CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-782

PHARMACOLOGY REVIEW(S)

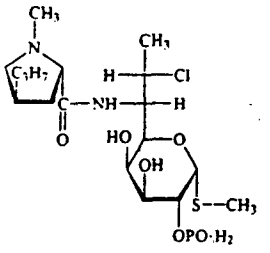
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: carcinogenicity, photococarcinogenicity
Reviewer Name: Paul C. Brown
Division Name: Division of Dermatologic and Dental Drug Products
HFD#540
Review Completion Date: June 21, 2000
Review number: 1
NDA number: 50-782
Serial number/date/type of submission: 000 / 27 January 2000 / original
Sponsor (or agent): Clindagel, LLC (Agent: Target Research Associates)
Manufacturer for drug substance: [redacted]

Drug:

Generic Name: clindamycin phosphate, USP
Chemical Name: [redacted]

CAS Registry Number: 24729-96-2
Molecular Formula/ Molecular Weight: $C_{18}H_{34}ClN_2O_8PS$, [redacted]
Structure:



Drug Class: antibacterial

Indication: acne vulgaris

Relevant INDs/NDAs/DMFs: IND-56,487

Clinical formulation:

Ingredient	% w/w
Clindamycin phosphate, USP	
Methylparaben, NF	
Carbomer 941, NF	
Propylene Glycol, USP	
Polyethylene Glycol 400, NF	
Sodium Hydroxide, NF	
Purified Water, USP	

Route of administration: topical to the skin

Proposed clinical use: For the once daily treatment of acne vulgaris.

Previous clinical experience:
Clindamycin phosphate is marketed in a variety of topical formulations for acne vulgaris at the same concentration used in Clindagel. Clindagel has been studied in one human clinical study in which 334 patients were administered the complete drug at least once a day for up to 12 weeks.

Introduction and drug history:
The sponsor has submitted this NDA under section 505(b)(2) of the FD&C Act and is referring to the approved NDA for Cleocin T gel (clindamycin phosphate, 1%) as evidence of the safety for this drug (NDA 50-615).

Studies reviewed within this submission:
The sponsor has submitted two studies not previously reviewed: a dermal carcinogenicity study and a photococarcinogenicity study. These studies were not conducted with Clindagel but were conducted with a 1% clindamycin phosphate gel formulation with composition similar to Clindagel. The sponsor did not conduct these studies but has received permission to use them.

Studies not reviewed within this submission:
These studies were previously submitted and reviewed in SN 000 of IND 56,487.
1. Primary Dermal Irritation in Rabbits (Study 0420XC52.002)
2. Primary Eye Irritation (Study 0421XC52.002)
3. Delayed Contact Hypersensitivity in Guinea Pigs (Study 0424XC52.002)

PHARMACOLOGY:
Summary of pharmacology:
Clindamycin binds to the 50S subunit of bacterial ribosomes and thereby interferes with bacterial protein synthesis. Clindamycin is primarily bacteriostatic. Clindamycin is active against gram positive cocci and most anaerobic gram negative organisms. Its activity against the anaerobe *Propionibacterium acnes* may account for its effectiveness in the treatment of acne vulgaris.

PHARMACOKINETICS/TOXICOKINETICS:
Summary:
Studies in rats and dogs show that clindamycin is readily absorbed from the gastrointestinal tract and is excreted in the urine and feces. In rat, the products excreted in the urine were 53% unchanged clindamycin, 31% clindamycin sulfoxide and 15% N-demethyl clindamycin. In dog, the products excreted in the urine were 36% unchanged clindamycin, 28% clindamycin sulfoxide, 28% clindamycin glucuronide and 9% N-demethyl clindamycin. Topical application in the rat and pig show that clindamycin can be retained in the skin and is released into the blood for several days after drug application.

Absorption of clindamycin from topical formulations has been measured in humans and ranges from undetectable up to approximately 7.5% of the applied clindamycin. In humans approximately 10% of clindamycin administered is excreted unchanged in the urine. Clindamycin is metabolized in humans to N-demethyl clindamycin and clindamycin sulfoxide, which are excreted in the urine and bile.

TOXICOLOGY:

Summary:

The toxicity of clindamycin has been investigated in a variety of studies. A summary of these studies and reprints of some published studies have been provided by the sponsor.

The most pronounced toxicity associated with clindamycin has been pseudomembranous colitis. While the rat and dog do not demonstrate this toxicity, it has been observed in hamsters, rabbits and humans. In the hamster, all animals given 40, 10 or 1 mg/kg topically for two weeks died from colitis. Four of seven animals given 0.1 mg/kg also died. A discussion of the potential for this toxicity is currently included in the Warnings section of the proposed label for Clindagel.

Long term studies in rats and dogs have been conducted with clindamycin hydrochloride and clindamycin palmitate hydrochloride. The maximum tolerated dose of clindamycin hydrochloride in a one year rat study was between 300 and 600 mg/kg. No specific morphologic alteration attributed to treatment with clindamycin hydrochloride was identified. Clindamycin palmitate hydrochloride doses of 100, 300 and 600 mg/kg were well tolerated by rats in a six month study.

