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APPLICATION NUMBER:

50-801

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA	21-709
Submission Date	12/22/2003; 1/16/2003; 5/5/2004; 8/6/2004
Brand Name	[—]
Generic Name	Clindamycin Phosphate
Reviewers	Lei Zhang, Ph.D.
Team Leader	Raman K Baweja, Ph.D.
OCPB Division	DPE III
OND Division	DDDDP (HFD-540)
Applicant	Connetics
Relevant IND	IND 64,577
Type of Submission; Code	505 (b)(2); 3S
Formulation; Strength(s)	Topical Foam; 1%
Indication	Topical application in the treatment of acne vulgaris

Executive Summary

The Sponsor is submitting this original New Drug Application (NDA) for Clindamycin Phosphate Foam, 1% (Clindamycin Phosphate Foam), a new dosage form of clindamycin phosphate, for topical application in the treatment of acne vulgaris. This is a 505(b)(2) application that uses the reference list drug in the Orange Book for clindamycin phosphate topical product, Clindagel® (clindamycin phosphate) Topical Gel, 1%, manufactured by [———] as the reference product.

To support efficacy and safety, the Sponsor conducted a single pivotal Phase 3 trial in 1026 patients. The safety database included 439 patients exposed to Clindamycin Phosphate Foam, 1%. The Sponsor conducted one comparative pharmacokinetics study (Study CLN.C.001) to compare the bioavailability of Clindamycin Phosphate Foam, 1% (Clindamycin Phosphate Foam) versus Clindagel® (clindamycin phosphate gel) topical gel, 1% (Clindagel). The results from this study show that the extent of systemic clindamycin absorption was comparable following the Clindamycin Phosphate Foam administration compared to Clindagel® administration. The mean C_{max} and mean AUC(0-12h) values in plasma on Day 5 were 23% and 9% lower, respectively, following the Clindamycin Phosphate Foam compared to Clindagel®.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed NDA 21-709. The Human Pharmacokinetics and Bioavailability Section of this submission is acceptable for meeting the requirements of 21CFR320. The sponsor needs to incorporate the following changes in the proposed labeling:

CLINICAL PHARMACOLOGY

Pharmacokinetics: In an open label, parallel group study in 24 patients with acne vulgaris, 12 patients (3 male and 9 female) applied 4 grams of [redacted] Foam once-daily for five days, and 12 patients (7 male and 5 female) applied 4 grams of Clindagel® (clindamycin phosphate) Topical Gel, 1%, once-daily for five days. On Day 5, the mean C_{max} and AUC(0-12h) were 23% and 9% lower, respectively, for [redacted] Foam than for Clindagel®.

Following multiple applications of [redacted] Foam less than 0.024% of the total dose was excreted unchanged in the urine over 12 hours on Day 5.

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Summary of Clinical Pharmacology Findings

The Sponsor conducted one comparative pharmacokinetics study (Study CLN.C.001) to compare the bioavailabilty of Clindamycin Phosphate Foam, 1% versus Clindagel® topical gel, 1%. The study report synopsis is attached in Appendix 1.

This was an open label, parallel group study in 24 patients (10 males and 14 females) with mild to moderate facial acne vulgaris (Appendix 2, Table 2.1). 12 patients (3 males and 9 females) applied Clindamycin Phosphate Foam (test), 1%, and 12 patients (7 males and 5 females) applied Clindagel® topical gel (reference), 1%. The test drug and the reference drug were applied once-daily as 4-gram administrations for five days. Blood samples were collected pre-dose on Day 1, and predose, 1, 2, 4, 8, and 12 hr post-dose on Day 5. All voided urine samples were collected over 12 hour period post dose on Day 5. Plasma and urine clindamycin concentrations in plasma and urine were analyzed using high-performance liquid chromatography with mass spectrometric detection. The method was developed and validated by [redacted] Standard curves for all acceptable analytical runs for human EDTA plasma

and for human urine used in this study covered a range of 0.500 to 65.000 ng/mL with a limit of quantitation of 0.500 ng/mL. The assay is acceptable.

