CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-802

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 50-802	Submission Date: 5/5/2006
Brand Name	ZIANA™
Generic Name	Clindamycin /Tretinoin
Reviewer	Sue-Chih Lee, Ph.D.
Acting Team Leader	Suliman Al-Fayoumi, Ph.D.
OCP Division	Division of Clinical Pharmacology III
OND division	Division of Dermatologic and Dental Products
Sponsor	Dow
Submission Type; Code	Resubmission
Formulation; Strength(s)	Gel (Clindamycin phosphate 1.2% and tretinoin 0.025%)
Proposed Indication	For the treatment of [redacted] acne vulgaris
Proposed Dosing Regimen	[redacted]

b(4)

BACKGROUND

The original NDA for this product was initially designated as NDA 21-739 and was submitted on Feb. 6, 2004. The NDA was later designated as NDA 50-802. The clinical pharmacology and biopharmaceutics section was reviewed by Dr. Chandra S. Chaurasia of OCPB and found to be acceptable (see review dated 11/4/04). A Not Approvable action letter was issued by the Agency on December 7, 2004, due to deficiencies in clinical data. The sponsor resubmitted the NDA on May 5, 2006, which addresses deficiencies in clinical data and CMC issues. There are no new clinical pharmacology and biopharmaceuitcs data in the resubmission and, therefore, no clinical pharmacology review of the resubmission is necessary.

RECOMMENDATION

A review of the original submission by Dr. Chandra S. Chaurasia of OCPB found that the clinical pharmacology and biopharmaceutics section was acceptable. This determination still holds. There are no new clinical pharmacology and biopharmaceuitcs data in the resubmission and, therefore, no clinical pharmacology review of the resubmission is necessary.

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/s/

Sue Chih Lee
8/22/2006 04:52:10 PM
BIOPHARMACEUTICS

Suliman Alfayoumi
8/22/2006 04:57:31 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-739/N000	
Brand Name:	Clin-RA Gel™
Generic Name:	Clindamycin Phosphate/Tretinoin
Dosage Form:	Topical Gel
Dosage Strength:	Clindamycin1%, Tretinoin 0.025%
Indication:	Treatment of Acne Vulgaris
NDA Type:	Original NDA 505 (b)(2)
Relevant IND	IND 65,531
Submission Date(s):	02/06/04, 07/15/04, 10/22/04
Sponsor:	Dow Pharmaceutical Sciences, Petaluma, CA
Reviewer:	Chandra S. Chaurasia, Ph.D.
Team Leader:	Raman K Baweja, Ph.D.
OCPB Division:	DPE III (HFD-880)
OND Division:	DDDDP (HFD-540)

EXECUTIVE SUMMARY

The Sponsor, Dow Pharmaceutical Sciences (DPS), is seeking approval of the new combination product Clin-RA Gel, containing 1% clindamycin (equivalent to 1.2% clindamycin phosphate) and 0.025% tretinoin under a 505(b)(2) application for the treatment of acne vulgaris. Currently, there is no US approved combination product containing both clindamycin and tretinoin moieties. However, clindamycin phosphate (equivalent to 1% clindamycin) as single ingredient product is approved as topical gel (Cleocin T, NDA 50-615, Pharmacia, Jan 7, 1987), lotion (Cleocin T, NDA 50-600, Pharmacia, May 31, 1989), and solution (Cleocin T, NDA 50-537, Pharmacia, prior to Jan 1, 1982) for the treatment of acne vulgaris. Similarly, products containing tretinoin are approved as topical gel in 0.01% and 0.025% strengths (Retin-A, NDA 17-955 and 17-579, Johnson and Johnson, prior to Jan 1, 1982), and in 0.04% and 0.1% strengths as micro-gel (Retin-A Micro, NDA 20-475, J &J, May 10, 2002 and Feb 7, 1997, respectively) for the treatment of acne vulgaris. In addition, tretinoin is also available as topical cream (0.025%-0.1%) and solution 0.05% strengths for the treatment of acne, and as tretinoin 0.02% and 0.05% emollient creams (Renova, NDA) for use in the mitigation of fine wrinkles and mottled hyperpigmentation.

To characterize the percutaneous absorption of clindamycin phosphate and tretinoin following daily application of Clin-RA Gel, the Sponsor conducted a pivotal, Phase 2, multiple dose study under maximal exposure conditions in 12 patients, male and female, ages 13 to 29 years. Plasma levels for clindamycin, tretinoin, and the key retinoid metabolites 13-*cis*-retinoic acid, and 4-oxo-13-*cis*-retinoic acid were analyzed at screening, Day 1 (baseline), Day 5, Day 10, and Day 14, hours 0 through 24, providing for the mean, standard deviation, and range for each timepoint. The limit of quantitation (LOQ) was 1 ng/mL for tretinoin and its metabolites, and 0.5 ng/mL for clindamycin.

AUC(0-24), Cmax, and Tmax were calculated for each subject using plasma concentrations from Day 14, Hour 0 through Day 14, Hour 24 for clindamycin, tretinoin, and its 13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid metabolites.

Tretinoin is a naturally occurring compound in humans, with endogenous plasma concentrations of approximately 1 to 4 ng/mL. The plasma concentrations of tretinoin post treatment were within this range indicating no significant systemic absorption of tretinoin following topical administration of the test product. Maximum clindamycin plasma concentrations generally did not exceed 3.5 ng/mL, with the exception of one subject whose plasma concentration reached 13.1 ng/mL.

There were no statistically significant overall differences in concentration levels across Day 1 to Day 14, Hour 0 ($p \geq 0.077$) for clindamycin, tretinoin, 13-cis-retinoic acid, or 4-oxo-13- cis-retinoic acid. There was not a statistically significant overall difference on Day 14, Hour 0 through Hour 24 for clindamycin, tretinoin, or 13-cis-retinoic acid ($p \geq 0.206$). There was a significant overall difference between the Day 14, Hour 0 to Hour 24 4-oxo-13-cis-retinoic acid concentrations ($p=0.013$), but the mean values were 2.78 and 2.30 ng/mL, respectively.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted in support of NDA 21-739 for clindamycin phosphate/tretinoin 1%/0.025% gel, and found it to be acceptable for meeting the requirements of 21CFR320.

OCBP Labeling:

The following changes in the labeling are recommended.

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Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The transdermal absorption of tretinoin and clindamycin are both well characterized and numerous studies have been published describing the safe and effective use of clindamycin and tretinoin in humans. The Agency agreed with DPS's proposal to use data available (using Medline and Toxline databases) for clindamycin and tretinoin to support the registration of this new combination product. Summaries from relevant publications support that the extent of systemic availability of both compounds after topical application is low, 1-7% and 1-5%, respectively, at their highest.

