacterial culturing procedures (samples taken on days 3, 6 and 10 post initial treatment) while the thoracic sites were left undisturbed and scored during

the clinical evaluation. Samples from both neck and thoracic lesions were cultured for the presence of aerobic and anaerobic bacteria at necropsy (day 14 post initial treatment). Clindamycin Minimum Inhibitory Concentrations (MICs) for the *Staphylococcus aureus, Bacteroides fragilis* and *Clostridium perfringens* isolates obtained from culturing the lesions post-treatment were all within one dilution of the isolates used in the challenge inoculum. This indicates no change in the susceptibility pattern of these bacteria due to the use of clindamycin.

5. Statistical Analysis: The statistical analysis used to determine an effective dosage regimen(s) for clindamycin oral solution was based on the culture results at day 6 post initial treatment. Differences among the least squares treatment means were tested for significance (< or = 0.05) using LSDs after testing for overall treatment effect.

6. Results: The least squares means of day 6 culture results are presented in Table 4.2. Significant differences at < or = 0.05 among means are indicated by differing superscripts.

Table 4.2 Least squares means of day 6 culture results. All treatments administered once orally every 24 hours for 10 consecutive days

	Treatments			
Study Group	1	2	3	4
Dosage	2 mL Sterile Water/Cat (Placebo)	2.5 mg Clindamycin/lb BW	5.0 mg Clindamycin/lb BW	10.0 mg Clindamycin/lb BW
*Culture results 6 days post treatment (least squares means)	16.49[a]	13.07[a]	6.79[b]	7.93[b]

*Means of the sum of scores based on numbers of pathogens isolated.

7. Decision Criteria: The dosage regimens of both 5.0 or 10.0 mg clindamycin hydrochloride (oral solution)/lb body weight administered once every 24 hours for 10 consecutive days were determined to be effective as therapy for induced feline infected wounds and abscesses. If more than one dosage regimen was determined to be effective, then the lowest effective dosage regimen would be evaluated further in a pivotal dose confirmation study with naturally occurring feline infected wounds and abscesses.

8. Conclusions: The dosage regimens of both 5.0 or 10.0 mg of clindamycin hydrochloride (oral solution) per pound body weight administered once daily for 10 days were determined to be effective as therapy for induced feline infected wounds and abscesses. Following the decision criteria, the lowest effective dosage regimen (5.0 mg clindamycin) was evaluated further during

a pivotal well-controlled clinical trial as antibiotic therapy for naturally occurring feline infected wounds and abscesses.

B. Pivotal Multilocation Dose Confirmation Clinical Study - Infected Wounds and Abscesses (US Study)

1. Type of Study: Pivotal well-controlled clinical field study to evaluate efficacy of clindamycin as therapy for naturally occurring feline infected wounds and abscesses. This study was conducted according to Guidelines for Good Clinical Practices.
2. Investigators

Dr. Kathleen M. Ivie
Ailurophile Cat Clinic
432 N. Homer Street
Lansing, MI 48912

Dr. John L. Augustine
Midland Animal Clinic
14210 Midland Road
Poway, CA 92064

Dr. Tim Howell
9512 Haverway
Indianapolis, IN 46240

Dr. Bernard R. Hecht
104 Gilcrease Museum Road
Tulsa, OK 74127

Dr. Jane E. Brunt
6701 York Road
Baltimore, MD 21212

Dr. Jan Bellows
9111 Taft Street
Pembroke Pines, FL 33024

Dr. Susan K. McDonough
226 S. 20th Street
Philadelphia, PA 19103

Dr. Robert W. Cannon
4314 Main
Kansas City, MO 64111

Dr. Tammy P. Sadek
Kentwood Cat Clinic
4443 A Breton Road, SE
Kentwood, MI 49508

Dr. Francis W. Gross
Nob Hill Cat Clinic
1540 California Street
San Francisco, CA 94109

Dr. Gary Johnson
Dr. Mary A. Crawford
481 Kinderkamack Road
Oradell, NJ 07649

3. General Design

a. Purpose of Study: The primary objective of this study was to evaluate the efficacy of a dosage regimem of 5.0 mg of clindamycin/lb of body weight administered orally once daily for at least seven consecutive days as therapy for feline infected wounds and abscesses compared to similarly treated amoxicillin controls.

b. Test Animals: One hundred ten (110) privately-owned domestic cats of either sex, any age or breed that had an infected wound or abscess were enrolled in the study. Cats with chronic diseases, gestating females and cats with known allergy to clindamycin or amoxicillin were

excluded. The cats were enrolled at 11 small animal practice sites and were distributed among the treatment groups as follows in Table 4.3.