Dogs given 30 and 100 mg/kg of clindamycin hydrochloride appeared healthy during a one year study but dogs receiving 600 mg/kg were clinically sick. Dogs in all three groups had elevated serum glutamic-pyruvic transaminase levels. Dogs receiving 600 mg/kg had bile stained ulcers of the gall bladder upon necropsy. Clindamycin palmitate hydrochloride doses of 30, 100 and 300 mg/kg were well tolerated by dogs in a six month study.

CARCINOGENICITY:

Study Title: **Dermal Carcinogenicity Study of an Admixture Active Gel (Clindaben – Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and its Components in Mice**

Study Number: Report No. 11484

Volume Numbers: 1-6

Test Facility: [redacted]

Study Date(s): 15 June 1993 to 4 July 1995

GLP Compliance: Yes

QA Report: Yes

Study Type: 2-year bioassay

Species/strain: mouse / CD-1

Number of animals per group: 60/sex
Age at start of study: approximately 6 weeks old at start of study
Animal housing: individual polypropylene cages
Drug Purity / Stability / Homogeneity: Samples of each formulation were taken at the beginning of the study and at week 13, 26, 52, 77 and 103. Analysis for active ingredients showed that the formulations contained the expected concentrations through out the study.

Formulations:

	% w/w			
Ingredient	Placebo Gel	Benzoyl peroxide 5% gel	Clindamycin phosphate 1% gel	Admixture active gel
Clindamycin phosphate				
Benzoyl peroxide				
Methylparaben, NF				
Propylparaben, NF				
Propylene Glycol, USP				
Carbomer 934P, NF				
Potassium Hydroxide				
Purified water, USP				

Methods:

Dosage groups:

Group	Test Article	Applied amount of test article (ml/kg)	Dose active ingredient (mg/kg)	
			Benzoyl Peroxide	Clindamycin Phosphate
1	Placebo gel	15.0	0	0
2	Placebo gel	15.0	0	0
3	Mixture gel	0.90	45	9
4	Mixture gel	2.70	135	27
5	Mixture gel	15.0	750	150
6	5% BP gel	2.70	135	0
7	5% BP gel	15.0	750	0
8	1% CP gel	2.70	0	27
9	1% CP gel	15.0	0	150

Note: Since Clindagel contains only clindamycin phosphate and not benzoyl peroxide, this review will primarily focus on the data from the control and clindamycin phosphate groups.

- Basis of Dose Selection: The sponsor states that the doses were selected to provide a maximum dose, which would not be expected to produce overt nephrotoxicity or more than a 10% body weight loss. The dose levels also take in to account the maximum practical dose volume to be applied to the mouse. For a mouse weighing 40g a dose of 15 ml/kg would require application of 0.6 ml to the approximately 5 cm^2 area used in this study.
- Relation to Clinical Use: The clinical use of Clindagel is proposed to be single daily application topically to the skin.
- CAC Concurrence: There is no record of CAC concurrence on the protocol.
- Route of Administration: Test article was applied topically to the backs of mice from which the hair is removed by clipping once weekly. The area

treated was approximately 5 cm^2, which represents approximately 10% of the total body surface area. No attempt was made to prevent ingestion of the test articles and the material was not removed at the end of the day. Occlusion was not used.

- Frequency of Drug Administration: Drug was applied once daily for 103 weeks to females and 104 weeks to males.
- Dual Controls Employed: Two groups containing 60 animals per sex each were administered the placebo gel.
- Unscheduled Sacrifices or Deaths: All animals found dead or sacrificed *in extremis* were subject to gross necropsy and histology.
- Deviations from Original Study Protocol: none noted

Study Results and Frequency of Monitoring:

- Clinical Observations: All animals were examined for reaction to the treatment daily. A detailed clinical examination was conducted on each animal weekly. Palpable mass examination was conducted weekly.

  Most clinical observations for animals treated with clindamycin phosphate gel were similar to control animals. Females treated with clindamycin phosphate had slightly increased incidences of skin texture changes, either increased or decreased elasticity, at the treatment site compared to control animals.

  There were no notable differences between the groups in either sex in the incidence of externally palpable masses.

- Mortality: Mortality and morbidity was checked twice per day. The reports states that females were terminated during week 103 due to low survival. The males were sacrificed at week 105.

  The number of decedents in the placebo and clindamycin treated groups are listed in the table below.

Sex	Group/dose level (mg/kg/day)			
	Placebo gel		Clindamycin phosphate 1% gel	
	Group 1 (0 mg/kg/day)	Group 2 (0 mg/kg/day)	Group 8 (27 mg/kg/day)	Group 9 (150 mg/kg/day)
Males	20/60	27/60	19/60	28/60
Females	33/60	39/60	30/60	32/60

In the report from [redacted], the table of decedents does not match the Kaplan-Meier survival curves or the individual animal data. The sponsor has provided the table of decedents above, which does appear to match the Kaplan-Meier survival curves and the individual animal data.

The report from [redacted] states that there were no statistically significant different increases in mortality between the control groups and the groups receiving the clindamycin phosphate 1% gel. The report does not make clear

which set of numbers were used in the statistical comparison. Nevertheless, it is clear that in the females the survival in clindamycin treated animals was at least as high as control and the survival in males treated with clindamycin is almost identical to control males.