Clindamycin concentrations were detectable in 11 of the 12 subjects following Clindamycin Phosphate Foam administration and in all 12 subjects following Clindagel administration (Appendix 2, Tables 2.2 and 2.3). For Subject 4 who received Clindamycin Phosphate Foam, clindamycin was not detected in plasma at all timepoints but levels were detected in urine (Appendix 2, Tables 2.2 and 2.4). One subject (Subject 21) following Clindagel administration had only one detectable sample at 2 hr of 0.507 ng/mL that is very close to the limit of quantitation (LOQ) (Appendix 2, Tables 2.3). Clindamycin levels were detected in urine samples (Appendix 2, Tables 2.5).

In this study, plasma concentrations were only monitored for half of dosing interval (0-12 hr) (Figure 1). AUC(0-12h) obtained would only represent partial AUC and would be lower than AUC(0-24h). For 2 subjects (Subjects 22 and 24) in the test treatment (A) and 1 subject (Subject 5) in the reference treatment (B), clindamycin concentrations were detected at 24 hr on Day 4 (Appendix 2, Tables 2.2 and 2.3).

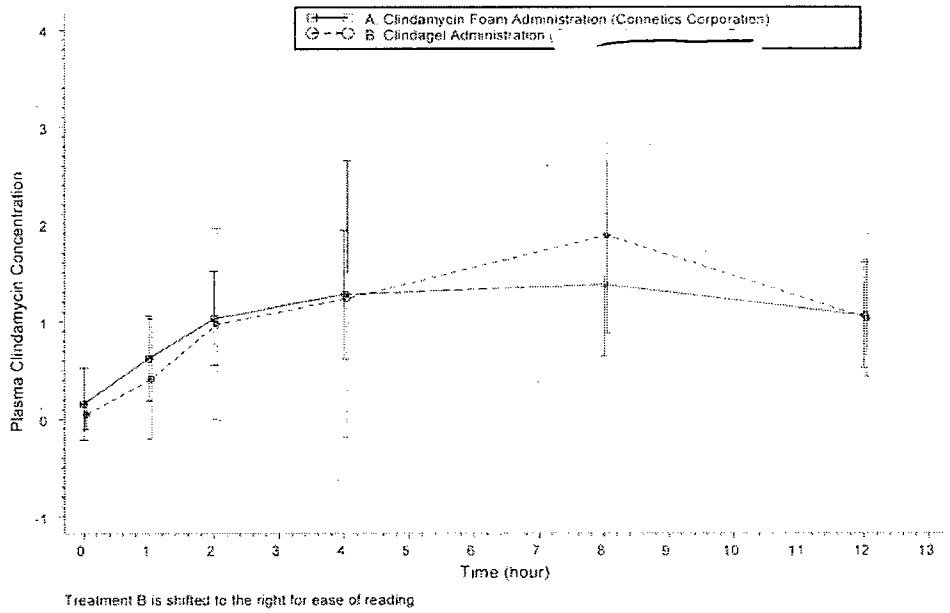

Figure 1. Plasma Concentration-Time Profile of Clindamycin (mean ± SD, linear scale).

The Sponsor conducted pharmacokinetics analysis for all subjects. Zero was used for plasma levels below LOQ (<0.5 ng/mL) (Table 1). Because there was one patient in each treatment group with plasma levels below or near LOQ, the Reviewer reanalyzed the plasma PK data excluding data from Subject 4 and Subject 21 (Table 1). By excluding Subjects 4 and 21, higher mean values and smaller SD values were obtained for both treatments. The ratios of mean C_{max} and AUC(0-12h) (test/reference) did not differ from what Sponsor obtained (Table 2).

Table 1: Pharmacokinetic Parameters (Arithmetic Mean ± SD) for Clindamycin.