Table 4.3 Cats/treatment groups - treatments were administered for at least 7 consecutive days

Study Group (Dosage; Oral)	Clindamycin hydrochloride (5.0 mg/lb BW)		Amoxicillin trihydrate (5.0 mg/lb BW)		
Sex (M, F)	M	F	M	F	NI*
No. of Test Cats	41	16	36	15	2

*NI=Sex not indicated.

c. Controls: Control animals received amoxicillin trihydrate oral suspension which is an FDA-approved drug for the treatment of feline infected wounds and abscesses.

d. Diagnosis: The study veterinarians (who conducted the study) diagnosed infected wounds and abscesses based on the clinical signs of observable lesions, exudate, swelling and rectal temperatures. Treatments were administered by the drug administrators (associate veterinarians, veterinary technicians) if the cats met the enrollment criteria for the study. Seventy-seven percent (77%) of the lesions in the clindamycin treated group were acute while 75% of the lesions were classified as acute in the amoxicillin treated group. Twenty-five percent (25%) of the lesions were classified as chronic in each treatment group. Pretherapy samples from the lesions of enrolled cats were cultured for the presence of aerobic bacteria. Hair clipping, cleansing of area with nonantibacterial soap or shampoo, lancing, debridement, irrigation with nonantiseptic, suturing, parenteral fluids and anesthetics were permitted during preparation of the lesion sites. The lesions could not be covered by a cast or bandage and no concurrent antibacterial therapy, antiseptics, anti-inflammatories, antihistamines or topical antiseptics could be used.

e. Dosage Forms: Each mL of clindamycin hydrochloride liquid contained clindamycin hydrochloride equivalent to 25 mg clindamycin.

Each 30 mL vial of amoxicillin trihydrate sterile powder was reconstituted with 23 mL of sterile water with each milliliter of the resulting suspension containing 50 mg of amoxicillin.

f. Route of Administration: All treatments were administered orally using calibrated dosing droppers.

g. Doses: The enrolled cats were randomly assigned to receive at least 7 consecutive treatments at 24 hour intervals of either clindamycin (5 mg/lb body weight) or amoxicillin (5 mg/lb body weight).

h. Test Duration: The maximum combined treatment and observation period was 20 days.

i. Pertinent Parameters Measured: The primary parameter used to determine the effectiveness of clindamycin hydrochloride was the overall therapeutic response evaluated 8 days post-treatment. For each enrolled cat, the clinical evaluators used the daily evaluation of lesion size, lesion granulation/scab formation, lesion exudate and rectal temperature for determining treatment response. The veterinarians evaluating the clinical response were not aware of which treatment the cats were administered.

4. Results: The study veterinarians determined if the treatment regimen resulted in a "cure" or "failure" 8 days post-treatment based on the daily evaluation of lesion size, lesion granulation/scab formation lesion and rectal temperatures. The calculated cure rates are illustrated in Table 4.4.

Table 4.4 Cure rates/treatment regime administered

Clinical Evaluation on Eighth Day Post treatment	Clindamycin hydrochloride Regime* % (n)	Amoxicillin trihydrate Regime** % (n)
"Cured" (Excellent or Good evaluation)	89.5 (51/57)	83.0 (44/53)
"Not Cured" (Fair or Poor evaluation)	10.5 (6/57)	17.0 (9/53)

*Each cat was administered clindamycin hydrochloride orally once daily to provide approximately 5 mg clindamycin/lb of body weight.
**Each cat was administered amoxicillin trihydrate oral suspension once daily to provide approximately 5 mg amoxicillin/lb of body weight.

No relapses (reoccurrence of the initial condition treated within the 20-day treatment and observation period) were observed for the clindamycin or amoxicillin treatment regimens. One cat administered amoxicillin vomited on days 6, 7 and 8 of therapy and was listed as an adverse reaction by the study veterinarian. It is not unusual for a cat to vomit during administration of oral therapy.

Microbiology Results: Prior to administration of therapy, samples from the infected lesions of the cats were cultured for the presence of aerobic bacteria. Table 4.5 presents the pretherapy bacterial susceptibility data and response to treatment regimens.

Table 4.5 Response* to therapy and aerobic bacteria susceptibility to clindamycin and amoxicillin following isolation of coagulase positive and coagulase negative staphylococci, streptococci, pasteurella and a mixture of aerobic and anaerobic bacteria from infected cat wounds and abscesses

Bacteria Isolated from Lesion Samples	Susceptibility to Clindamycin		Response to Clindamycin		Susceptibility to Amoxicillin		Response to Amoxicillin Therapy (Cases)	
	S n (%)	R n (%)	Cure n (%)	Not Cured n (%)	S n (%)	R n (%)	Cure n (%)	Not Cured n (%)
Coagulase positive staphylococci (20 cats)	18 (90)	2 (10)	10 (100)	None	11 (55)	9 (45)	9 (90)	1 (10)
Coagulase negative staphylococci (17 cats)	9 (64)	5 (36)	8 (80)	2 (20)	9 (64)	5 (36)	7 (100)	None
Streptococcus spp. (31 cats)	21 (72)	8 (28)	15 (88)	2 (12)	29 (100)	None	10 (71)	4 (29)
Pasteurella spp. (41 cats)	1 (3)	32 (97)	21 (100)	None	39 (98)	1 (2)	16 (80)	4 (20)
Aerobic bacteria plus anaerobic bacteria (29 cats)	6 (25)	18 (75)	13 (93)	1 (7)	19 (68)	9 (32)	14 (93)	1 (7)

* Due to polymicrobial etiology, some cases are reported more than once.
** Susceptibility for aerobes only, Kirby-Bauer procedure.