- Body Weight: Body weight was obtained for each animal weekly during the first 14 weeks and then every two weeks thereafter.

  Body weight gains through out the study were similar in placebo and Clindamycin phosphate treated animals. Group mean body weights at the end of the study were not statistically significantly different.

- Food Consumption: Food consumption was measured for each animal weekly during the first 14 weeks and then once every four weeks thereafter.

  Both sexes receiving 15 ml/kg/day 1% clindamycin phosphate gel showed slightly increased food consumption compared to the animals treated with placebo gel.

- Organ Weights: Organs weighed are indicated in the table included as an appendix below.

  No statistically significant differences in organ weights were noted when comparing animals treated with the 1% clindamycin phosphate gel with the animals treated with the placebo gel.

- Gross Pathology: A gross necropsy was conducted on all animals whether they died early, were sacrificed early or were sacrificed as scheduled.

  There were no notable necropsy findings that were attributable to treatment with the 1% clindamycin phosphate gel.

- Histopathology: Histopathology was conducted for all groups on the tissues listed in the table in the appendix below.
  - Non-Tumor:
    Focal hyperplasia of the pituitary was noted in males in all groups.

    The incidence of epithelial hyperplasia at the treatment site was mildly increased in the animals receiving 15 ml/kg/day of the 1% clindamycin phosphate gel. This increased incidence was statistically greater than the placebo control incidence for females only. The severity of the hyperplasia was also increased in females. In females treated with 15 ml/kg/day of the 1% clindamycin phosphate gel, the increased incidence of epithelial hyperplasia extended to the skin adjacent to the treatment site.

Abscess in the ovaries were observed in the groups treated with the 1% clindamycin phosphate gel with an incidence of 3/60 and 6/60 in groups 8 and 9, respectively. The increase in abscess in the ovaries in group 9 was statistically significantly greater than control.

- Tumor:
  Carcinomas of the parotid salivary gland were noted in one male that received 2.7 ml/kg/day of the 1% clindamycin phosphate gel and one male that received 15 ml/kg/day of the 1% clindamycin phosphate gel. A carcinoma of the parotid salivary gland was also recorded in one female that received 15 ml/kg/day of the 5% benzoyl peroxide gel.

  Adenomas of the rete testis were observed in one male that received 2.7 ml/kg of the 1% clindamycin phosphate gel and in 2 males that received 2.7 ml/kg of the 1% clindamycin phosphate/ 5% benzoyl peroxide mixture gel. Testicular interstitial cell adenomas were noted in all control and clindamycin phosphate treated groups.

  A number of other tumors were noted in various tissues but these were generally of similar incidence in control and treated groups and were also generally similar to historical control values.

  A summary table of all neoplastic findings is included as an appendix below. Copies of the sections of the sponsor's table of histopathological findings that contain information on the treatment site, skin, salivary gland and testes are also attached as appendices to this section.

- Toxicokinetics:
  Toxicokinetic analysis was not performed in this study. The increased hyperkeratosis and epithelial hyperplasia noted at the treatment site in both sexes suggest that the high dose may have been an MTD. Increased intestinal stasis in males, intestinal dilation in males and females and ovarian abscesses in females suggest that the clindamycin phosphate doses were also sufficient to cause systemic effects although some of this exposure may have occurred from ingestion of the test article.

Overall Interpretation and Evaluation:

- Adequacy of the carcinogenicity studies and appropriateness of the test model:
  The basis of the dose selection is described above. The sponsor was previously asked whether dose response studies were conducted and whether the dose selection was discussed with the FDA. The sponsor has responded that they could not confirm whether dose-range finding studies were conducted since the dermal carcinogenicity study was conducted by another sponsor. They were also unaware whether the dose selection was discussed with the FDA. The study appears to have achieved a dermal MTD based on the elevated hyperkeratosis and epithelial hyperplasia noted at the treatment site in both males and females in the high dose

group. Survival and weight gain were similar between treated and control groups. Systemic exposure is suggested by increased intestinal stasis in males and increased dilation in various segments of the gastrointestinal tract in both males and females in the high dose groups; however, some of this exposure could be due to ingestion of test compound. The sponsor notes that the two dose levels administered in the study are 160 and 900 times higher than the anticipated human dose on a mg/kg basis. This assumes human use of 1 ml of the gel per day. Actual maximum human use might be closer to 5 ml per day. The doses used in the mouse dermal carcinogenicity study are approximately 3 and 15 fold higher than the maximum human dose assuming complete absorption on a mg/m^2 basis. (see appendix for calculations). The formulation used in the study contained the same concentration of clindamycin phosphate (1%) as the clinical formulation and is adequate for the evaluation of local skin effects.