Pharmacokinetic Parameters	Clindamycin Phosphate Foam (Test)		Clindagel (Reference)	
	N=12 (Sponsor)	N=11 (Reviewer, excluding Subject 4)	N=12 (Sponsor)	N=11 (Reviewer, excluding Subject 21)
Plasma Clindamycin				
C_{max} (ng/mL)	1.56 ± 0.81	1.70 ± 0.68	2.08 ± 1.24	2.22 ± 1.19
AUC (0–12h) (ng*hr/mL)	13.69 ± 6.25	14.94 ± 4.74	15.12 ± 10.26	16.47 ± 9.58
T_{max} (hr)	6.18 ± 2.08 (N=11)	-	6.66 ± 2.46	-
Urine Clindamycin				
Xu (0-12h) (ng)	9580.2 ± 4387.1	-	12076 ± 7560.1	-
CLr[1] (mL/hr)	677.97 ± 219.26 (N=11)	677.97 ± 219.26	2652.2 ± 6386.0	810.62 ± 303.39
Urine concentration (ng/mL)	13.44 ± 10.9	-	16.03 ± 10.18	-

[1] The assessment of CLr is only an estimate of true CLr because the values are calculated based on plasma and urine data from only half of the dosing interval.

Table 2: PK Parameter Comparison for Clindamycin Phosphate Foam (Test) and Clindagel (Reference).

	Ratio Clindamycin Phosphate Foam (Test)/Clindagel (Reference)	
	N=12 (Sponsor)	N=11 (Reviewer)
Cmax	0.75	0.77
AUC(0-12h)	0.91	0.91
Xu (0-12h)	0.79	-
CLr[1]	-	0.84

[1] The assessment of CLr is only an estimate of true CLr because the values are calculated based on plasma and urine data from only half of the dosing interval.

The results from this study suggested that the extent of systemic clindamycin absorption was comparable following the Clindamycin Phosphate Foam administration compared to Clindagel® administration. The mean C_{max} and mean AUC(0-12h) values in plasma on Day 5 were 23% and 9% lower, respectively, following the Clindamycin Phosphate Foam compared to Clindagel®.

For urine, the assessment of CLr is only an estimate of true CLr because the values are calculated based on plasma and urine data from only half of the dosing interval. Based on the data from these first 12 hours, it appears that the differences in urinary clindamycin excretion parallel those observed in plasma, with Xu (0-12h) and CLr at 21% and 16% lower, respectively, following the Clindamycin Phosphate Foam compared to Clindagel® (Table 2). Consistent with previous findings for Clindagel®, the fraction of clindamycin dose excreted unchanged in urine was marginal following both treatments, at 0.024% following the Clindamycin Phosphate Foam application compared to 0.030% following Clindagel application.

Demographic data, individual plasma concentration and PK data are included in Appendix 2.

Discussion

Although this NDA is a 505(b)(2) application, it has its own safety and efficacy studies. The Foam has demonstrated efficacy. For this topical product (Clindamycin Phosphate Foam, 1%), the site of therapeutic action is the skin and this action occurs earlier than the level of the drug seen in the blood. The measurement of drug in systemic circulation is therefore one of safety assessment. The results show that the Foam has comparable exposure to the Gel.