5. Statistical Analysis: The primary parameter used to determine the effectiveness of clindamycin was the overall therapeutic response, evaluated 8 days post-treatment. Percent cure for each treatment group for each investigator was calculated and these percents were used as the basis for the statistical analysis. The mean cure rate for animals treated with clindamycin was numerically superior than that of animals treated with amoxicillin. Hence the decision criterion for efficacy, that is, that the cure rate for animals treated with clindamycin not be significantly less than that of the animals treated with amoxicillin, was met. The difference between the mean cure rate for animals treated with clindamycin and that of animals treated with amoxicillin was tested for significance at 0.05 (one-sided). The results are summarized in Table 4.6.

Table 4.6 Analysis of variance table of cure rates for cats orally administered a treatment regimen of approximately 5 mg of clindamycin/lb body weight once daily or a treatment regimen of approximately 5 mg of amoxicillin/lb body weight once daily

Source	df	Mean Square	F	P-Value
Location	10	373.84		
Treatment	1	315.66	1.94	0.19
Error	10	162.32		

The significance level of the overall test of the treatment effect indicates that the cure rates of the two treatments did not differ significantly when tested at < or = 0.05.

6. Conclusions: Under the conditions of this pivotal clinical study, 5 mg of clindamycin/lb body weight administered orally once daily for at least 7 days is effective therapy for feline infected wounds and abscesses. The mean cure rate for the cats treated with clindamycin was numerically superior to the cure rate for the amoxicillin treated cats; the difference was not statistically significant (< or =0.05). Clindamycin was effective therapy for feline infected wounds and abscesses caused by or associated with susceptible *Staphylococcus* spp., *Streptococcus* spp., and a mixture of aerobic and anaerobic bacteria.

C. Pivotal Multilocation Clinical Study - Dental Infections (UK Study)

1. Type of Study: Clinical field study to demonstrate and evaluate the efficacy of clindamycin hydrochloride as therapy for feline dental infections.

2. Investigators: Five of the six investigators contracted to conduct the study provided case report data.

Dr. P. A. Eves
Goddard Veterinary Group
740 Barking Road
London E13

Dr. A. K. Vinnicombe
Downland Veterinary Group
Stirling Lodge
2 Stirling Road
Chichester, W. Sussex

Dr. G. J. G. Shawcross
The Veterinary Hospital
College Road
Margate
Kent

Dr. R. M. R. Grose
Downland Veterinary Group
Park Vale Clinic
71 Havant Road
Emsworth, Hants

Dr. J. P. Sauvage
Brooksden
Cranbrook
Kent TN17 3DT

Dr. F. J. McKeating
The Hospital Hospital
Rye Street
Bishops Stortford
Herts CM23 2HA

3. General Design

a. Purpose of Study: The primary objective was to evaluate the efficacy of 2.5 mg of clindamycin/lb body weight administered twice daily (total daily dose of 5 mg/lb body weight) for 5 to 10 consecutive days (with dental treatment or dental cleaning - prophylaxis also performed five days after start of clindamycin therapy) compared to dental treatment (dental cleaning - prophylaxis) only as treatment for clinical cases of feline dental infections.

b. Test Animals: Twenty-nine (29) privately-owned domestic cats of either sex, any age or breed that had dental infections were enrolled in the study. The cats were successfully enrolled at five small animal practice sites and were distributed among the treatment groups as follows in Table 4.7.

Table 4.7 Cats/treatment groups - clindamycin was administered for 5 to 10 days

Diagnosis	Group 1 2.5 mg clindamycin/lb BW twice daily and dental treatment (n)	Group 2 Dental treatment only (n)	All
Periodontal disease	7	10	17
Gingivitis and gingival hyperplasia	3	0	3
Periodontal disease and ulceration	1	0	1
Periodontal disease and subgingival resorptive lesions	0	1	1
Not stated	5	2	7
TOTAL (cats)	16	13	29

c. Controls: Controls received dental treatment (scaling, polishing and tooth extraction) as treatment.

d. Diagnosis: The study veterinarians diagnosed the dental infections based on the clinical signs of infections observed during examination of the cats' gingiva, teeth and oral mucosa.

e. Dosage Form: Clindamycin hydrochloride in capsules.

f. Route of Administration: Clindamycin was administered orally.

g. Dose: Animals were randomly assigned to receive 2.5 mg clindamycin/lb body weight twice daily (total daily dose of 5 mg/lb body weight) for 5 to 10 days.

h. Test Duration: The maximum combined treatment and observation period was 12 days.

i. Pertinent Parameters Measured: Resolution of the dental infection was the primary parameter evaluated. The study veterinarians evaluated the response to therapy 12 days after initial treatments, taking the type of lesion into consideration.