Clinical Program:

The clinical study program included two pivotal Phase 3, randomized, double-blind, 4-arm trials to compare the safety and efficacy of Clin-RA Gel vs. Clindamycin Phosphate 1.2% Gel vs. Tretinoin 0.025% Gel vs. Vehicle in the Treatment of Acne Vulgaris. Primary measurements of efficacy for the comparison between Clin-RA Gel and Clindamycin Gel and Tretinoin, were:

1) Two out of three of the following lesion counts:
   Mean percent change from baseline at Week 12 in inflammatory lesion counts
   Mean percent change from baseline at Week 12 in non-inflammatory lesion counts
   Mean percent change from baseline at Week 12 in total lesion counts
2) Percent of subjects who were clear or almost clear at Week 12, as judged by an Evaluator's Global Severity Score.

Clinical Pharmacology Program:

The Sponsor conducted a single-center, open-label, multiple dose evaluation to assess the absorption and safety of Clin-RA Gel under maximal exposure conditions. The site enrolled 13 subjects with acne vulgaris with approximately 1000 to 2500 cm^2 involved area (facial area, chest and back). Other inclusion/exclusion criteria were similar to standard guidelines for evaluating anti-acne drugs. Twelve subjects completed the study and one subject (Subject 8) refused to have blood drawn for the laboratory tests and was not included in the study. Subject ages ranged from 13 to 29 years, with a mean of 20.08 years. Seven subjects (58%) were male and five subjects (42%) were female. Nine subjects (75%) were Caucasian, one subject (8%) was African-American, one subject (8%) was Asian, one subject (8%) was Slavic.

Subjects visited the clinic daily for 14 days and study staff applied a 4-gram weighed dose of Clin-RA Gel to the face, neck, back and chest. A 4-gram application was selected based on surface area of the face, back and chest. It is estimated that these areas equal approximately 1000 to 2500 cm2, and approximately 4 ± 0.5 grams is required to cover these areas entirely. Pre-dose blood samples were drawn on Days 1, 5, 10 and 14. On Day 14, blood was drawn at 2, 4, 6, 8, 10 and 12 hours post-dosing. A final 24-hour post-dosing blood draw was taken on Day 15. Two additional single daily blood draws were made in the morning before noon at screening and on Pre-Day 1 for the determination of baseline endogenous plasma levels of clindamycin, tretinoin, and key metabolites, 13- *cis* -retinoic acid and 4-oxo-13-*cis*-retinoic acid.

Clinical Pharmacology Results:

Table 1 summarizes plasma concentrations for clindamycin, tretinoin, and the retinoic metabolites for Day 1 (baseline), Day 5, Day 10, and Day 14, Hours 0 through 24, providing the mean, standard deviation, and range for each timepoint.

Plasma concentrations at screening revealed tretinoin concentrations ranging from 1.0 to 1.3 ng/mL (mean of 1.07 ng/mL); 13-*cis*-retinoic acid concentrations ranged from 1.0 to 1.7 ng/mL (mean of 1.08 ng/mL); and 4-oxo-13-*cis*-retinoic acid ranged from 1.3 to 5.3 ng/mL (mean of 2.81 ng/mL). Pre-Day 1 plasma concentrations revealed the subjects to have tretinoin concentrations ranging from 1.0 to 1.8 ng/mL (mean of 1.12 g/mL); 13-*cis*-retinoic acid concentrations ranged from 1.0 to 1.6

ng/mL (mean of 1.07 ng/mL); and 4-oxo-13-*cis*-retinoic acid ranged from 1.5 to 4.7 ng/mL (mean of 2.63 ng/mL).

In 11 of the 12 patients, maximum clindamycin concentrations ranged from 0.67 ng/mL to about13 ng/mL over the course of the study (14 days), with mean Cmax of 2.8 ng/mL. Tretinoin concentrations ranged from 1.0 (LOQ) to 1.6 ng/mL over the course of the study, with mean concentrations ranging from 1.00 to 1.13 ng/mL; 13-*cis*-retinoic acid concentrations ranged from 1.00 (LOQ) to 1.4 ng/mL over the course of the study, with mean concentrations ranging from 1.00 to 1.06 ng/mL; and 4-oxo-13-*cis*-retinoic concentrations ranged from 1.2 to 6.5 ng/mL, with mean concentrations ranging from 2.30 to 3.04 ng/mL. Six of the 12 patients (50%) exhibited undetectable plasma tretinoin concentration at the LOQ of 1 ng/mL.

Table 1. Plasma concentrations for tretinoin, clindamycin and the retinoic metabolites for Day 1 (baseline), Day 5, Day 10, and Day 14, Hours 0 through 24

			Baseline			Day 14, Hour							
	Screening	Pre-Day 1	Day 1[a]	Day 5	Day 10	0	2	4	6	8	10	12	24
Tretinoin													
Mean	1.07	1.12	1.04	1.05	1.02	1.00	1.13	1.05	1.00	1.00	1.05	1.04	1.08
STD	0.10	0.24	0.08	0.13	0.05	0.01	0.20	0.11	0.00	0.01	0.12	0.09	0.12
Range	1.0-1.3	1.0-1.8	1.0-1.3	1.0-1.5	1.0-1.2	1.0-1.1	1.0-1.6	1.0-1.3	1.0-1.0	1.0-1.1	1.0-1.4	1.0-1.2	1.0-1.3
Clindamycin													
Mean	0.50	0.50	0.50	0.55	0.53	0.57	2.04	2.19	1.82	1.69	1.48	1.24	0.71
STD	0.00	0.00	0.00	0.16	0.10	0.11	3.52	2.96	1.85	1.19	0.89	0.58	0.29
Range	0.5-0.5	0.5-0.5	0.5-0.5	0.5-1.0	0.5-0.9	0.5-0.8	0.5-13.1	0.5-11.2	0.5-7.2	0.5-4.8	0.5-3.5	0.5-2.3	0.5-1.2
13-*cis*-Retinoic Acid													
Mean	1.08	1.07	1.04	1.06	1.02	1.00	1.04	1.02	1.00	1.00	1.02	1.00	1.01
STD	0.20	0.18	0.10	0.12	0.05	0.01	0.09	0.06	0.00	0.00	0.05	0.01	0.03
Range	1.0-1.7	1.0-1.6	1.0-1.3	1.0-1.4	1.0-1.1	1.0-1.0	1.0-1.3	1.0-1.2	1.0-1.0	1.0-1.0	1.0-1.2	1.0-1.1	1.0-1.1
4-oxo-13-*cis*-Retinoic Acid													
Mean	2.81	2.63	2.81	3.04	2.97	2.78	2.90	2.69	2.65	2.60	2.57	2.74	2.30
STD	1.03	0.94	0.74	1.15	1.33	0.94	0.86	0.62	0.78	0.79	0.70	0.66	0.71
Range	1.3-5.3	1.5-4.7	1.9-4.0	2.0-5.9	1.6-6.5	1.6-5.0	1.7-4.9	2.0-4.2	1.8-4.3	1.8-4.4	1.8-4.0	1.7-4.2	1.2-3.9

[a] Pre-dose administration.