Appendix 1. Synopsis of Study Report

2. SYNOPSIS

Name of the Sponsor: Connetics Corporation	Individual Study Table Synopsis Referring to Part of The Dossier **Volume:** **Page:**	*For National Authority Use Only*
Name of Finished Product: Clindamycin Phosphate Foam, 1%		
Name of Active Ingredient: Clindamycin Phosphate		
Title of Study: A Randomized, Open-Label Study to Evaluate the Comparative Absorption of Clindamycin Phosphate Foam, 1% Versus Clindagel (clindamycin phosphate gel) Topical Gel, 1%, in Subjects with Acne Vulgaris		
Investigator(s) and Study Center(s): James C. Kisicki, MD MDS Pharma Services 621 Rose Street Lincoln, NE 68502		
Publication(s): Not applicable		
Study Period: 23 June 2002 27 June 2002	**Development Phase:** I	
Objectives: The objectives of this study were to compare the absorption of Clindamycin Phosphate Foam, 1% (Clindamycin Phosphate Foam) versus Clindagel (clindamycin phosphate gel) topical gel, 1% (Clindagel). An additional objective was to obtain safety information for Clindamycin Phosphate Foam.		
Methodology: This was a single center, randomized, open-label study of male and female subjects, with mild to moderate facial acne vulgaris. At the first visit (Screening), written informed consent was obtained, a medical history/review of systems and physical examination were conducted; concomitant medication use was determined; vital signs (temperature, blood pressure, pulse), were measured; laboratory tests (hematology, chemistry, HIV and Hepatitis [HBsAg/HCAb] were performed; urine was collected for drug screening purposes; and serum pregnancy tests were performed on females of child bearing potential. Weight and height were measured and the Body Mass Index (BMI) calculated (subjects aged 12 to 20 years required a BMI index-for-age percentile of 35 to 85%; subjects aged ≥ 21 years required a BMI under 30). An Investigator's Static Global Assessment (ISGA) was performed to assess the extent and severity of acne vulgaris of the face (all lesions to be treated); this score had to be 2 or 3 at study entry. At Visit 2/Day 1 eligibility was reconfirmed for ISGA; changes to medical history and concomitant medication use were reviewed and vital signs (blood pressure, pulse) were measured. Eligible subjects were assigned a subject number and were randomized to either Clindamycin Phosphate Foam or Clindagel. A plasma sample was collected prior to the first application of study drug for Baseline bioavailability evaluation of clindamycin phosphate. Drug applications occurred at Visits 2 to 6/Days 1 to 5; male subjects (with facial hair) were to shave ≥ one hour prior to study drug applications and all subjects were instructed to wash the areas of application with a mild soap, and to allow the areas to dry fully prior to application of study drug. Subjects then self-administered 4 grams of study drug under the observation of the study nurse/coordinator to their entire face (forehead, nose, cheeks and chin) before treating the neck, upper chest, and upper back, regardless if acne was present on these areas. Subjects were also queried for concomitant medication use and AEs at the study drug application visits. At Visit 6/Day 5 subjects were instructed to empty their bladders within 15 minutes prior to treatment. All voided urine was collected over the 12-hour period. Plasma samples for bioavailability evaluation were collected within 30 minutes prior to treatment and at 1, 2, 4, 8, and 12 hours after treatment with study drug. At this visit subjects were		

Name of the Sponsor: Connetics Corporation	Individual Study Table Synopsis Referring to Part of The Dossier	*For National Authority Use Only*
Name of Finished Product: Clindamycin Phosphate Foam, 1%	**Volume:** **Page:**	
Name of Active Ingredient: Clindamycin Phosphate		

queried for concomitant medication use and AEs both prior to study drug application and again at the end of the 12-hour post application period. Subjects received lunch (at approximately 12:00 p.m.) and dinner (at approximately 6.00 p.m.); they were discharged from the clinic provided there were no ongoing serious AEs and they were in a clinically stable condition. Following completion of the study, plasma and urine samples collected for determination of bioavailability of topically administered clindamycin phosphate were analyzed at a laboratory independent of the clinical study group.

Number of Subjects Planned: 24

Number of Subjects Enrolled: 24

Gender: 10M, 14F | **Age:** 13–46 y

Ethnicity (Race): 92% Caucasian, 4% Hispanic, 4% Black

Diagnosis and Main Criteria for Eligibility: Eligible subjects were male or female, 12 years of age or older, in good general health with mild or moderate facial acne. Subjects were required to have an Investigator's Static Global Assessment score of 2 or 3 at both Visit 1/Screening and Visit 2/Day 1 to enroll in the study.

Test Product, Dose, Duration, Mode of Administration, and Batch Number: The test product was Clindamycin Phosphate Foam (Treatment A) containing clindamycin phosphate (1% as clindamycin), manufactured by Connetics Corporation, Lot No.: SDDG-C, expiration date: 16 May 2004. Subjects randomized to Treatment A self-administered 4 grams of Clindamycin Phosphate Foam once daily to the face, neck, upper chest, and upper back for 5 days.