4. Results: The study veterinarians evaluated the treatments according to the following criteria:

- Excellent (complete resolution of lesion)
- Good (nearly complete resolution of lesion)
- Fair (incomplete resolution of lesion)
- Poor (no response, therapy changed during or after 10 days course of clindamycin, if given)

The responses to the treatments are presented in Table 4.8.

Table 4.8 Evaluation/treatments administered – clindamycin was administered for 5 to 10 days

Diagnosis	Group 1 2.5 mg clindamycin/lb BW twice daily and dental treatment (n)	Group 2 Dental treatment only (n)
Excellent	5 16/16 (100%)	3 10/12 (83%)
Good	11	7
Fair	0	1
Poor	0	1
Died	0	1*
TOTAL (cats)	16	13

*Cat died from kidney failure four days after dental and so no assessment could be made.

The 16 cats which received clindamycin plus dental treatment all responded in a positive manner 100% while 10 of the 12 cats (83%) which received the dental treatment responded in a positive manner.

5. Conclusions: Under the conditions of this study, cats given dental treatment (scaling and cleaning) exhibited excellent or good clinical response when also administered a regimen of 2.5 mg of clindamycin/lb body weight twice daily for 5 to 10 days (started five days prior to the dental treatment). Clindamycin was well tolerated in the cats enrolled in the study.

6. Adverse Reactions: None observed during the study.

D. Pivotal Pharmacokinetic Study - Clindamycin Capsules vs. Clindamycin Liquid.

1. Type of Study: This GLP clinical laboratory pharmacokinetic study compared the plasma disposition of clindamycin equivalent activity after

administration of clindamycin hydrochloride aqueous solution and clindamycin hydrochloride in capsules.

2. Investigator: Study director, Dawn M. Boothe, Assistant Professor, College of Veterinary Medicine, Texas A&M University, College Station, Texas.

3. General Design:

   a. Purpose of Study: To compare the plasma disposition of clindamycin equivalent activity after administration of clindamycin hydrochloride aqueous solution or capsules in cats; 8 cats (2.5-5.5 kg body weight) were administered approximately 11 mg clindamycin equivalents/kg BW (5 mg/lb BW) orally as either capsules (25 mg clindamycin equivalents/capsule) or aqueous solution (25 mg clindamycin equivalents/mL) in a single dose, two-period, two-treatment crossover design.

   b. Test Animals: Domestic shorthair cats; males and females 1 to 3 years old and weighing 2.5 to 5.5 kg were utilized for the study. The cats were randomly assigned to one of two groups. Both groups received clindamycin hydrochloride aqueous solution and clindamycin hydrochloride capsules in a two-treatment, two-period crossover design, using the following treatment scheme illustrated in Table 4.9.

Table 4.9

Period	Group 1 (n=4)	Group 2 (n=4)
First (Phase I)	Solution (Treatment A)	Capsules (Treatment B)
Second (Phase II)	Capsules (Treatment B)	Solution (Treatment A)

One cat from each treatment group was studied on the same day; i.e., the study was conducted in pairs of cats simultaneously. Treatment A cats and Treatment B cats were randomly paired and studied on each of 4 days. A 14 to 17 day washout period elapsed between the 24 hour blood sampling of Phase I and the dose of Phase II.

   c. Controls: Not required for cross-over type study.

   d. Dosage Form(s):

   Clindamycin hydrochloride liquid 25 mg/ml (Treatment A).
   Clindamycin hydrochloride in capsules (Treatment B).

e. Route of Administration: The clindamycin hydrochloride test formulations were administered orally.

f. Dose: Animals were randomly assigned to receive 11 mg of clindamycin/kg BW (5.0 mg/lb BW) once during each of the 2 phases of the study.

g. Test Duration: Phase I had a 24 hour blood sampling period followed by a 14 day washout period before initiation of Phase II with a 24 hour blood sampling period. Blood samples were obtained before dosing 0 hr and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 hours after administration of the test drugs.

h. Pertinent Parameters Measured: Clindamycin plasma concentrations versus time data; areas under concentration time curves (AUC_{O-LOQ}) maximum plasma concentration (C_{max}) and time of maximum concentration (t_{max}).

4. Results: The results are presented in Table 4.10.

Table 4.10 Plasma Concentrations of Clindamycin Equivalent Activity After Clindamycin Hydrochloride Administered as Capsules.

C_{max}	<µg/mL > : 7.37 ± 1.73
t_{max}	< hours > : 0.5 - 1.5
AUC_{O-LOQ}	<µg/h/hr> : 42.6 ± 12.2
$t_{1/2}$	<hours > : 16.4 ± 15.4

Plasma Concentrations of Clindamycin Equivalent Activity After Clindamycin Hydrochloride Administered as Aqueous Solution.

