CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-782

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 50-782 **Submission Dates:** 01/27/00, 04/26/00, 08/16/00 & 09/14/00

Product: Clindagel™ (clindamycin phosphate [redacted] gel), 1%

Applicant: Clindagel, LLC, Santa Rosa, CA **Reviewer:** Abimbola Adebowale Ph.D.

Review of an NDA

I. Background

Clindagel™ is a topical antimicrobial drug product containing 1% clindamycin phosphate in a gel vehicle developed by the applicant for the once a day treatment of acne vulgaris. Three topical formulations of clindamycin phosphate 1% are currently marketed by prescription as a gel (Approved 1987), a solution (Approved 1980) and, a lotion (Approved 1989) under the trade name Cleocin-T® (Pharmacia - Upjohn). Each of these products, marketed by Pharmacia - Upjohn is indicated for twice-daily topical application in the treatment of acne vulgaris.

In the human pharmacokinetics and bioavailability section the applicant included the report of a comparative absorption study of Clindagel (QD) and Cleocin T gel (BID) in patients with acne vulgaris (C-GEL-005). Also an *in vitro* skin penetration study report (by [redacted] of ^{14}C-Clindamycin from topical formulations (Clindagel™, Cleocin-T gel and Cleocin -T solution) and, literature references of human biopharmaceutics and pharmacokinetic studies (4 for topical route, 13 for oral, IV, IM and vaginal routes) were included. The literature references will be incorporated into the review as deemed pertinent.

Ii. Recommendation

The data submitted by the applicant demonstrated that clindamycin systemic exposure after clinical topical use of Clindagel™ and Cleocin-T® gel in patients with acne vulgaris was comparable between the two treatments. Based on the data submitted the applicant has met the requirements outlined in 21CFR 320 and their application is acceptable from a clinical pharmacology and biopharmaceutics perspective. However, the applicant should adequately address the labeling comments on pages 9 and 10.

Question Based Review of Clindagel™

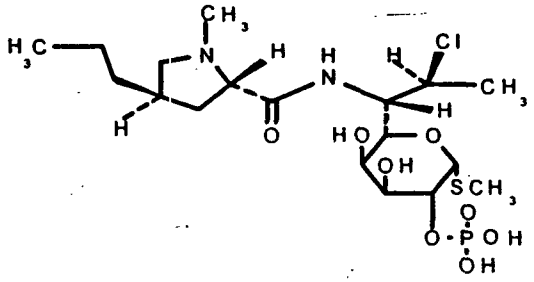
Table of Contents

III. Physicochemical Properties and Formulation

What is Clindagel ™ and how does it work?

Physicochemical Properties and Mechanism of Action of the Drug Substance:

The active drug substance in Clindagel ™ is clindamycin phosphate. Chemically Clindamycin phosphate is a water soluble ester with the chemical name, Methyl 7-chloro-6, 7, 8-trideoxy-6- (1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate) and, an empirical formula of $C_{18}H_{34}ClN_2O_8P_8S$. The chemical structure is:



Clindamycin Phosphate

The molecular weight [redacted]

In acne vulgaris the proposed mechanism of action involves the enzymatic hydrolyses of the prodrug clindamycin phosphate to clindamycin in vivo. Clindamycin is a lincosamide antibiotic that binds to the 50S subunit of bacterial ribosomes and thereby interferes with bacterial protein synthesis in bacteria responsible for buildup of free fatty acids within the pilosebaceous follicular wall. It has been proposed that buildup, along with sebum and keratin blockages result in comedone formation (noninflammatory lesions) which, in the presence of bacteria result in the formation of inflammatory lesions called papules and/or pustules in acne vulgaris.

Proposed Dosage and Administration:

Apply a thin film of Clindagel ™ once daily to the skin where acne lesions appear. Use enough to cover the entire affected area lightly.

Formulation:

The applicant stated that the proposed formulation for Clindagel™ contains Clindamycin phosphate, USP at a concentration equivalent to 10 mg clindamycin per gram (1% w/w) in a gel vehicle. Inserted below is a copy of the proposed composition of the finished drug product.

[redacted] the

2. *Validation Results of Assay Methods for Clindamycin in Human Plasma and Urine*

Plasma

[redacted]

3. *Analytical Conclusions:*

The data submitted indicate that the assay methods used for the determination of clindamycin in human plasma and urine were reproducible and accurate. From a clinical pharmacology and biopharmaceutical standpoint, the analytical methods and validation data included in this submission are acceptable.