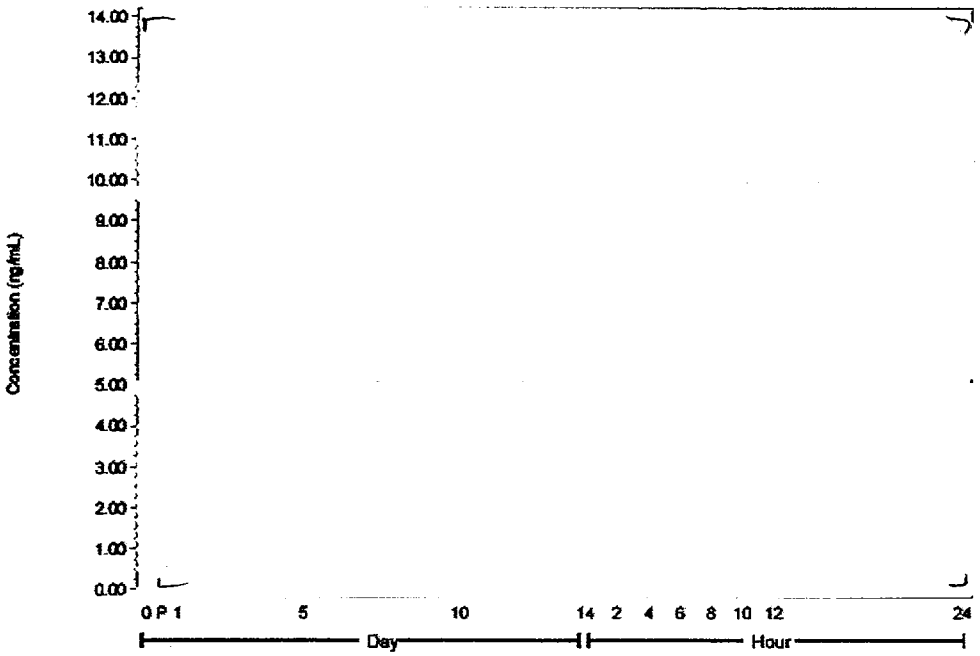
Table 2 summarizes pharmacokinetic measures with the mean, standard deviation, and percent CV for Cmax, AUC0-24 and Tmax for tretinoin, clindamycin, and the key metabolites. Figures 1-4 depict the individual and mean concentration (ng/mL) levels of clindamycin, tretinoin and its metabolites at each evaluation during the study.

Table 2. Pharmacokinetic parameters for tretinoin, clindamycin and the retinoid metabolites with the mean, standard deviation, and percent CV.

Concentration	*N*	*Mean*	*STD*	*Percent CV*
Tretinoin				
Cmax (ηg/mL)	12	1.18	0.20	0.17
Tmax	12	4.34	7.02	1.62
$AUC_{(0\text{-}24)}$ (ηg/mL•hour)	12	25.47	1.82	0.07
Clindamycin				
Cmax (ηg/mL)	12	2.62	3.40	1.30
Tmax	12	6.34	3.82	0.60
$AUC_{(0\text{-}24)}$ (ηg/mL•hour)	12	32.00	24.78	0.77
13-*cis*-Retinoic Acid				
Cmax (ηg/mL)	12	1.05	0.10	0.09
Tmax	12	3.26	7.26	2.22
$AUC_{(0\text{-}24)}$ (ηg/mL•hour)	12	24.46	0.48	0.02
4-oxo-13-*cis*-Retinoic Acid				
Cmax (ηg/mL)	12	3.15	0.89	0.28
Tmax	12	4.33	4.51	1.04
$AUC_{(0\text{-}24)}$ (ηg/mL•hour)	12	63.13	16.24	0.26

[a] For each subject, Cmax, Tmax, and $AUC_{(0\text{-}24)}$ was calculated using plasma concentrations from Day 14, Hour 0 through Day 14, Hour 24.

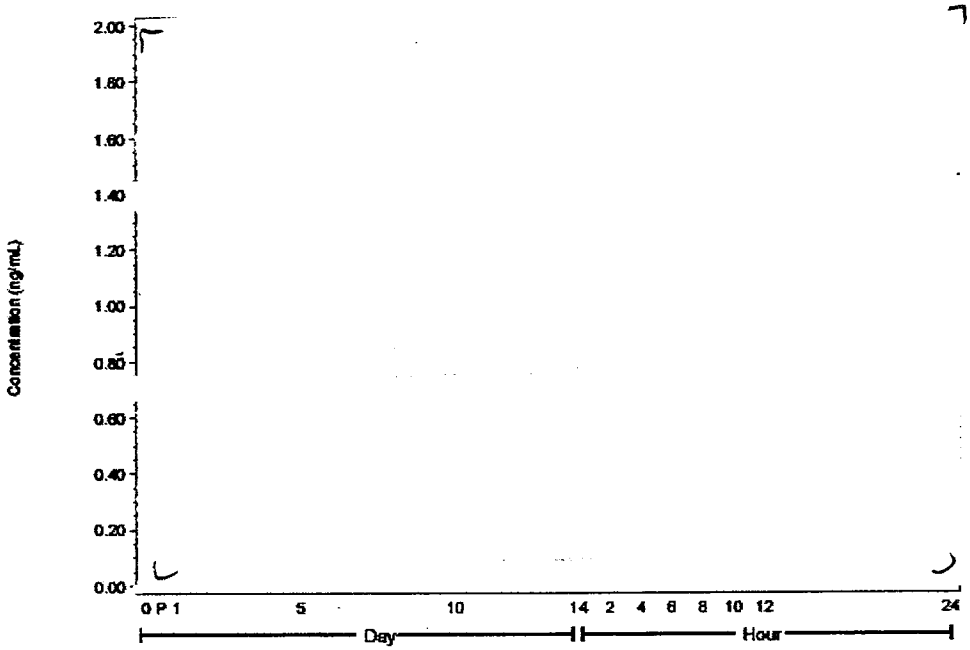
Figure 1. Individual and mean concentration levels of clindamycin (ng/mL).



b(4)

Note: The mean concentrations are represented by the connected ×'s. Day 'P' is Pre-Day 1 on the CRF.