C_{max}	<µg/mL > : 6.59 ± 2.20
t_{max}	< hours > : 0.5 - 1.5
AUC_{O-LOQ}	<µg/h/hr> : 35.1 ± 9.22
$t_{1/2}$	<hours > : 7.49 ± 1.71

5. Statistical Analysis: The pharmacokinetic values from the two dosage formulations were tabulated unadjusted for dose; all data are reported as mean +/- standard deviation. Area under the concentration-time curve (AUC_{O-LOQ}), maximum plasma concentration (C_{max}), and time of maximum concentration (t_{max}) were analyzed on an experimental unit basis using sums of squares analysis of variance procedures.

6. Conclusions: In cats, clindamycin hydrochloride administered either as aqueous solution or as capsules provides clindamycin equivalent activity greater than 0.2 mcg clindamycin equivalent activity/mL of plasma for 24 hours after oral administration of approximately 11 mg clindamycin equivalents/kg body weight (5 mg/lb BW). Maximum concentrations are achieved with the two formulations within 1.5 hours of administration.

There were no significant differences in C_{max}, t_{max}, or AUC between the two formulations. Based on these data, it was determined that cats administered clindamycin hydrochloride (either in capsules or solution) at once-a-day doses of 5 mg/lb body weight will have antibacterial concentrations of clindamycin in their plasma between dosing periods.

E. Overall Conclusions: Data from the pivotal dose finding, dose determination and clinical dental infection studies determined the dosage range of 5.0 to 10.0 mg of clindamycin/lb body weight (total daily dosage) orally administered to cats to be effective for feline infected wounds, abscesses and dental infections. Infected wounds, abscesses and dental infections may vary in degree of severity from moderate to severe. Therefore depending on the severity of these conditions, a clindamycin daily dosage range of 5.0 to 10.0 mg of clindamycin/lb body weight is indicated as follows:

F. Corroborative Studies (6): Five laboratory studies, three *in vitro* bacteria susceptibility studies and two *in vivo* pharmacokinetic studies are presented. One efficacy study concerning the use of clindamycin as therapy for feline dental infections is also provided.

The data from these studies support the clinical efficacy of 5.0 to 10.0 mg of clindamycin/lb body weight administered once orally every 24 hours (depending on the severity of the condition) as antibacterial therapy for feline infected wounds, abscesses and dental infections.

1. Laboratory Studies - Bacterial Susceptibility Data

   a. Susceptibility of anaerobic bacteria to clindamycin: Data outlined in a published review article determined when 99 isolates of obligate anaerobic bacteria (obtained from clinical material) were tested for susceptibility to clindamycin that regardless of the species of animal from which the isolates were obtained, 90%-95% were inhibited by < or = 1 mcg clindamycin/mL. No differences between MIC values of isolates from dogs and cats were observed.

   b. Susceptibility of aerobic bacteria to clindamycin: During a laboratory study, 101 isolates of staphylococci were assessed from 91 dogs and 10 cats. Forty-four (44) out of 101 (43.6%) were *Staphylococcus intermedius*, 18/101 (17.6%) *Staphylococcus aureus* and 39/101 (38.6%) *Staphylococcus* spp. These isolates were recovered from skin, wounds and abscesses, bones, joints, mouth, upper respiratory tract and urogenital tract. Ninety-eight (98) of the 101 (97%) of the isolates were susceptible to clindamycin.

   c. Data from a published laboratory study during which the skin lesions of 45 cats were cultured bacteriologically for staphylococci: Thirty-two (32) staphylococcal isolates were recovered from 30 cats and were biotyped, using biochemical tests contained in a staphylococcal identification system. Of 23 isolates considered coagulase-positive, 16 were identified as *Staphylococcus aureus*, 5 as *S. intermedius*,

and 2 as *S. hyicus.* Of 9 isolates considered coagulase-negative, 6 were identified as *S. simulans,* 2 as *S. epidermidis,* and 1 as *S. xylosus*. Antimicrobial susceptibility tests were done on all staphylococcal isolates, using a disk-diffusion method. Susceptibility to clindamycin was determined for 13/16 (81%) isolates of *Staphylococcus aureus*, 3 of 5 (60%) of the *Staphylococcus intermedius* isolates and 6 of 6 (100%) of the *Staphylococcus simulans* isolates.

2. Clinical Laboratory Data - Pharmacokinetic Data

   a. During a well-controlled pharmacokinetic study, 18 healthy cats were allocated into three treatment groups and orally dosed with clindamycin aqueous solution for 10 days at a dosage rate of (1) 5.5 mg/kg (2.5 mg/lb) twice daily; (2) 11 mg/kg (5 mg/lb) twice daily; or (3) 22 mg/kg (10 mg/lb) once daily. Serum disposition of clindamycin was determined after the first and last dose of clindamycin was given. Data from this study indicated that oral clindamycin solution appears to be safe in cats, with minor palatability problems. Serum concentrations can be maintained above the MIC for most *S. aureus* infections using either 5.5 mg/kg (2.5 mg/lb) every 12 hours or 11 mg/kg (5 mg/lb) every 12 hours, whereas 11 mg/kg (5 mg/lb) every 12 hours or 22 mg/kg (10 mg/lb) every 24 hours produces serum concentrations above the MIC for many anaerobic bacteria. No clinical signs of drug intoxication were observed and no drug related necropsy findings were evident.