- Evaluation of Tumor Findings:

The occurrence of three tumors of the salivary gland in this study is noteworthy since these tumors are uncommon. The report states that [redacted] quotes a spontaneous incidence of 2/478 salivary gland tumors in female CD-1 mice between 21 and 24 months old and 0/480 in males of the same age. A database from [redacted] entitled Spontaneous Neoplastic Lesions in the [redacted] BR Mouse does not list any neoplastic lesions observed in 2577 salivary glands examined from male mice in 46 different studies [redacted]). However, the salivary gland tumors observed in the current study can not specifically be considered an effect of clindamycin phosphate since one of the tumors occurred in an animal receiving 5% benzoyl peroxide alone. As noted above, no attempt was made to prevent ingestion of the test articles. According to published reports, salivary gland inflammation has been observed in rats treated orally with clindamycin hydrochloride and nuclear atypia of salivary gland cells has been described in rats receiving clindamycin palmitate hydrochloride in the diet. These effects have been ascribed to opportunistic infections of the salivary gland. In particular, this type of lesion has been attributed to coronavirus infections in rodents. It may be possible that the effects observed in the current study are due to the ingestion of clindamycin and benzoyl peroxide with subsequent alterations of the bacterial flora of the mouth leading to opportunistic infections. This mechanism would not be relevant to human topical use of clindamycin phosphate.

In general, it appears that tumors of the testes are not uncommon in mice from control groups of two year bioassays although, the historical database mentioned above from [redacted] does not specifically list tumors of the rete testis. The study report notes that the incidence of the adenomas of the rete testis did not show any dose-response relationship to either test material. McConnell et al. (JNCI, 76:283, 1986) suggest that stromal neoplasms of the testes may be combined. If the interstitial cell and rete testis adenomas are combined then the incidence in the two control groups and the 2.7 and 15 ml/kg clindamycin phosphate groups are 2, 3, 4 and 2, respectively. Therefore, the occurrence of stromal

neoplasms of the testes does not appear to be associated with clindamycin phosphate exposure. Focal hyperplasia of the interstitial cells of the testes and the rete testis was noted in both control groups and in the animals receiving 2.7 ml/kg of the 1% clindamycin phosphate gel but not in animals receiving 15-ml/kg. This further suggests that the testicular effects are not associated with clindamycin phosphate.

Summary Conclusions and Recommendations:

- Acceptability of Study(s) or Overall Testing Approach:
  The study is acceptable as an evaluation of the carcinogenicity of clindamycin phosphate by the dermal route for the drug product under review. The study used a closely related formulation and the same concentration of clindamycin phosphate as the product under review. The doses used in the study appear to have achieved an MTD based on dermal criteria. The doses are approximately 3 and 15 fold higher than the anticipated maximum human exposure assuming complete absorption based on a mg/m^2 comparison and appear to be the maximum feasible amount of material that could be applied. (See calculations attached at end of review.)

- Major Tumor Findings:
  Carcinomas of the salivary gland were observed in one male each treated with 2.7 or 15 ml/kg/day of the clindamycin phosphate 1% gel. This study does not, however, establish a clear association between these tumors and clindamycin phosphate treatment. Furthermore, it is not clear that these tumors would be relevant to the topical use of clindamycin phosphate in humans.

- Non-neoplastic Findings:
  Epithelial hyperplasia was noted in clindamycin treated mouse skin in this study. This did not appear to contribute to the development of skin tumors in any of the treated mice.

  Ovarian abscesses appear to be associated with clindamycin treatment in this study. The report suggests that these may be due to clindamycin altering the normal dermal/vaginal bacterial flora thereby predisposing animals to infections from the overgrowth of opportunistic bacteria.

Addenda:

- CAC Report: The executive carcinogenicity assessment committee met on June 6, 2000 and discussed the results of the study described above. The committee concluded that the study was adequate for the evaluation of topical clindamycin phosphate. The occurrence of the salivary tumors was not considered a relevant finding based on the small incidence, the occurrence of a salivary gland tumor in a benzoyl peroxide treated animal and the lack of relevance to human use of a topical product. The committee recommended that the study be described in the label as showing no

significant increase in tumors. (See also a copy of the minutes of the meeting attached at the end of this review.)

Addenda continued on next page

Summary Table of Incidence of Neoplastic Findings: Males and Females, In Survivors at Termination and Premature Decedent Animals, Control and Clindamycin Phosphate 1% gel

	Incidence of lesions							
	Males				Females			
Findings	Grp 1 0 mg/kg	Grp 2 0 mg/kg	Grp 8 27 mg/kg	Grp 9 150 mg/kg	Grp 1 0 mg/kg	Grp 2 0 mg/kg	Grp 8 27 mg/kg	Grp 9 150 mg/kg
Abdomen								
Sarcoma [M]								1
Adrenals								
Cortical adenoma [B]	1							
Phaeochromocytoma [M]				1				
Phaeochromocytoma [B]	1							
Bone								
Osteosarcoma [M]						1		
Osteoma [B]				1	1			
Cervix								
Stromal sarcoma [M]						1		
Polyp [B]					1			
Duodenum								
Adenocarcinoma [M]			1					
Harderian Gland								
Adenoma [B]	1		1	2				
Head								
Fibroma [B]				1				
Jejunum								
Adenocarcinoma [M]			1					
Kidney								
Hemangiosarcoma [M]	1							
Bilateral Tubular Adenoma [B]		1						
Unilateral Tubular Adenoma [B]			2	1				
Liver								
Hepatocellular carcinoma multiple [M]	1			1				
Hepatocellular carcinoma [M]	1	6	2	5				
Hepatocellular adenoma multiple [B]	2	1	1					
Hepatocellular adenoma [B]	10	4	7	5	2	2	1	
Hemangiosarcoma multiple [M]			1		1			
Hemangiosarcoma [M]	1					2		1
Hemangioma [B]	1							
(Associated) Hepatocellular Adenoma Multiple [B]				1				
(Associated) Hepatocellular Adenoma [B]		1	1					