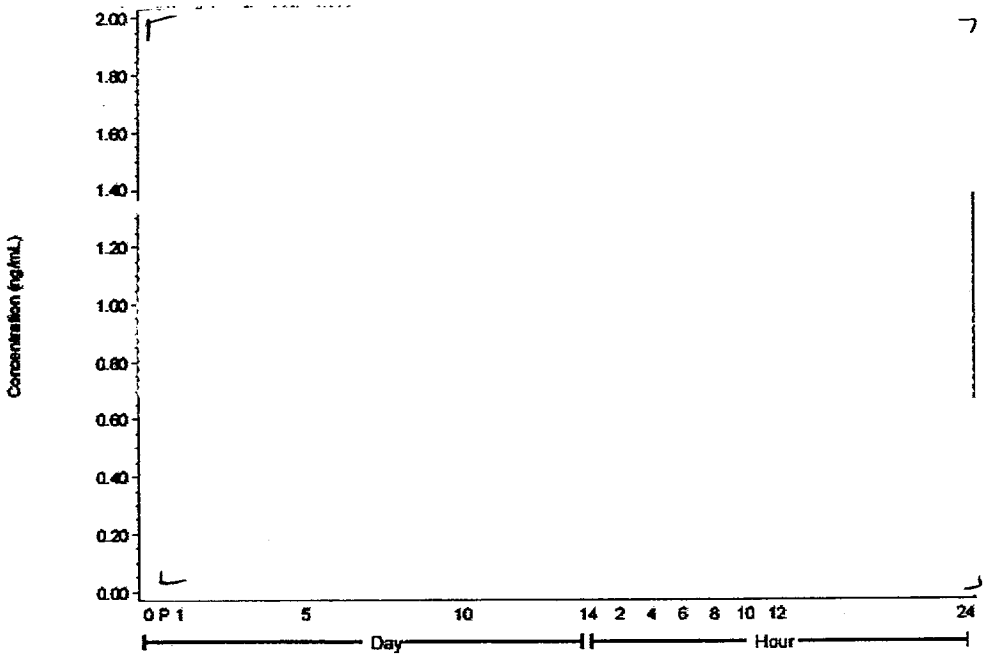
Figure 2 Individual and mean concentration levels of tretinoin (ng/mL).



b(4)

Note: The mean concentrations are represented by the connected ×'s. Day 'P' is Pre-Day 1 on the CRF.

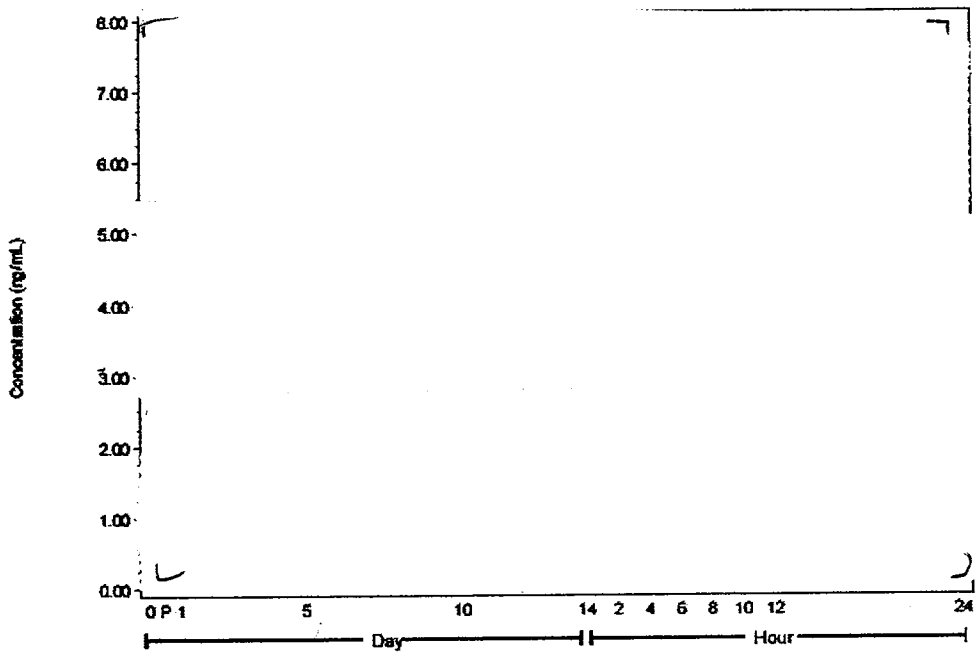
Figure 3. Individual and mean concentration levels of 13-cis-retionic acid (ng/mL)



b(4)

Note: The mean concentrations are represented by the connected ×'s. Day 'P' is Pre-Day 1 on the CRF.

Figure 4. Individual and mean concentration levels of 4-oxo-13-cis-retinoic acid (ng/mL)



b(4)

Note: The mean concentrations are represented by the connected ×'s. Day 'P' is Pre-Day 1 on the CRF.

No events suggestive of systemic toxicity associated with Clin-RA Gel or clindamycin (i.e. intestinal/abdominal discomfort, diarrhea) were reported by any subjects. Neither tretinoin nor its metabolites showed any increase in plasma concentration levels post treatment when compared to their respective plasma concentration levels measured at baseline.

In 11 of the 12 patients, maximum clindamycin concentrations ranged from 0.67 ng/mL to about 13 ng/mL over the course of the study (14 days), with mean Cmax 2.8 ng/mL indicating minimal systemic absorption of clindamycin following Clin-RA Gel topical application.

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Raman K. Baweja, Ph.D.. _____ Date: _____
Team Leader
Division of Pharmaceutical Evaluation III

CC: NDA 21-739, HFD-850 (P. Lee), HFD-540 (J. Smith), HFD-880 (J. Lazor, A. Selen, R. Baweja, C. Chaurasia)

Appendices

Proposed Package Insert (Original and Annotated)

Proposed by the Sponsor in the original NDA 21-739 submission, only Clinical Pharmacology Section is included by the reviewer.

Package Insert

b(4)

Appears This Way
On Original

Individual Study Review

Title of Study: Protocol No. 7001.G2HP.C-02-02: Absorption Evaluation of Clindamycin and Tretinoin Following Maximum Topical Exposure to Clin-RA Gel in Subjects with Moderate to Severe Acne Vulgaris

Investigator: Karl R. Beutner, MD, Ph. D

Study Centers: Solano Clinical Research, A Division of Dow Pharmaceutical Sciences, 127 Hospital Drive, #202, Vallejo, CA 94589

Studied period: October 24, 2002 to November 16, 2002

Phase of Development: II

Objectives: The purpose of this study was to investigate the plasma levels of tretinoin, key tretinoin metabolites, and clindamycin, as well as safety, following maximal daily applications of Clin-RA Gel (clindamycin phosphate 1.2% [clindamycin 1%], tretinoin 0.025%) for 14 days in subjects with significant, widespread acne vulgaris.

Methodology: Single center, open label, multiple dose

Number of subjects (planned and analyzed): Twelve subjects were planned and the study enrolled 13 subjects. Twelve subjects completed the study. One subject (Subject 8) received study drug only on Day 1, had vital signs collected through the Day 2 visit, and returned on Day 15 for collection of vital signs, physical examination, and a pregnancy test. This subject (Subject 8) was excluded from all analyses except reporting of adverse events. The patients' demography is as follows:
Age (Years) Mean 20.08 STD 4.93 Range 13.0-29.0
Gender Male 7 (58%) Female 5 (42%)
Race Caucasian 9 (75%) African American 1 (8%) Hispanic 0 (0%) Asian 1 (8%) Other1 (8%)
Height (in) Mean 67.33 STD 3.41 Range 64.0-72.5
Weight (lb) Mean 156.25 STD 25.98 Range 123.0-214.0

Diagnosis and main criteria for inclusion:
Male or female subjects, 12 years of age and older, with moderate to severe acne vulgaris defined as having approximately 1000 to 2500 cm2 of total acne-involved area on the face, chest and back, and an Acne Global Grade of III or IV on a I – IV scale in at least one of these three areas.