   b. Tissue concentrations of clindamycin were determined in cats following dosing during a well-designed pharmacokinetic study: Eighteen (18) healthy cats were allocated into two blocks with three treatment groups and orally dosed with clindamycin aqueous solution at 5.5 mg/kg (2.5 mg/lb) twice daily (Group 1), 11 mg/kg (5.0 mg/lb) twice daily (Group 2), or 22 mg/kg (10 mg/lb) once daily (Group 3). After 10 days, all cats were killed and tissues taken for clindamycin concentration analysis. Concentrations were highest in the lung, with tissue:serum ratios greater than 3 in all groups. Concentrations were higher in Group 3 than Group 1 ($P<0.05$). Only liver concentrations in Group 3 were statistically higher than in Group 2, although all tissues except bone marrow and CSF had numerically higher concentrations in Group 3 than Group 2. The tissue:serum ratio was greater than 1 in all tissue studies except bone, cerebrospinal fluid, brain, and skeletal muscle. Bacterial MICs or "therapeutic" levels of clindamycin were provided in liver, kidney, lung, spleen, heart, jejunum, colon, bone marrow and at the dosage regime of 5.5 mg/kg (2.5 mg/lb) twice a day (total daily dose of 5 mg/lb) for 10 days.

   c. Clinical Effectiveness Study - Dental Infection: During a single site study, the efficacy of clindamycin hydrochloride (capsules) for

treating feline dental infections was evaluated. Denmark study. Treatment of dental infections in cats with clindamycin hydrochloride combined with tooth scaling was compared with tooth scaling alone. In the group with combination treatment (clindamycin and tooth scaling) 29 patients were included, and in the group with only tooth scaling, 31 patients were included. The clindamycin dosage regime administered was 5.0 mg/kg (2.5 mg/lb) body weight twice daily for 10 days. At the re-examination visit 10 days after initial treatment, the efficacy of the treatments were evaluated. Seventy percent (70%) of the cats receiving the combination treatment had good/excellent efficacy while only four cats showed no improvement. The frequency of gingivitis and halitosis before and after treatment was markedly reduced. There was a 92% and 78% reduction in the incidence of gingivitis and halitosis, respectively, for the treatments. In the group of cats treated by scaling, the disease was of a much milder character. Fourteen (14) patients had signs of gingivitis, and in seven (50%) of the cases, the gingivitis had disappeared at the re-examination visit. Responses to tooth scaling and cleaning was evaluated as good or fair in 60% of the cats receiving this treatment.

V. ANIMAL SAFETY

Summary: Two pivotal studies addressed target animal safety; a 15-day oral tolerance study in domestic shorthair cats and a 42-day oral target animal safety study in domestic shorthair cats. These two pivotal safety studies determined that clindamycin is safe for use in cats within the daily dosage range of 5.0 to 10.0 mg clindamycin/lb body weight administered for a maximum of 14 days if clinical judgement indicates.

Pivotal Studies

1. Acute Tolerance Study in Cats

   a. Type of Study: This GLP study was a 15-day acute oral tolerance evaluation of clindamycin hydrochloride in domestic shorthaired cats. The cats were orally administered clindamycin at 10 times the normally recommended dose for 15 days and compared to cats which were orally administered the drug vehicle (controls). The cats were observed daily for any adverse clinical signs and at the conclusion of the study all cats were euthanized and selected tissues examined histologically for evidence of toxicity.

   b. Investigator: Study Director: CE Hunt, DVM, PhD, The Upjohn Company, Kalamazoo, MI 49001.

   c.. General Design

      i. Purpose of Study: The study was performed to support the safety of clindamycin hydrochloride for the treatment of

bacterial infections in cats. The objective was to characterize the pharmacotoxic effects of a formulation containing clindamycin hydrochloride following oral administration once daily for 15 days in domestic shorthair cats at 10X (110 mg/kg/day [50 mg/lb/day]) the normally recommended daily therapeutic dose (11 mg/kg/day [5 mg/lb/day]). This study was conducted in compliance with all applicable GLP regulations.

ii. Test Animals: Twenty barrier reared domestic shorthair cats (10 males, 10 females) weighing 2.8 kg (6.2 lb) to 4.6 kg (10.1 lb) were distributed among the treatment groups as follows:

Table 5.1 Cats/treatment groups

Study Group (mg clindamycin/kg/day)	Group 1 0 (vehicle)		Group 2 110	
Sex (M, F)	M	F	M	F
Total cats	5	5	5	5
	10		10	

iii. Controls: Control cats received 4.4 mL of vehicle per/kg/body weight.

iv. Dosage Forms: Clindamycin hydrochloride oral liquid. Each mL of the liquid contained clindamycin hydrochloride equivalent to 25 mg clindamycin.