Incidence of Neoplastic Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals
Control and Clindamycin Phosphate 1% gel
(Continued)

Findings	Males				Females			
	Grp 1 0 mg/kg	Grp 2 0 mg/kg	Grp 8 27 mg/kg	Grp 9 150 mg/kg	Grp 1 0 mg/kg	Grp 2 0 mg/kg	Grp 8 27 mg/kg	Grp 9 150 mg/kg
Lung								
Alveolar/Bronchiolar Carcinoma Multiple [M]	1		2	2				
Alveolar/Bronchiolar Carcinoma [M]	5	5	6	7	3	3	2	5
Alveolar/Bronchiolar Adenoma Multiple [B]	4	1	2	3	1	1	1	
Alveolar/Bronchiolar Adenoma [B]	12	6	4	5	5	7	5	1
(Associated) Alveolar/Bronchiolar Adenoma Multiple [B]	1		1					
(Associated) Alveolar/Bronchiolar Adenoma [B]	1	1	4	1				
Lymphoreticular/Hemopoietic								
Histiocytic Sarcoma [M]	1	3	1		7	2	6	6
Lymphoma [M]	5	3	4	5	15	10	11	8
Leukemia [M]				1				
Mammary gland								
Adenoma [B]							1	
Carcinoma [M]					2	2	2	
Ovaries								
Unilateral Granulosa/Thecal Cell Tumor [M]						1		1
Unilateral Granulosa/Thecal Cell Tumor [B]					1			
Unilateral Tubular Adenoma [B]						1		
Cystadenoma (TA) [B]					1	2	1	
Pancreas								
Islet Adenoma [B]		1					2	1
Pituitary								
Metastasizing Carcinoma [M]							1	
Intermediate Lobe Adenoma [B]		1						
Adenoma [B]	1	1		1	2	1		1
Salivary Gland								
Carcinoma [M]			1	1				
Seminal Vesicles								
Unilateral Adenoma [B]			1					
Skeletal Muscle								
Metastasizing Hemangiosarcoma [M]		1						

Incidence of Neoplastic Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals
Control and Clindamycin Phosphate 1% gel
(Continued)

	Males				Females			
Findings	Grp 1 0 mg/kg	Grp 2 0 mg/kg	Grp 8 27 mg/kg	Grp 9 150 mg/kg	Grp 1 0 mg/kg	Grp 2 0 mg/kg	Grp 8 27 mg/kg	Grp 9 150 mg/kg
Skin								
Squamous Cell Carcinoma [M]				1				
Fibrosarcoma [M]			1		1		1	1
Fibrosarcoma Multiple [M]								1
Sarcoma [M]	1	1			1	1		
Fibrous Histiocytoma [M]			1					
Basal Cell Tumor [B]				1				
Spleen								
Metastasizing Hemangiosarcoma [M]							1	
Hemangiosarcoma [M]		1						
Testes								
Bilateral Interstitial Cell Adenoma [B]		1						
Unilateral Interstitial Cell Adenoma [B]	2	2	3	2				
Unilateral ReteTestis Adenoma [B]			1					
Thyroid								
Unilateral Follicular Adenoma [B]			1					
Urinary Bladder								
Sarcoma [M]					1			
Uterus								
Leiomyosarcoma [M]					1			
Leiomyoma [B]					1	1	1	
Adenocarcinoma [M]					1			
Stromal Sarcoma [M]					1	1		
Hemangiosarcoma [M]							1	
Polyp Multiple [B]								1
Polyp [B]					5	7	3	4
Vagina								
Polyp [B]						2		
Hemangiomas and Hemangiosarcomas combined from all tissues	3	2	1		1	2	2	1

- Selected Sections of the Sponsor's Incidence of Histopathology Findings:

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
BONE:			(1)		(1)	(2)	(1)		
No abnormality detected						1			
OSTEOSARCOMA [M]							1		
OSTEOMA [B]					1	1			
Localised hyperostosis			1						
BRAIN:		(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
No abnormality detected		60	60	59	60	58	58	58	59
Infiltration by lymphoma cells							1		
Metastasis from primary in pituitary								1	
Arteritis				1					
Meningeal lymphocytic infiltration						1			
Focal haemorrhage(s)						1	1		
Diffuse vacuolation							1	1	1
CAECUM:		(57)	(58)	(58)	(59)	(59)	(60)	(57)	(58)
No abnormality detected		31	38	36	37	43	46	38	40
Infiltration by lymphoma cells		1	1			3	2	2	1
Worm(s)		23	16	13	11	7	9	10	6
Dilatation		2	1	3	9	2	2	3	7
Submucosal oedema		2	1	2		5		3	4
Enlarged Peyer's patches				1					