Test product, dose and mode of administration, batch number: Clin-RA Gel (batch #772), four (4) ± 0.5 grams, applied topically once daily to the face, neck, chest, and back areas.

Duration of Treatment: Once daily for 14 days

Criteria for evaluation:

Blood samples were collected at screening (Baseline), Pre-Day 1 (Baseline), pre-dose on Days 1 (Baseline), 5, 10, and 14 for the determination of plasma concentrations of clindamycin, tretinoin,

and key retinoid metabolites. In addition, after the final dose on Day 14, blood samples were collected at Hours 2, 4, 6, 8, 10, and 12. A final blood sample was also collected on Day 15 (24 hours after the last dose application).

Clinical safety laboratory tests were conducted at screening and Day 15 and included hematology, serum chemistry, and urinalysis. Physical examinations were conducted at screening and Day 15. Subject's height was measured at screening and weight was measured at screening and Day 15. Vital signs including blood pressure, respirations, pulse, and temperature were collected at screening and Days 1 through 15. Adverse events were collected from Day 1 through Day 15.

Analytical Method:

Samples were analyzed for clindamycin, tretinoin and the retinoid metabolites 13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid using HPLC/MS/MS method. The method was developed and validated by [redacted] The assay for clindamycin was validated for a range of 0.50 to 80.0 ng/mL with a limit of quantitation of 0.5 ng/mL. The assay procedure was found to be linear (r^2 0.9995) and the precision and accuracy ranged from 0.07% to 4.3%. The long term stability samples at -20 °C for 6 weeks were within 15% of their theoretical concentrations. b(4)

The assay for tretinoin, 13-cis-retonic acid and 4-oxo-13-cis-retionic acid was validated for a range of 0.50 to 20.0 ng/mL with r^2 in the range of 0.9972-0.9984. The precision and accuracy ranged from 4.3% to 9.4% and 0.74% to 4.6%, respectively. The limit of quantitation was 1 ng/mL for tretinoin and its metabolites. The long term stability samples for tretinoin and its metabolites at -70 °C for 27 weeks were within 15% of their theoretical concentrations.

The analytical method was found acceptable.

Safety:

Vital signs, clinical laboratory tests (chemistry, hematology, and urinalysis), physical exam findings, and occurrence of adverse events were collected at pre-specified intervals throughout the study.

Pharmacokinetics:

Plasma samples were analyzed for concentrations of clindamycin, tretinoin (all-*trans*-retinoic acid) and the retinoid metabolites: 13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid.

The concentrations of clindamycin, tretinoin and tretinoin metabolites in the plasma provided for the determination of area under the curve AUC(0-24h), as well as Cmax and Tmax. Mean, standard deviation, and percent CV were calculated for each of these parameters.

The post-dose and baseline levels of clindamycin, tretinoin, and the tretinoin metabolites were compared. Individual concentrations and the mean concentrations were graphed at each evaluation for clindamycin, tretinoin, 13-*cis*-retinoic acid, and 4-oxo-13-*cis*-retinoic acid. A repeated measures analysis of variance was conducted on the concentrations (a) on Day 1 (baseline) to Day 14, Hour 0 as well as (b) on Day 14, Hour 0 to Day 14, Hour 24 for clindamycin, tretinoin, and the tretinoin metabolites. Paired t-tests were conducted at each time point to examine if there was a statistically

significant post-dose change in the concentrations of clindamycin, tretinoin, 13-*cis*-retinoic acid, and 4-oxo-13-*cis*-retinoic acid, each compared to Baseline. The results of the paired t-tests were significant at the 0.05 level of significance if and only if the overall p-value from the repeated measures analysis of variance was significant at the 0.05 level of significance.

Vital signs and clinical laboratory data were summarized with descriptive statistics at each evaluation. Adverse events were tabulated by body system, severity, and relationship to study treatment.

Results:

The PK results are summarized in Tables 1-3, and graphically represented in Figures 1-4 below.

Table 1. Individual plasma pharmacokinetic parameters

Listing 10.2: Pharmacokinetic Parameters
(Page 1 of 1)

	Age/	Tretinoin			Clindamycin			13-*cis*-Retinoic Acid			4-oxo-13-*cis* Ret. Acid		
Subject	Gender	Cmax	Tmax	$AUC_{(0-24)}$	Cmax	Tmax	$AUC_{(0-24)}$	Cmax	Tmax	$AUC_{(0-24)}$	Cmax	Tmax	$AUC_{(0-24)}$
1	23/F	1.00	0.00	24.53	1.08	4.18	15.05	1.01	0.00	24.61	3.43	8.25	72.14
2	13/M	1.06	2.05	24.29	0.50	0.00	12.03	1.00	0.00	24.07	2.86	12.07	61.20
3	20/M	1.12	2.32	24.46	2.32	10.23	33.79	1.00	0.00	24.20	2.27	2.32	47.89
4	17/M	1.45	2.42	29.99	1.86	10.42	25.99	1.05	2.42	24.92	4.25	6.58	83.18
5	29/F	1.33	4.35	25.60	1.21	12.25	21.25	1.00	0.00	24.25	1.97	4.35	39.88
6	18/M	1.55	2.37	27.62	0.67	4.30	13.49	1.11	24.38	25.31	3.01	0.00	61.21
7	22/F	1.00	0.00	24.15	13.10	2.10	103.30	1.00	0.00	24.15	2.19	4.02	48.20
8	33/F												
9	29/F	1.00	0.00	24.27	2.03	4.18	30.20	1.00	0.00	24.27	3.00	2.27	59.29
10	19/F	1.24	12.08	26.17	1.10	8.20	18.26	1.16	10.12	24.35	3.00	12.08	65.12
11	18/M	1.34	2.45	26.39	1.83	10.00	26.64	1.00	0.00	24.03	3.92	0.00	66.12
12	16/M	1.02	24.00	24.12	3.48	4.02	47.73	1.00	0.00	24.00	2.89	0.00	54.05
13	17/M	1.00	0.00	24.10	2.21	6.17	36.22	1.32	2.25	25.32	5.02	0.00	99.25