Vehicle - same vehicle as used for the test drug but containing no clindamycin hydrochloride.

v. Route of Administration: All treatments were administered orally via stomach tube.

vi. Doses: The cats in the clindamycin treatment group were administered 4.4 mL/kg of the test formulation containing 25 mg/mL (total of 110 mg clindamycin/kg body weight). The cats in the control treatment group were administered 4.4 mL/kg of the vehicle containing 0 mg/clindamycin/kg body weight. All treatments were administered once every 24 hours.

vii. Test Duration: The cats were dosed once daily for 15 days.

ix. Pertinent Parameters: Clinical observations, food consumption, water consumption, body weights; hematology, clinical chemistry, urinalyses, organ weights, necropsy findings, and histologic findings.

d. Results: Clindamycin hydrochloride was administered to domestic shorthair cats at 10X (50 mg/lb/day) the normally recommended daily therapeutic dose of 11 mg/kg/day (5 mg/lb/day) for 15 days. Clinical signs were limited to the gastrointestinal tract, i.e., emesis, soft feces and diarrhea, and occurred in vehicle control and treated cats but were more frequent in the treated group. Diarrhea was marked in one control male and two treated females; it was severe in one of these females for one day. Cats in both groups maintained body weight or gained weight throughout the study. Some cats administered clindamycin hydrochloride salivated just before dosing during the second week and this probably was in anticipation of dosing the drug. There were no obvious drug-related alterations in hematology, serum chemistry or urinalysis parameters. Although gross evidence of drug effects was not seen at necropsy, there was microscopic evidence of lymphocytic inflammation in gallbladder in the majority of treated animals and in two cases there was accompanying eosinophilic inflammation. Other histologic findings were considered incidental or variants to be anticipated in the domestic cat.

e. Statistical Analysis. A statistical evaluation of the results were not performed.

f. Conclusions: Clindamycin hydrochloride was tolerated with little evidence of toxicity in domestic shorthair cats orally administered 110 mg/kg/day (50 mg/lb/day), 10X the minimum recommended daily therapeutic dose, for 15 days. Emesis, soft feces and diarrhea were observed in vehicle control and treated groups but were more frequent in cats administered clindamycin hydrochloride. Salivation was seen just before dosing after the first week in some cats administered clindamycin hydrochloride. Lymphocytic inflammation of the gallbladder was associated with administration of clindamycin hydrochloride in males and females.

2. Subacute Tolerance Study in Cats

a. Type of Study: This GLP study was a 42-day subacute oral tolerance evaluation of clindamycin hydrochloride in domestic shorthaired cats. The cats were orally administered clindamycin at 0, 1X, 3X and 5X the minimum recommended dose of 11 mg/kg/day (5 mg/lb/day). The cats were observed daily for any adverse clinical signs and at the conclusion of the study, all cats were euthanized and selected tissues examined histologically for evidence of toxicity.

b. Investigator: Study Director: CE Hunt, DVM, PhD, The Upjohn Company, Kalamazoo, MI 49001.

c. General Design

i. Purpose of Study: This study was to support the safety of clindamycin hydrochloride for the treatment of bacterial infections in cats. The objective was to characterize the pharmacotoxic effects of a formulation containing clindamycin hydrochloride following oral administration once daily for 42 days (3X the maximum proposed clinical treatment of 14 days) in domestic shorthair cats at 1X, 3X, and 5X the minimum recommended daily therapeutic dose (11 mg/kg/day [5 mg/lb/day]). Following the dosing period, two animals per sex per group in both the control and high-dose groups were maintained on study without drug to assess reversibility of drug effects for an additional 27/28 days (females/males). A statistical evaluation of the results was not performed. This study was conducted in compliance with all applicable GLP regulations.

ii. Test Animals: Forty (40) barrier reared domestic shorthair cats weighing 2.4 kg (5.3 lb) to 4.9 kg (10.8 lb) were distributed among the treatment groups as follows:

Table 5.2 Cats/treatment groups

Study Group	Group 1 Controls	Group 2 2X	Group 3 3X	Group 4 5X
mg clindamycin/ kg/day	0	11	33	55
Sex (M, F)	M F 6 6	M F 4 4	M F 4 4	M F 6 6
Total cats	12	8	8	12

iii. Controls: Control cats received 2.2 mL of drug vehicle/kg body weight.

iv. Dosage Forms: Clindamycin hydrochloride liquid. Each mL of liquid contained clindamycin hydrochloride equivalent to 25 mg/mL clindamycin.

Vehicle - Same vehicle as used for the test drug formulation but containing no clindamycin hydrochloride.

v. Route of Administration: All treatments were administered orally via stomach tube.

vi. Doses: Table 5.3 presents the dose levels and dose volumes for treatment group.