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
CAECUM:		(57)	(58)	(58)	(59)	(59)	(60)	(57)	(58)
Arteritis					1				
Mucosal lymphocytic infiltration				1				1	
Goblet-cell hypertrophy						1			
Inflammation, mucosal/submucosal			2	2					1
Mucosal erosion(s)		1							
Mucosal necrosis					1	1	1		
Glandular atrophy							1		
Localised glandular hyperplasia									1
Amyloid			2	1	1	1			
CERVICAL LYMPH NODE:					(1)				(1)
Infiltration by lymphoma cells					1				1
CERVIX:						(4)	(3)		(2)
STROMAL SARCOMA [M]							1		
POLYP [B]						1			
Inflammation by histiocytic sarcoma cells							1		
Cystic glands						2			
Increased collagen									1
Stromal hyperplasia						1	1		

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
CERVIX:						(4)	(3)		(2)
Abscess(es)									1
COAGULATING GLANDS:			(1)						
Dilatation			1						
COLON:		(59)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
No abnormality detected		57	57	58	49	55	54	57	53
Infiltration by lymphoma cells					1	1	1		1
Worm(s)		2	1		2	3	1	1	2
Congestion					1				
Dilatation			1	2	8	1	2	1	4
Submucosal oedema			1					1	
Inflammation								1	1
Glandular hyperplasia					1		2		
Glandular atrophy							1		
DIAPHRAGM:				(1)					
Metastasis from primary in lung				1					

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
DUODENUM:		(59)	(53)	(58)	(60)	(59)	(60)	(59)	(60)
No abnormality detected		54	46	55	55	50	57	47	58
ADENOCARCINOMA [M]				1					
Infiltration by lymphoma cells		1		1		3		1	
Dilatation					1		1	1	
Amyloid		3	6	1	1	4	1	4	2
Fibrinoid necrosis of small arterioles						1		1	
Submucosal oedema			1						
Mucosal lymphocytic infiltration						1	1	1	
Mucosal inflammation					1				
Villous erosion(s)					1	1			
Focal mucosal necrosis				1					
Glandular hyperplasia					1	3		6	
Infiltration by histiocytic sarcoma cells		1							
EYES:		(59)	(59)	(58)	(60)	(59)	(60)	(60)	(60)
No abnormality detected		56	58	56	56	56	58	59	59
Infiltration by lymphoma cells			1			1		1	
Metastasis from primary in lung				1					
Only one examined			1	2	3	2		1	5
Arteritis						1	1		
Retro-orbital haemorrhage(s)		1							

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
HEART:		(60)	(60)	(60)	(60)	(59)	(60)	(60)	(60)
Total incidence for score expanded finding		25	20	15	25	13	15	12	17
Amyloid		2	1	1	2	2	1	1	1
ILEUM:		(56)	(59)	(58)	(57)	(59)	(59)	(58)	(59)
No abnormality detected		44	47	42	43	50	43	39	44
Worm(s)				1					
Dilatation				2	4	1	2	1	6
Diverticulum								1	
Lymphangiectasis								1	
Serosal inflammation								1	
Submucosal oedema			1						
Mucosal oedema								1	
Mucosal lymphocytic infiltration				1					
Mucosal inflammation					1				
Localised glandular hyperplasia					1				
Amyloid		12	11	13	10	8	14	14	11
INJECTION/TREATMENT SITE(S):		(60)	(60)	(60)	(60)	(60)	(60)	(59)	(60)
No abnormality detected		55	52	54	43	54	56	51	28
Infiltration by lymphoma cells						1	2		

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
INJECTION/TREATMENT SITE(S):		(60)	(60)	(60)	(60)	(60)	(60)	(59)	(60)
Follicular atrophy			1						
Hyperkeratosis									
very mild		1			3		1	2	3
Total incidence for score expanded finding		1			3		1	2	3
Epithelial hyperplasia									
very mild		3	7	5	13	5	1	5	28
mild					1				2
Total incidence for score expanded finding		3	7	5	14	5	1	5	30
Localised subcutaneous inflammation								1	
Dermal lymphocytic infiltration				1					
Inflammatory cell infiltrate							1		
Dermatitis									
very mild		1					1		
Total incidence for score expanded finding		1					1		
Diffuse necrosis							1		
INTESTINES:		(1)	(3)	(2)	(6)	(2)	(3)	(3)	
No abnormality detected						1	1		
Intestinal stasis		1	1	1	6		2	1	

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
INTESTINES:		(1)	(3)	(2)	(6)	(2)	(3)	(3)	
Amyloid			1	1		1		1	
JEJUNUM:		(59)	(55)	(59)	(59)	(57)	(60)	(59)	(59)
No abnormality detected		55	48	53	51	53	56	52	51
ADENOCARCINOMA [M]				1					
Infiltration by lymphoma cells		1		1			1		
Infiltration by histiocytic sarcoma cells		1							
Dilatation				1	3		1	2	1
Cystic glands		1							
Submucosal oedema			1						
Mucosal inflammation					1				
Amyloid		2	6	3	4	4	2	5	7
KIDNEYS:		(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
No abnormality detected		13	15	17	20	17	21	16	20
Unilateral HAEMANGIOSARCOMA [M]		1							
Bilateral TUBULAR ADENOMA [B]			1						
Unilateral TUBULAR ADENOMA [B]				2	1				
Infiltration by lymphoma cells		4	3	3	3	10	8	8	5
Infiltration by leukaemic cells					1				