Clindamycin

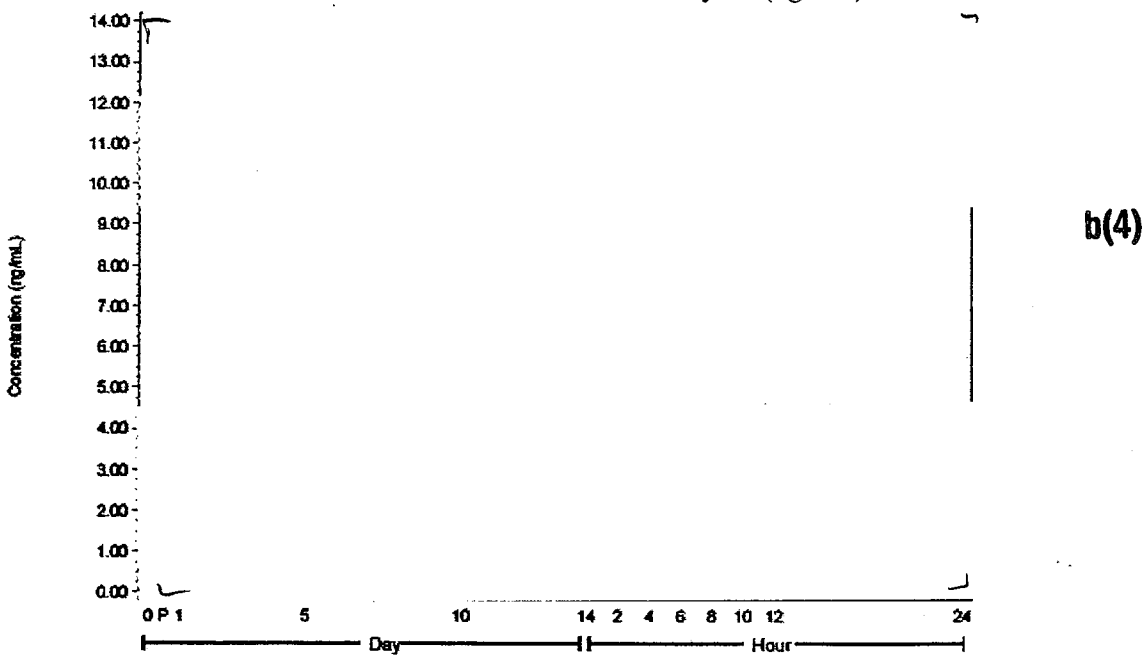
Figure 1 graphs the individual and mean concentration levels of clindamycin (ng/mL) at each evaluation during the study. Table 2 summarizes the results of the analysis of the change in mean clindamycin concentrations across Day 1 (pretreatment) through Day 14, Hour 0, and Day 14, Hour 0 through Day 14, Hour 24. An analysis of mean concentrations showed no statistically significant overall difference in concentration levels on Day 14 during Hours 0 to 24 (p=0.206).

Table 2. Plasma concentrations for tretinoin, clindamycin and the retinoic metabolites for Day 1 (baseline), Day 5, Day 10, and Day 14, Hours 0 through 24

			Baseline			Day 14, Hour							
	Screening	Pre-Day 1	Day 1[a]	Day 5	Day 10	0	2	4	6	8	10	12	24
Tretinoin													
Mean	1.07	1.12	1.04	1.05	1.02	1.00	1.13	1.05	1.00	1.00	1.05	1.04	1.08
STD	0.10	0.24	0.08	0.13	0.05	0.01	0.20	0.11	0.00	0.01	0.12	0.09	0.12
Range	1.0-1.3	1.0-1.8	1.0-1.3	1.0-1.5	1.0-1.2	1.0-1.1	1.0-1.6	1.0-1.3	1.0-1.0	1.0-1.1	1.0-1.4	1.0-1.2	1.0-1.3
Clindamycin													
Mean	0.50	0.50	0.50	0.55	0.53	0.57	2.04	2.19	1.82	1.69	1.48	1.24	0.71
STD	0.00	0.00	0.00	0.16	0.10	0.11	3.52	2.96	1.85	1.19	0.89	0.58	0.29
Range	0.5-0.5	0.5-0.5	0.5-0.5	0.5-1.0	0.5-0.9	0.5-0.8	0.5-13.1	0.5-11.2	0.5-7.2	0.5-4.8	0.5-3.5	0.5-2.3	0.5-1.2
13-*cis*-Retinoic Acid													
Mean	1.08	1.07	1.04	1.06	1.02	1.00	1.04	1.02	1.00	1.00	1.02	1.00	1.01
STD	0.20	0.18	0.10	0.12	0.05	0.01	0.09	0.06	0.00	0.00	0.05	0.01	0.03
Range	1.0-1.7	1.0-1.6	1.0-1.3	1.0-1.4	1.0-1.1	1.0-1.0	1.0-1.3	1.0-1.2	1.0-1.0	1.0-1.0	1.0-1.2	1.0-1.1	1.0-1.1
4-oxo-13-*cis*-Retinoic Acid													
Mean	2.81	2.63	2.81	3.04	2.97	2.78	2.90	2.69	2.65	2.60	2.57	2.74	2.30
STD	1.03	0.94	0.74	1.15	1.33	0.94	0.86	0.62	0.78	0.79	0.70	0.66	0.71
Range	1.3-5.3	1.5-4.7	1.9-4.0	2.0-5.9	1.6-6.5	1.6-5.0	1.7-4.9	2.0-4.2	1.8-4.3	1.8-4.4	1.8-4.0	1.7-4.2	1.2-3.9

[a] Pre-dose administration.

Figure 1. Individual and mean concentration levels of clindamycin (ng/mL)



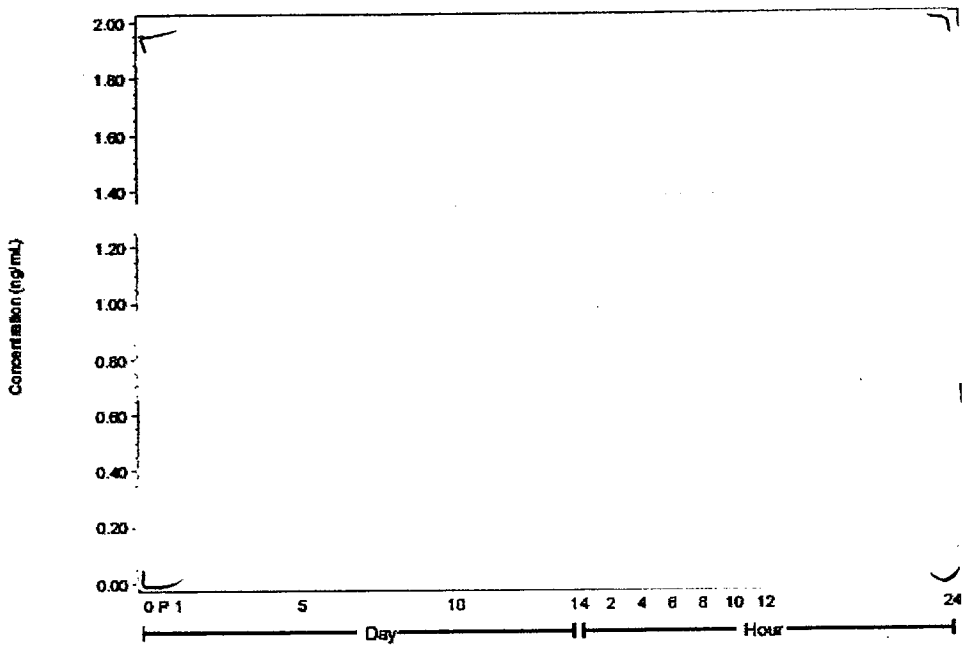
Note: The mean concentrations are represented by the connected ✕'s. Day 'P' is Pre-Day 1 on the CRF.