Table 5.3 Clindamycin HCl dose levels/dose volumes/treatment groups

Groups*	Dose Level (mg/kg/day)	Dose Volume (mL/kg)
1	0 (control)	2.2
2	11	0.44
3	33	1.32
4	55	2.2

*4 cats in group 1 and 4 cats in group 4 were maintained for drug reversibility studies.

vii. Test Duration: The cats were dosed daily for 42 days with eight cats retained and observed for an additional 27 to 28 days to assess drug reversibility.

ix. Pertinent Parameters: Clinical observations; food consumption; water consumption; body weight; hematology; clinical chemistry; urinalysis; organ weight; necropsy findings; histological findings; ophthalmic examination; toxicokinetic findings.

d. Results: Results of this 42-day oral target animal safety study with clindamycin hydrochloride at 1X, 3X, and 5X the minimum recommended daily therapeutic dose of 11 mg/kg/day (5 mg/lb/day) were similar to those of the 15-day oral tolerance study at 10X (110 mg/kg/day [50 mg/lb/day]) the recommended dose. Changes included gastrointestinal disturbance, i.e., emesis, soft feces and diarrhea. Diarrhea is known to be associated with oral administration of some antibiotics. Drug-related lymphocytic inflammation of the gallbladder, which was found in the tolerance study, was not present in this target animal safety study (high dose = 55 mg/kg/day [25 mg/lb/day]). Minimal or mild lymphocytic inflammation of the gallbladder was seen in sections of gallbladder from one male in each group and one female in the 11 mg/kg/day (5 mg/lb/day) group, but these changes were not as extensive or severe as in the previous study and, therefore, were not interpreted as drug-related. Serum concentrations of clindamycin hydrochloride at 11 mg/kg/day (5 mg/lb/day) were lower than plasma concentrations reported in a study comparing single oral doses (11 mg/kg [5 mg/lb/day]) as either in capsules or aqueous solution. Capsules or aqueous solution provided serum clindamycin activity > 0.2 mcg/mL for 24 hours after dosing compared to 0.08 mcg/mL 24 hours after the first dose at 11 mg/kg/day (5 mg/lb/day) in the present study. The highest serum concentration at 24 hours was 0.57 mcg/mL on day 14 at the 55 mg/kg/day (25 mg/lb/day) dose. Maximum serum concentrations at 11 mg/kg/day (5 mg/lb/day) in the present study also were lower, with a high of 4.11 mcg/mL on day 14, than the maximum

clindamycin levels after administration of capsules or aqueous solution in the comparison study. Serum disposition results from the present study and the previous comparative study indicate that clindamycin does not tend to accumulate during multiple dosing in the cat.

e. Statistical Analysis: Repeated measures analysis of variance was used to analyze data for body weights, hematology, serum chemistry, and urinalyses. Data from the reversibility phase were not analyzed. Data for organ weights were analyzed by one-way analysis of variance.

f. Conclusions : Clindamycin hydrochloride liquid was tolerated when administered orally once daily for 42 days at 11, 33, and 55 mg/kg/day (5, 15 and 25 mg/lb/day) in young adult male and female domestic shorthair cats. Peak clindamycin levels 24 hours after dosing generally increased in proportion to dose. However, the minimum values indicated that there was little accumulation in serum at 11 or 33 mg/kg/day (5 or 15 mg/lb/day) and mild accumulation at 55 mg/kg/day (25 mg/lb/day). Soft feces and diarrhea were seen in some controls and in all treated animals. Emesis occurred shortly after dosing or was a delayed response in some cats in the 33 and 55 mg/kg/day (15 and 25 mg/lb/day) groups. These gastrointestinal signs were not accompanied by significant effects on food consumption or body weight; they receded and disappeared during the reversibility phase of the study.

VI. HUMAN SAFETY

Human safety data are not required since the cat is considered a non-food animal.

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and demonstrates that Antirobe Aquadrops Liquid (clindamycin hydrochloride) is safe and effective when used as labeled (5 to 10 mg/lb body weight once every 24 hours depending on the severity of the condition and clinical judgment) for the treatment of feline dental infections and infected wounds and abscesses caused by or associated with susceptible strains of *Staphylococcus aureus, Staphylococcus intermedius, Streptococcus spp., Clostridium perfringens,* and *Bacteroides fragilis.*

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The Agency's Finding of No Significant Impact (FONSI) and the evidence supporting that finding is contained in an environmental assessment and will be available for display in the Dockets Management Branch, HFA-305.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for an additional claim for use in cats for the treatment of infected wounds, abscesses and dental infections. This approval relied upon the new safety and effectiveness data submitted in the supplemental application, and it did not require the reevaluation of the safety and effectiveness data in the parent application.

Under section 5129(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (FFDCA), this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the cat for new indications for which this supplemental application is approved. This exclusivity period will expire three years from the date of this letter.

Since multiple etiologies may cause soft tissue, skin, and dental infections, it requires the expertise of a veterinarian to determine the appropriate antibiotic therapy and to perform corrective dental procedures. The Agency, therefore, concluded that Antirobe Aquadrops should be provided to the public on a prescription basis.

VIII. APPROVED PRODUCT LABELING

Package insert
Carton label