V. Summary of BIO/PK Characteristics

Is the systemic exposure of Clindagel™ comparable to that of the currently marketed Cleocin-T Gel under clinical use conditions?

Study # CGEL-005, an open-label randomized, single center, parallel comparative treatment study conducted to characterize the systemic absorption of Clindagel™ and Cleocin-T gel in patients with acne vulgaris addresses this question. Twenty four patients (12 female and 12 male) aged 13-37 years old, previously diagnosed with acne vulgaris (found to have 25 - 100 inflammatory facial lesions and 20 - 100 noninflammatory lesions at screening) completed the study. All subjects received in-clinic product applications on the mornings of Day 1 through Day 5, and for patients assigned to Cleocin-T an additional application in the evenings of Day 1 though Day 5. On Day 1 and 5 blood samples were collected at baseline (hour 0), and hours 4, 6, 8, 12, 16, and 24 post application. Urine

– 29,000 ng/ml)[2] following an intravenous administration of 600mg to patients with different kinds of infections [For a dose of ~120 mg I.V. (same as highest topical dose) serum concentrations would be ~1200 –5800 ng/mL].

[1]Hugo H et.al. Studies on the clinical efficacy, serum levels and side effects of clindamycin phosphate administered intravenously. Scand J infect Dis 9:221-226, 1977.

Urine:

Table 3: Statistical Comparison of Urinary Excretion data for both treatments groups

	Mean (CV%) percentage of total dose excreted in Urine $_{0-24h}$ (%)	
	Day 1	**Day 5**
Clindagel ™ (N =11)[a]	0.02 (51)	0.03 (50)
Cleocin-T® (N = 12)	0.01 (94)	0.02 (68)
ANOVA (P-Value)	0.054	0.087

[a] Applicant stated that data for patient # 8 was excluded from the statistical analysis because this patient's baseline UE was greater than zero (

The data in the above table also suggests that the percentage of the total dose excreted on day 1 and 5 was somewhat higher for Clindagel ™ compared to Cleocin-T®. However, when one examines the large variability associated with the percentage of total dose excreted this difference is questionable. The applicant stated that the ANOVA statistical test used to compare the mean amount excreted demonstrated that the differences between the amount excreted on each day were not statistically significant ($p>0.05$). It is difficult to assess the significance of this statistical comparison due to the large variability obtained with the data.

The urinary data for both treatments however, suggests that the amount absorbed systemically is very low with less than 0.04 % of the total dose of clindamycin being excreted in the urine.

The applicant also included the results of an in vitro skin permeation study that evaluated the potential for systemic exposure to clindamycin following topical application in humans. The study was conducted using human cadaver skin in a diffusion cell system. The potential penetration of radiolabeled Clindagel™, Cleocin-T gel and Cleocin-T solution at a dose of ~ 100 μg/cm^2 was determined over a 48-hour timeframe. The sum of radiolabeled clindamycin found in the receptor fluid plus skin was used to estimate potential penetration in man. Details of the study methods and results are attached in the Appendix pages 8-10.

The in vitro study results also indicated that the amount of radiolabeled clindamycin measured in the receptor fluid for all three formulations was relatively low (<1%). The estimated skin penetration of Clindagel™, Cleocin-T gel and Cleocin-T solution as measured by the appearance of radiolabeled drug in the receptor fluid and skin was 23±8, 40±19 and 27±13 (mean percent of applied dose recovered) respectively. These results indicate that the skin penetration of Clindagel™ is lower than that of Cleocin-T gel, but similar to that of Cleocin-T solution.

These findings are the opposite of the results obtained in vivo for Clindagel™ and Cleocin-T gel, suggesting that the results in vitro do not necessarily reflect the conditions in vivo and, should be interpreted with caution. The applicant however, stated that the difference in the percent recovery for all three formulations were not statistically significant

using a one-way ANOVA at the 0.05 level of significance. This statement could not be confirmed because the statistical analysis results were not included in the submission.

Are there any drug-drug interactions with Clindamycin phosphate that are clinically significant?

The applicant included a reference from Goodman and Gilman[2] in which the following statement was made:
"Clindamycin can inhibit neuromuscular transmission and may potentiate the effect of a neuromuscular blocking agent administered concurrently". Based on this one would exercise caution in using Clindagel™ in patients receiving such agents. The applicant included a similar cautionary statement in the Clindagel™ label under the heading "Precautions", subheading "Drug interaction" based on this reference. Considering the low systemic exposure obtained after topical application of Clindagel™, the likelihood of this interaction being clinically significant appears unlikely, however this would require further evaluation.
[2] Goodman and Gilman's "the Pharmacological Basis of Therapeutics". 9th Edition, chapter 47, pp 1141-1143.