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
PITUITARY:		(54)	(53)	(55)	(57)	(60)	(60)	(59)	(59)
Focal hyperplasia									
	mild	2	1	4	1				
	moderate				2			1	
	severe	1	1				1	1	
Total incidence for score expended finding		6	2	5	4		1	2	
Intermediate lobe cystoid degeneration					1				
PROSTATE:		(59)	(60)	(59)	(59)				
No abnormality detected		56	53	58	56				
Infiltration by lymphoma cells		1	2	1	1				
Arteritis					1				
Acinar dilatation			2						
Inflammation		3	3		1				
RECTUM:		(59)	(59)	(60)	(59)	(59)	(60)	(60)	(60)
No abnormality detected		54	55	56	49	56	53	55	57
Infiltration by lymphoma cells			1						
Dilatation		2	1	1	9	1	2	2	1
Worm(s)		3		2	1			1	
Submucosal oedema						2		2	2

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
RECTUM:		(59)	(59)	(60)	(59)	(59)	(60)	(60)	(60)
Mucosal oedema						1			
Inflammation			2	2	1		2		
Glandular hyperplasia			1		2		3		
Glandular atrophy							1		
REPRODUCTIVE SYSTEM:		(1)	(2)	(2)					
PENIS: congestion			1						
PENIS: inflammation		1	1	2					
SALIVARY GLAND:		(60)	(60)	(60)	(60)	(60)	(60)	(60)	(59)
No abnormality detected		56	54	53	51	44	48	51	52
CARCINOMA [M]				1	1				
Infiltration by lymphoma cells		2	2	2	2	7	6	4	4
Periductal lymphocytic infiltration		4	4	4	5	8	6	3	3
Arteritis					1	1		1	
Atrophy								1	
Amyloid						1			
SCIATIC NERVE:		(59)	(60)	(58)	(58)	(60)	(60)	(60)	(60)
No abnormality detected		53	55	54	49	52	47	57	52

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
SKELETAL MUSCLE:		(60)	(60)	(60)	(60)	(59)	(60)	(60)	(60)
Myositis			1					1	
SKIN/SUBCUTIS:		(60)	(60)	(60)	(60)	(60)	(60)	(59)	(60)
No abnormality detected		55	53	50	53	50	53	48	48
SQUAMOUS-CELL CARCINOMA [M]					1				
FIBROSARCOMA [M]				1		1		1	1
FIBROSARCOMA MULTIPLE [M]									1
SARCOMA [M]		1	1			1	1		
FIBROUS HISTIOCYTOMA [M]				1					
Infiltration by lymphoma cells		1	1			3	2	1	
Infiltration by histiocytic sarcoma cells									1
[illegible] from primary in lung				1					
Subcutaneous oedema						1		1	
Localised follicular atrophy				1					1
Dermal cyst(s)		1					1		
Haematoma			1						
Epithelial hyperplasia									
very mild		2	3	2	3	1	1	5	10
mild						1			
moderate								1	
severe				1					

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
SKIN/SUBCUTIS:		(60)	(60)	(60)	(60)	(60)	(60)	(59)	(60)
Total incidence for score expanded finding		2	3	3	3	2	1	6	10
Dermal lipid deposition						1			
Hyperkeratosis									
	very mild			2			1	2	
	mild			1					
Total incidence for score expanded finding				3			1	2	
Dermatitis									
	very mild		1						
	mild				1				
	moderate			2	1	1	2		
	very severe	1							
Total incidence for score expanded finding		1	1	2	2	1	2		
Localised subcutaneous necrosis							1		
Abscess(es)								1	
BASAL CELL TUMOUR [B]					1				
SPINAL CORD:		(59)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
No abnormality detected		59	59	57	59	60	56	58	56
Infiltration by lymphoma cells							1		

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
TESTES:		(60)	(60)	(60)	(60)				
No abnormality detected		12	20	17	19				
Bilateral INTERSTITIAL-CELL ADENOMA [B]			1						
Unilateral INTERSTITIAL-CELL ADENOMA [B]		2	2	3	2				
Unilateral rete testis ADENOMA [B]				1					
Infiltration by lymphoma cells		2	2	2	1				
Infiltration by histiocytic sarcoma cells		1							
Metastasis from primary in lung in the epididymis				1					
Only one examined				1					
Arteritis			1	1					
Spermatocoele(s)			2		1				
Unilateral haematoma				1					
Tubular atrophy		43	36	40	40				
Focal interstitial cell hyperplasia									
	mild	1	1	1					
	severe			1					
Total incidence for score expanded finding		1	1	2					
Rete testis hyperplasia									
	very mild		1	1					
	mild	2							
Total incidence for score expanded finding		2	1	1					

Figures in brackets represent the number of animals from which this tissue was examined histologically.