Duration of Treatment: 5 days

Reference Therapy, Dose and Mode of Administration, Lot Number: The reference therapy was Clindagel (Treatment B) containing 1% clindamycin phosphate, USP at a concentration equivalent to 10 mg clindamycin per gram, manufactured by [ ]. expiration date: [ ] Subjects randomized to Treatment B self-administered 4 grams of Clindagel once daily to the face, neck, upper chest, and upper back for 5 days.

Criteria for Evaluation:

Efficacy: No efficacy measurements were made or planned.

Bioavailability: The pharmacokinetics of clindamycin were evaluated over a 12-hour period in plasma and urine following 5 once daily doses of 4 g administered as foam (Treatment A) or gel (Treatment B) to the face, neck, upper chest, and upper back. The plasma parameter values of Cmax, $AUC_{(0\text{-}12)}$, and T_{max} were reported. Clindamycin concentrations in urine were reported, as required in the protocol. Additionally, urine volume excreted, amount excreted (Xu), and partial estimated renal clearance (CLr) were also reported.

Safety: Safety assessments included vital signs, hematology and chemistry laboratory tests, physical examinations, and reported AEs.

Statistical Methods:
Mean, median, standard deviation, minimum and maximum were reported for clindamycin concentrations and pharmacokinetic parameters by treatment for both plasma and urine.

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Descriptive statistics were calculated for demographics and vital signs by treatment groups. AEs were coded using MedDRA (Version 4.1). Concomitant medications were coded using the WHO dictionary. All safety data were listed.

SUMMARY AND CONCLUSIONS

Bioavailability Results: Clindamycin concentrations were detectable in 11 of the 12 subjects following Clindamycin Phosphate Foam administration and in all 12 subjects following Clindagel administration. The overall arithmetic means and standard deviation of the clindamycin pharmacokinetic parameters in both plasma and urine are summarized in the following table. Values of zero for C_{max} and $AUC_{(0-12)}$ for the subject who had no detectable clindamycin concentrations were included in these summary statistics.

Pharmacokinetic Parameters	Clindamycin Phosphate Foam		Clindagel	
	Arithmetic		Arithmetic	
Plasma Clindamycin	**Mean**	**SD**	**Mean**	**SD**
C_{max} (ng/mL)	1.562	0.813	2.075	1.239
T_{max} (hr)	6.18	2.08	6.66	2.46
$AUC_{(0-12)}$ (ng*hr/mL)	13.69	6.248	15.12	10.26
Urine Clindamycin				
Xu (ng)	9580.2	4387.1	12076	7560.1
CLr (mL/hr)	677.97	219.26	2652.2	6386.0
Urine concentration (ng/mL)	13.44	10.90	16.03	10.18

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Name of Active Ingredient: Clindamycin Phosphate		

Safety Results: Few AEs were reported during this trial with only 4 of 24 subjects (17%) reporting a total of 4 events. Most AEs were mild in severity and considered unrelated to study drug. No subjects discontinued the trial due to an AE. There were no deaths, serious AEs, episodes of diarrhea, or other significant AEs in this study. Clinical laboratory, vital signs, and physical assessments were only performed prior to dosing.

Conclusion: The extent of systemic clindamycin absorption was lower following the Clindamycin Phosphate Foam administration compared to Clindagel administration. The mean C_{max} and mean $AUC_{(0-12)}$ values in plasma on Day 5 were 25% and 9% lower, respectively, following the Clindamycin Phosphate Foam compared to Clindagel, while the amount excreted in urine during the first 12-hours postdose and the estimated renal clearance were 21% and 74% lower, respectively.

Overall, the fraction of clindamycin dose excreted unchanged in urine was marginal following both treatments, at 0.024% following the Clindamycin Phosphate Foam application compared to 0.030% following Clindagel application.