How do Clindamycin levels in noninflammatory or inflammatory lesions found in acne vulgaris patients relate to the drug's clinical effectiveness?

The applicant included a literature reference by Guin JD and LummisWL[3] in which the authors reported that comedonal levels of free clindamycin were determined following a 2- to 4- week topical application of a 1% solution of clindamycin phosphate. The levels of clindamycin were determined in ~30 comedones (~ 10 per visit) removed from facial skin of 20 subjects (10F, 10M) aged 13-26 years of age with 18-95 inflammatory lesions on the face (moderately inflammatory acne). Positive specimens containing levels of clindamycin (levels ranged from 60 to 1490 ng/mg) were obtained from 16 subjects after 2 weeks and 18 subjects after 4 weeks. Mean levels for all 20 subjects (positive and negative specimens) was 390±80 ng/mg at 2 weeks and 600±110 ng/mg at 4 weeks.

The authors also stated that the clindamycin level found in comedonal material does not necessarily parallel the drug's clinical effectiveness. Two persons in this study who seemed to improve during treatment did not have measurable comedonal levels of clindamycin. Also local factors (such as formulation differences) will influence the uptake of clindamycin and, resistant strains of the bacteria involved in acne (Propionibacterium acnes) are known. The literature reference indicates that although free clindamycin levels have been determined in comedones after topical application of 1% clindamycin phosphate solution this does not necessarily mean that the clinical effectiveness of topical clindamycin is dependent on comedonal levels. This suggests that the information on the comedonal levels of free clindamycin following topical administration although interesting has limited application clinically.

[3] Guin JD, Lummis WL. Comedonal levels of free clindamycin following topical treatment with a 1% solution of clindamycin phosphate. J Am Acad Dermatol 7:265-268, 1982.

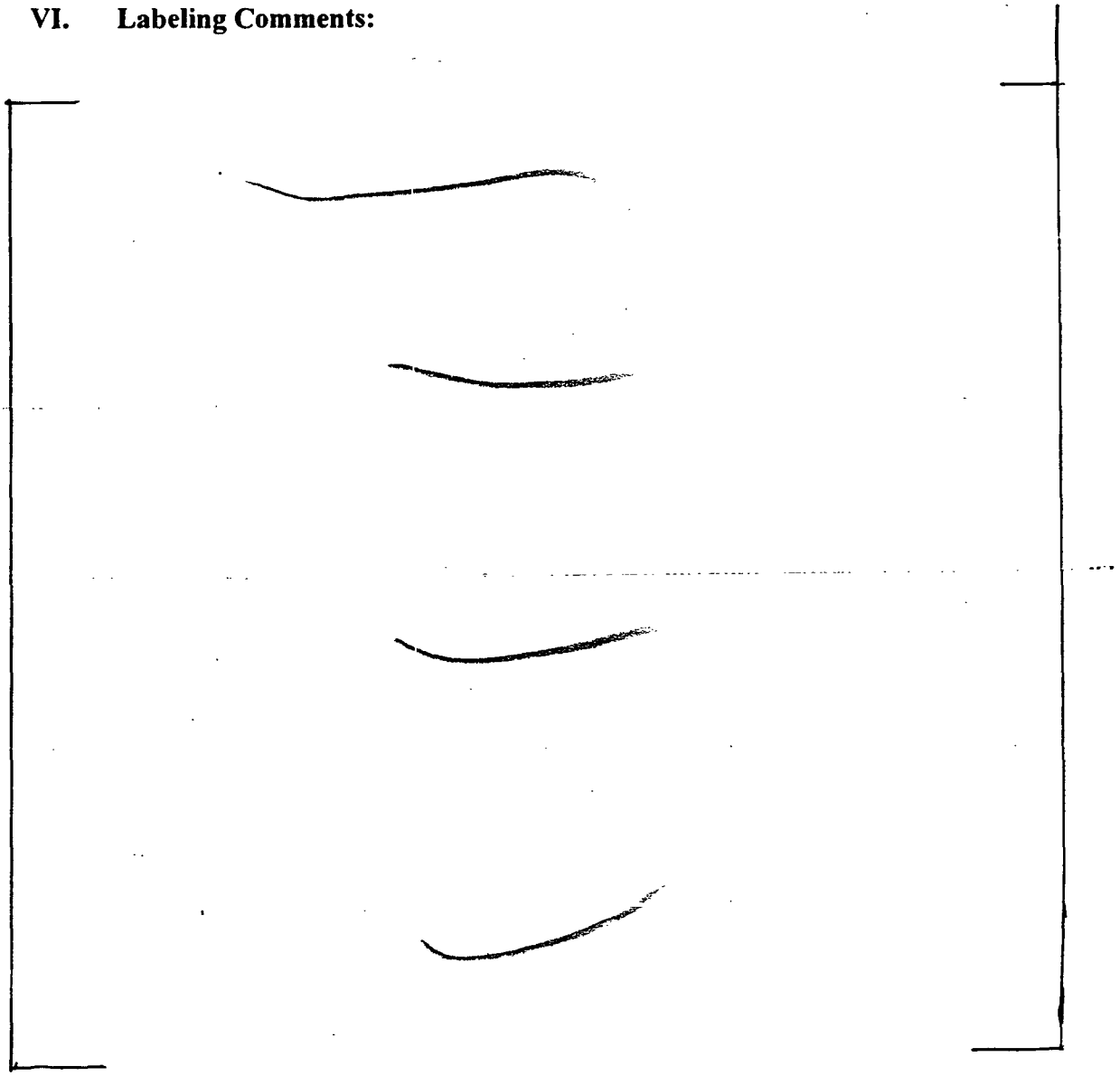
V. Overall Conclusions:

1. The plasma data from the comparative absorption study demonstrated that the levels (0.5-5.3 ng/ml) of clindamycin attained in the plasma following single and multiple topical

applications of Clindagel™ and Cleocin-T® to patients with acne vulgaris are well below the serum levels attained after an I.V.administration of an equivalent dose to patients with different kinds of infection.

2. The urinary data demonstrated that <0.04% of the total dose is excreted in the urine for both treatments following single and multiple applications of Clindagel™ and Cleocin-T® also suggesting low systemic absorption.
3. The plasma and urinary data demonstrated that systemic exposure to Clindagel™ is comparable to that of Cleocin-T® gel under clinical use conditions.
4. The in vitro permeation study was supportive of the in vivo findings in terms of the mean percent of applied dose recovered in the receptor fluid being comparable and relatively low (< 1% in 48 hours) for Clindagel ™ and Cleocin-T.
5. The Literature reference evaluating the relationship between the levels of clindamycin in the acne lesions and its clinical effectiveness is limited in its application because the reference suggested that these levels do not parallel the clinical effectiveness of clindamycin after topical administration.

VI. Labeling Comments:



[redacted]

[redacted] /S/ 11/17/00

Abimbola O. Adebowale Ph.D.
Office of Clinical Pharmacology /Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Dennis Bashaw, Pharm.D. [redacted] /S/ 11/17/00

CC:
NDA 50-782
HFD-540 (Div. File)
HFD-540 (CSO/Kumar)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Adebowale)
HFD-340 (Viswanathan)
CDR: ATTN: Barbara Murphy

APPENDIX

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Study Summary Sheet

NDA/IND#	50-782	Suppl/Amend#	Original Amendment	Submission Date:	01/27/00
Study Type	Phase 1	Study #	CGEL-005	Volume #	2.1 –2.3
Study Title	An Open-Label Randomized Study of the Comparative Absorption of Clindagel™ versus Cleocin-T® in subjects with Acne Vulgaris				

Clinical Investigator	[redacted]	Analytical Investigator	[redacted]
Study Site	[redacted]	Study Site:	[redacted]

Single Dose		Multiple Dose	X	Washout Period	None
Cross-Over		Parallel	X	Other Design:	NA
Fasted		Food Study		FDA Breakfast?	NA

If Fasted, how long, (hrs) NA

Subject Breakdown

Normal [ ] Patients [X] Young [X] Elderly [ ] Renal [ ] Hepatic [ ]

Subject Type					Clindagel								
Wt	Mean	145.98 ±49.17	Range	100-277	Group	1	N=	12	M=	6	F=	6	
Age	Mean	18.21± 4.67	Range	14-28	Group	1		12		6		6	
Subject Type					Cleocin-T								
Wt	Mean	147.46 ±46.97	Range	105-175	Group	2	N=	12	M=	6	F=	6	
Age	Mean	19.84± 7.43	Range	14-37	Group	2		12		6		6	
Subject Type					ALL								
Wt	Mean	152.08 ±39.6	Range	100-277	Group	1 & 2	N=	24	M=	12	F=	12	
Age	Mean	19.83± 6.27	Range	13-37	Group	1 & 2		24		12		12	