Tretinoin (all-*trans*-retinoic acid)

Figure 2 graphs the individual and mean concentration levels of tretinoin (ng/mL) at each evaluation during the study. Table 2 summarizes the results of the analysis of the change in mean tretinoin concentrations across Day 1 through Day 14, Hour 0, and Day 14, Hour 0 through Day 14, Hour 24. Pretreatment levels of tretinoin analyzed at screening, Pre-Day 1 and prior to dose application on

Day 1 exhibited a range between 1.0 ng/mL (limit of quantitation) and 1.79 ng/mL. Baseline concentrations were computed as an average of the three pretreatment levels and were subtracted from the tretinoin concentration at Days 5, 10 and 14 to determine the change in concentration for each subject. An analysis of mean concentrations showed no statistically significant overall difference in concentration levels across Day 1 (pretreatment) to Day 14 at Hour 0 (p=0.499). Further, there was no statistically significant overall difference on Day 14 during Hours 0 to 24 (p=0.554).

Figure 2 Individual and mean concentration levels of tretinoin (ng/mL).



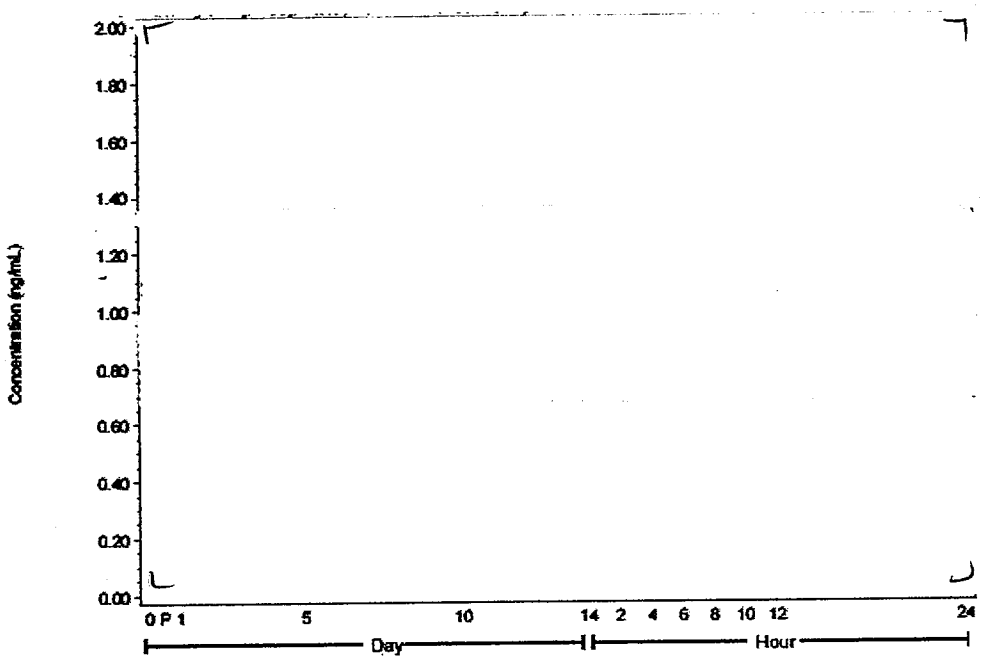
b(4)

Note: The mean concentrations are represented by the connected ×'s. Day 'P' is Pre-Day 1 on the CRF.

13-*cis*-Retinoic Acid

Figure 3 graphs the individual and mean concentration levels of 13-*cis*-retinoic acid (ng/mL) at each evaluation during the study. Table 2 summarizes the results of the analysis of the change in mean 13-*cis*-retinoic acid concentrations across Day 1 through Day 14, Hour 0, and Day 14, Hour 0 through Day 14, Hour 24. There was not a statistically significant overall difference in concentration levels across Day 1 to Day 14 at Hour 0 (p=0.339), nor was there a statistically significant overall difference on Day 14 during Hours 0 to 24 (p=0.481).

Figure 3. Individual and mean concentration levels of 13-cis-retionic acid (ng/mL)



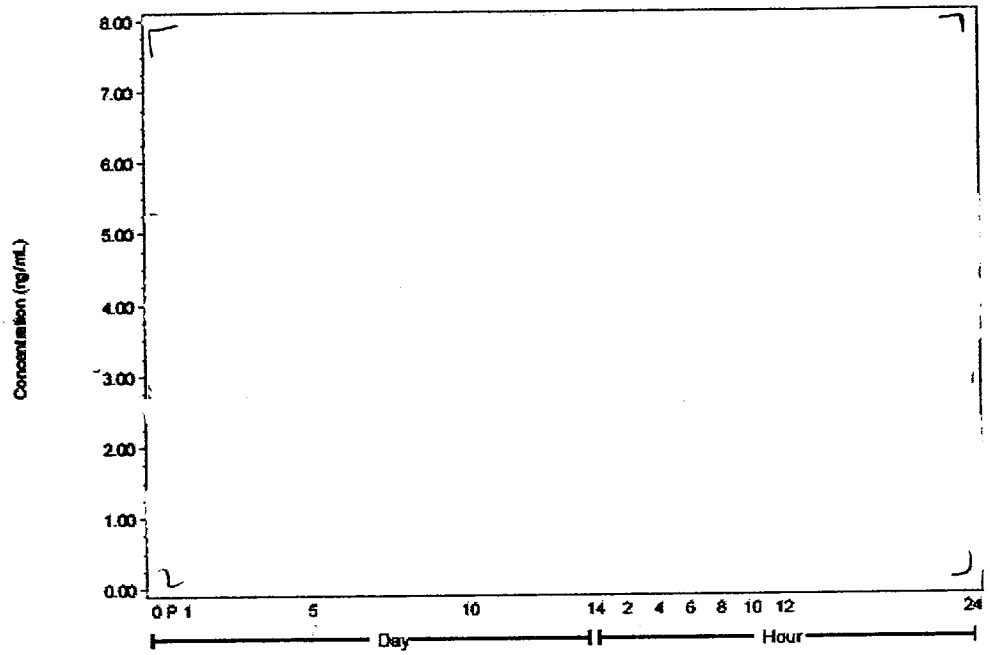
Note: The mean concentrations are represented by the connected X's. Day 'P' is Pre-Day 1 on the CRF.

b(4)

4-oxo-13-*cis*-Retinoic Acid

Figure 4 graphs the individual and mean concentration levels of 4-oxo-13-*cis*-retinoic acid (ng/mL) at each evaluation during the study. Table 2 summarizes the results of the analysis of the change in mean 4-oxo-13-*cis*-retinoic acid concentrations across Day 1 through Day 14, Hour 0, and Day 14, Hour 0 through Day 14, Hour 24. There was not a statistically significant overall difference in concentration levels across Day 1 to Day 14 at Hour 0 (p=0.402). There was a significant overall difference for the Day 14, Hour 0 to Hour 24 concentration (p=0.013).