Appendix 2. Demographic data, individual plasma concentration and PK data

Table 2.1: Demographics

a)

Subject Number	Date Of Birth	Age (yrs)	Gender	Race	Height (in)	Weight (lb)	Body Mass Index x (kg/m²)
2		16	MALE	CAUCASIAN	71.0	157.0	21.90
3		16	FEMALE	CAUCASIAN	67.0	125.0	19.66
4		20	FEMALE	CAUCASIAN	67.0	146.0	22.89
5		14	FEMALE	CAUCASIAN	68.0	170.0	25.87
6		46	FEMALE	CAUCASIAN	68.0	181.0	27.56
7		14	MALE	CAUCASIAN	66.0	116.0	17.65
8		18	FEMALE	CAUCASIAN	67.0	149.0	23.36
9		13	MALE	CAUCASIAN	65.0	134.0	22.32
10		20	FEMALE	CAUCASIAN	69.0	145.0	21.43
11		14	FEMALE	CAUCASIAN	62.0	134.0	24.53
12		15	MALE	CAUCASIAN	67.0	152.0	23.83
13		43	FEMALE	CAUCASIAN	66.0	170.0	27.46
14		14	FEMALE	BLACK	65.0	118.0	19.65
15		13	MALE	CAUCASIAN	65.0	127.0	21.15
16		17	MALE	CAUCASIAN	67.0	162.0	25.40
17		15	MALE	CAUCASIAN	66.0	131.0	21.16
18		14	MALE	CAUCASIAN	68.0	130.0	19.78
19		22	FEMALE	CAUCASIAN	64.0	139.0	23.88
20		16	FEMALE	CAUCASIAN	66.0	153.0	24.72
21		15	MALE	HISPANIC	68.0	162.0	24.65
22		17	FEMALE	CAUCASIAN	67.0	113.0	17.71
23		15	MALE	CAUCASIAN	68.0	182.0	27.70
24		30	FEMALE	CAUCASIAN	66.0	185.0	29.89
25		16	FEMALE	CAUCASIAN	71.0	125.0	17.45

b)

Variable		Treatment: Clindamycin Phosphate Foam	Clindagel	Total
Age	N	12	12	24
	Mean	21	17	19
	SD	9	6	9
	Minimum	14	12	12
	Median	18	16	16
	Maximum	46	43	46
Race	BLACK	1	0	1
	CAUCASIAN	11	11	22
	HISPANIC	0	1	1
Height (in)	N	12.0	12.0	24.0
	Mean	66.6	67..	66.9
	SD	2.3	1.7	2.0
	Minimum	62.0	65.0	62.0
	Median	67.0	67.0	67.0
	Maximum	71.0	71.0	71.0
Weight (lb)	N	12.0	12.0	24.0
	Mean	146.6	145.6	146.1
	SD	22.3	21.9	21.9
	Minimum	113.0	116.0	113.0
	Median	145.5	144.0	145.5
	Maximum	185.0	182.0	185.0

Table 2.2: Plasma Clindamycin Concentrations (ng/mL) Following Clindamycin Phosphate Foam Administration, Day 5 (Treatment A)

Subject Number	Study Period	(Treatment A) Sample Times (hr) -96	0	1	2	4	8	12
2	1	0.000	0.000	0.000	0.795	0.837	1.247	1.079
4	1	0.000	0.000	0.000	0.000	0.000	0.000	0.000
6	1	0.000	0.000	0.531	0.775	0.810	1.176	0.866
8	1	0.000	0.000	0.697	1.025	1.099	1.070	0.712
10	1	0.000	0.000	1.257	1.639	1.885	1.533	1.468
11	1	0.000	0.000	0.661	1.288	2.583	1.480	1.000
14	1	0.000	0.000	0.545	1.159	1.898	1.210	0.760
16	1	0.000	0.000	0.000	0.512	1.040	0.952	0.999
18	1	0.000	0.000	0.801	1.768	1.620	3.075	2.291
19	1	0.000	0.000	0.926	1.187	1.294	1.331	0.952
22	1	0.000	0.767	0.896	1.007	0.998	1.231	1.215
24	1	0.000	1.095	1.163	1.245	1.226	2.180	1.351
Mean		0.000	0.155	0.623	1.033	1.274	1.374	1.059
Median		0.000	0.000	0.639	1.093	1.163	1.230	1.000