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Treatment Group	Dose	Dosage Form	Strength	Batch #	Batch size
Clindagel™ (DPT Laboratories)	Study personnel applied a thin layer of the study gel to the affected and unaffected areas of the subject's face, neck, shoulder's, chest and back. topically once daily in the morning for 5 days.	GEL	1% (Between 11.26g and 27.64 g was applied)	NBIU	[redacted]
Cleocin T® (Pharmacia and Upjohn)	Study personnel applied a thin layer of the study gel to the affected and unaffected areas of the subject's face, neck, shoulder's, chest and back. topically twice daily in the morning & evening for 5 days.	GEL	1% (Between 36.58g and 57.43g was applied)	Not reported	Not reported

Sampling Times

Plasma	Baseline (hour 0), 4, 6, 8, 12, 16 and 24 hours on Days 1 and 5
Urine	Baseline (hour 0), 0-12 and 12-24 hour intervals on Days 1 and 5

Assay Method	[redacted]	
Assay Sensitivity	Plasma and Urine = [redacted]	
Assay Accuracy	**Accuracy:** *Within-day:* [redacted]	
	Between-day:	
	Precision: *Within-day* [redacted]	
	Between-day	
	Linearity: [redacted]	

Results: Plasma levels ranged from [redacted]. < 0.04% of the total dose is excreted in the urine. Systemic exposure is comparable for both Clindagel™ and Cleocin-T gel, < than I.V. levels. 7 adverse events reported in 6 patients. 2 mild and drug product related, 4 mild and 1 moderate not related to drug product (review by MO).

Labeling Claims from Study

Pharmacokinetics

In one open-label, parallel, comparative absorption study, topical daily application (approximately 3-10 grams/patient/day) of CLINDAGEL™ (clindamycin phosphate topical gel, 1%) versus twice-daily application of Cleocin T® 1% gel for 5 days in 24 patients with acne vulgaris who had 25-100 inflammatory lesions and 20-100 noninflammatory lesions, concentrations of clindamycin in the blood were not significantly different between the two treatments. The mean AUC_{0-24} for Cleocin T® on day 1 was 11.77±13.91 ng/mL compared with 17.04±14.83 ng/mL for Clindagel™ (p=0.38). On day 5, the mean AUC_{0-24} for the two treatments were also similar (22.90±18.57 ng/mL for Cleocin T® and 23.82±26.45 ng/mL for Clindagel™, p=0.92). Likewise, urinary excretion of clindamycin was not significantly different between the treatments. Mean urinary excretion for both groups is summarized in the following table:

[redacted]				
1	0 to 12	4.87 ± 6.04	6.93 ± 4.95	0.39
	12 to 24	10.08 ± 12.65	9.83 ± 6.35	0.95
	0 to 24	14.95 ± 18.54	16.76 ± 8.76	0.77
5	0 to 12	9.58 ± 8.58	10.73 ± 6.66	0.72
	12 to 24	14.16 ± 12.04	13.21 ± 6.87	0.82
	0 to 24	23.72 ± 19.07	23.93 ± 12.34	0.97

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Confidential,
Commercial Information

(W)

Plasma Data Analysis for NDA 50782 (Clindagel)

Clindagel	Visit 1		Visit 5	
SUBJECT No.	*Peak concentration*	*Time of Peak Concentration*	*Peak concentration*	*Time of Peak Concentration*
Subject	(ng/ml)	(h)	(ng/ml)	(h)
1		8		4
3		8		4
7		8		12
8		8		8
10		0		16
12		6		4
14		16		8
16		12		4
17		6		8
18		16		0
22		8		8
23		8		6
Total	16.233	104	17.586	82
Mean	1.35	8.67	1.47	6.83
STD	0.84	4.38	1.28	4.22
CV%	62.12	50.50	87.60	61.72

Cleocin-T				
Subject				
2		0		4
4		16		8
5		6		16
6		12		4
9		16		8
11		12		16
13		6		16
15		16		16
19		0		6
20		24		4
21		0		0
24		16		4
Total	11.475	124	17.796	102
Mean	0.96	10.33	1.48	8.50
STD	0.92	7.85	1.16	5.92
CV%	95.87	76.01	78.28	69.60