Figure 4. Individual and mean concentration levels of 4-oxo-13-cis-retinoic acid (ng/mL)



b(4)

Note: The mean concentrations are represented by the connected ×'s. Day 'P' is Pre-Day 1 on the CRF.

The limit of quantitation (LOQ) was 1 ng/ml for tretinoin and its metabolites and 0.5 ng/ml for clindamycin. Plasma concentrations that were undetected were set to the LOQ, resulting in higher values than actually measured. The percentage of subjects with undetectable plasma concentrations for tretinoin at tmax was 50%, and ranged from 50% to 92% at any given time-point. The considerable number of higher than actual reported plasma levels for tretinoin is reflected in the values presented for Cmax and mean plasma concentrations in Table 3 below.

AUC(0-24), Cmax, Tmax, and were calculated for each subject using plasma concentrations from Day 14, Hour 0 through Day 14, Hour 24 for tretinoin, clindamycin, and the key metabolites 13-*cis*retinoic acid and 4-oxo-13-*cis*-retinoic acid. Calculation of AUCs was done using the linear trapezoidal rule. Table 3 summarizes the pharmacokinetic parameters for clindamycin, tretinoin, and the retinoid metabolites with the mean, standard deviation, and percent CV. The mean AUC(0-24) was 25.47, 32.00, 24.46, and 63.13 ng·hr/mL for tretinoin, clindamycin 13-cis-retinoic acid, and 4-oxo-13-cis-retinoic acid respectively. The mean Cmax values were 1.18, 2.62, 1.05, and 3.15 ng/mL for tretinoin, clindamycin 13-cis-retinoic acid, and 4-oxo-13-cis-retinoic acid, respectively. The corresponding mean Tmax values were 4.34, 6.34, 3.26, and 4.33 hours.

Table 3. Pharmacokinetic parameters for tretinoin, clindamycin and the retinoid metabolites with the mean, standard deviation, and percent CV.

Concentration	*N*	*Mean*	*STD*	*Percent CV*
Tretinoin				
Cmax (ng/mL)	12	1.18	0.20	0.17
Tmax	12	4.34	7.02	1.62
$AUC_{(0\text{-}24)}$ (ng/mL•hour)	12	25.47	1.82	0.07
Clindamycin				
Cmax (ng/mL)	12	2.62	3.40	1.30
Tmax	12	6.34	3.82	0.60
$AUC_{(0\text{-}24)}$ (ng/mL•hour)	12	32.00	24.78	0.77
13-*cis*-Retinoic Acid				
Cmax (ng/mL)	12	1.05	0.10	0.09
Tmax	12	3.26	7.26	2.22
$AUC_{(0\text{-}24)}$ (ng/mL•hour)	12	24.46	0.48	0.02
4-oxo-13-*cis*-Retinoic Acid				
Cmax (ng/mL)	12	3.15	0.89	0.28
Tmax	12	4.33	4.51	1.04
$AUC_{(0\text{-}24)}$ (ng/mL•hour)	12	63.13	16.24	0.26

[a] For each subject, Cmax, Tmax, and $AUC_{(0\text{-}24)}$ was calculated using plasma concentrations from Day 14, Hour 0 through Day 14, Hour 24.

Conclusions:

1. Under the conditions of this study there was no indication of systemic absorption of tretinoin. Maximum clindamycin plasma concentrations generally did not exceed 3.5 ng/ml, with the exception of one subject whose plasma concentration reached 13.1 ng/ml. Adverse events reported by this subject were related to local dermal irritation, which may have contributed to the higher level of absorption. It is uncertain whether the dermal irritation reported by this subject was patient and/or study drug induced.

2. Results from the repeated measures analysis of variance indicated no statistically significant overall differences in concentration levels across Day 1 to Day 14, Hour 0 ($p \geq .077$) for clindamycin, tretinoin, 13-*cis*-retinoic acid, or 4-oxo-13-*cis*-retinoic acid.

3. There was also not a statistically significant overall difference on Day 14, Hour 0 through Hour 24 for clindamycin, tretinoin, or 13-*cis*-retinoic acid ($p \geq 0.206$). There was however, a significant overall difference for the Day 14, Hour 0 to Hour 24 4-oxo-13-*cis*-retinoic acid concentration ($p=0.013$).

4. Neither tretinoin nor its metabolites showed any increase in plasma concentration levels post treatment when compared to their respective plasma concentration levels measured at baseline.

5. In 11 of the 12 patients, maximum clindamycin concentrations ranged from 0.67 ng/mL to about 13 ng/mL over the course of the study (14 days), with mean Cmax 2.8 ng/mL indicating a minimal systemic absorption of clindamycin following Clin-RA Gel topical application.

Brief Summary of Adverse Events
Six of the 13 subjects (46%) reported a total of 11 adverse events. There were no severe adverse events reported. Events reported were related to skin and subcutaneous tissues, nervous system disorders, general disorders and administration site conditions, the reproductive system and breast disorders, and respiratory, thoracic and mediastinal disorders.

Safety Conclusions
Adverse events were reported in 6 of the 13 subjects with a total of 11 adverse events and no severe adverse events. Eight of the adverse events were classified as mild and three were classified as moderate. The relationship of the adverse events to Clin-RA were as follows; seven events were classified as definitely unrelated or unlikely related to Clin-RA, three events were reported as possibly related to Clin-RA, and one was classified as having a probable relationship to Clin-RA (skin irritation), which was mild in intensity, treated, and had improved by the end of the study. Events reported were related to skin and subcutaneous tissues disorders (dermatitis NOS, dry skin, skin burning sensation, skin irritation), nervous system disorders (headache), general disorders and administration site conditions (pain NOS, pyrexia, rigors), the reproductive system and breast disorders (dysmenorrhoea), and respiratory, thoracic and mediastinal disorders (nasal dryness). No events suggestive of systemic toxicity associated with Clin-RA Gel or clindamycin (i.e. intestinal/abdominal discomfort, diarrhea) were reported by any subjects. In general, Clin-RA was well-tolerated by the subjects who participated in the study.

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Chandra S. Chaurasia
11/4/04 10:38:44 AM
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