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Study Summary Sheet

NDA/IND#	50-782	Suppl/Amend#	Original Amendment	Submission Date:	01/27/00
Study Type	Phase 1	Study #		Volume #	1.17
Study Title	In Vitro Skin Permeation of ^{14}C-Clindamycin from Topical Formulations				

Single Dose	X	Multiple Dose		Washout Period	NA
Cross-Over		Parallel	X	Other Design:	NA
Fasted		Food Study		FDA Breakfast?	NA

If Fasted, how long, (hrs) NA

Leg Skin Donor Breakdown

Normal [ ] Cadavers [X] Young [X] Elderly [ ] Renal [ ] Hepatic [ ]

Cadavers were from patients who died of Myocardial Infarction

Subject Type			Donors	3	Donor #	1	2	3
Sex M	Age Range	45-55	# of Skin Samples per donor	30		10	10	10

"Split-thickness" skin composed of the epidermis and the outermost portion of the dermis containing the papillary dermis with a thickness of ~ 0.25 – 0.75 mm was used in this study. Ten skin samples from different donors were used per formulation.

Treatment s	Dose	Dosage Form	Strength	Batch #
	(All radiolabeled with ^{14}C-Clindamycin phosphate)			
Clindagel™ (DPT Laboratories)	~ 8 mg was applied to 0.8 cm^2 (dose ~100µg/ cm^2) of exposed (donor chamber) excised human skin mounted on penetration cells in diffusion chambers with a small stainless steel rod, one end of which was flattened to obtain a circular area.	Gel	1%	GLP-004
Cleocin T® (Pharmacia and Upjohn)		Gel		43BMP
Cleocin T® (Pharmacia and Upjohn)	8 microliters was applied to 0.8 cm^2 (dose ~100µg/ cm^2) of exposed excised human skin mounted on penetration cells in diffusion chambers with a Hamilton Syringe.	Solution		122XF

Sampling Times

Receptor fluid collection	8, 24 and 48 hr

Assay Method	[redacted]
Assay validation	Not reported except that, a [redacted] curve was constructed and used to calculate DPM based on the external standard method. Background [redacted] was counted with each batch of experimental samples and, subtracted from each sample.
Receptor fluid	8, 24 and 48 hr

Data Analysis and Methods

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Results: The results indicate that the estimate of skin penetration in man for all three formulations as mean percent recovery was (23±8 for Clindagel™; 40±19 for Cleocin-T gel; and 27±13 for Cleocin-T solution). The mean percent recovery drug in the receptor fluid was (0.20±0.16 for Clindagel™; 0.20±0.12 for Cleocin-T gel; and 0.41±0.51 for Cleocin-T solution i.e. ≤ 0.5% of the applied dose at 48hours for all three formulations (see attached Appendix, page 7). Applicant stated that ANOVA demonstrated that these values were not statistically significant (ANOVA results not submitted).

Conclusions: Data demonstrated that penetration of clindamycin, as measured by the appearance of radiolabel in skin and receptor fluid was comparable for the test formulation (Clindagel™) and the control formulations (Cleocin-T gel and Cleocin-T solution). In vitro findings do not correlate with in vivo findings, interpret cautiously.

Labeling Claims from Study: None

Table 4. Distribution of radioactivity (mean ± S.D. of percent of applied dose) after topical application of ^{14}C-Clindamycin in Cleocin-T Gel, Cleocin-T Solution and Clindagel[4].

Formulation	Total Receptor Fluid	Skin Digest	Receptor Fluid and Skin Digest	Skin Wipes and Tape Strips	Donor Cell Rinse	Total Recovery	N
Cleocin-T Gel	0.20±0.12[a]	40 ± 19[b]	40 ± 19[c]	47 ± 20	8.0 ± 2.8	95 ± 2	8
Cleocin-T Solution	0.41±0.51[a]	26 ± 13[b]	27 ± 13[c]	67 ± 16	7.1 ± 7.2	101± 6	10
Clindagel	0.20±0.16[a]	23 ± 8[b]	23 ± 8[c]	64 ± 12	6.2 ± 2.3	93 ± 6	8

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[4]Table excludes Cleocin-T Gel replicates 1 and 4 and Clindagel replicates 1 and 5 because these cells had receptor fluid values more than 2 standard deviations higher than the mean values for the remaining replicates. Values having the same superscript letter were not significantly different (ANOVA, $p = 0.05$).