TABLE 44 (continued)

Incidence of Histological Findings: Males and Females
In Survivors at Termination and Premature Decedent Animals Combined - Clindamycin phosphate 1% Gel

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day	Grp 1 0 ml/kg /day	Grp 2 0 ml/kg /day	Grp 8 2.7 ml/kg /day	Grp 9 15.0 ml/kg /day
TESTES:		(60)	(60)	(60)	(60)				
Lymphocytic infiltration in the epididymis		1	1	2					
Inflammation in the epididymis			1						
Tubular dilatation in the epididymis				2	1				
Spermatocoele(s) in the epididymis		2	1						
EPIDIDYMIS: segmental atrophy					1				
Foamy macrophage aggregate(s) in the epididymis				1					
Amyloid			1	2					
THORAX:								(2)	(2)
Suppurative inflammation								2	2
THYMUS:		(52)	(53)	(50)	(51)	(58)	(59)	(59)	(59)
No abnormality detected		43	43	39	40	30	35	30	28
Infiltration by lymphoma cells		3	2	3	3	10	6	11	6
Infiltration by histiocytic sarcoma cells			1	1				1	2
Metastasis from primary in lung		1		1	1				
Fibrinoid necrosis of small arterioles						2	2	3	
Arteritis				1					
Congestion						1		2	1

Figures in brackets represent the number of animals from which this tissue was examined histologically.

List of Organs and Tissues Examined:

Histopathology Inventory for Study Report No. 11484

Tissue	
Adrenals	X*
Aorta	X
Bone Marrow smear	X
Bone (femur)	X
Brain	X*
Cecum	X
Cervix	
Colon	X
Duodenum	X
Epididymis	X
Esophagus	X
Eye	X
Fallopian tube	
Gall bladder	
Gross lesions	X
Harderian gland	
Heart	X
Ileum	X
Treatment Site	X
Jejunum	X
Kidneys	X*
Lachrymal gland	X
Larynx	
Liver	X*
Lungs	X
Lymph nodes, mediastinal	X
Lymph nodes submandibular	X
Lymph nodes, mesenteric	X
Mammary Gland	X
Nasal cavity	
Optic nerves	
Oral cavity (cheek)	X
Ovaries	X*
Pancreas	X
Parathyroid	X
Peripheral nerve	
Pharynx	
Pituitary	X
Prostate	X
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X
Skeletal muscle	X
Skin	X
Spinal cord	X
Spleen	X
Sternum	X
Stomach	X
Testes	X*
Thymus	X
Thyroid	X
Tongue	X
Trachea	X
Urinary bladder	X
Uterus	X
Vagina	X
Zymbal gland	

* organ weight obtained

APPEARS THIS WAY
ON ORIGINAL

Study Title: **A Photococarcinogenesis Study Of An Admixture Active Gel (Benzoyl Peroxide 5% And Clindamycin Phosphate 1%) And Its Components In Albino Hairless Mice**

Note: Since Clindagel contains only clindamycin phosphate and not benzoyl peroxide, this review will primarily focus on the data from the control and clindamycin phosphate groups.

Study Number: [redacted] protocol C-609-001, [redacted] Report No. [redacted]
Volume Numbers: 8-10
Test Facility: [redacted]
Study Date(s): August 10, 1993 to December 27, 1994
Date of Submission: January 27, 2000
GLP Compliance: Yes
QA Report: Yes
Study Type: topical photococarcinogenicity
Species/strain: Albino hairless mice Crl:SKH1(hr/hr)BR
Number of animals per group; age at start of study: 36/sex/group; 35 to 37 days
Animal housing: individual stainless steel cages
Drug Lot/Batch number(s): Clindamycin phosphate 1% gel: 3G218D229, 3K345K342, 3M321B328, 3M321B328A, 4E646C252. Placebo gel: 3G218D230, 3K345K343, 3M321M318B, 3M321C253, 4E646C253
Formulations:

	% w/w	
Ingredient	Clindamycin Phosphate 1% gel	Placebo Gel
Clindamycin phosphate	1.000	
Methylparaben, NF	[redacted]	
Propylparaben, NF		
Propylene glycol, USP		
Carbomer 934P, USP		
Potassium hydroxide		
Purified water, USP		

Doses:

- Basis of Dose Selection: The doses to be used in the 52 week photococarcinogenicity study were determined from the results of 1 week and 8 week range-finding and tolerance studies.

  In the one week dose range finding study, mice were treated with up to 100 mg/kg clindamycin phosphate by applying up to 0.2 ml of the 1% gel. Some animals were also treated with 0.2 ml of the placebo gel or were left untreated. Treated and untreated sites were then irradiated with up to 2.7 times the mouse MED using a [redacted]

  Mice were examined for signs of inflammation of the irradiated site at approximately 24, 48 and 72 hours after irradiation. Neither the placebo nor the clindamycin gel enhanced nor inhibited the acute effects of the light on the skin of the mice. Therefore, 50 and 100 mg/kg clindamycin phosphate were used in the 8 week tolerance study.

In the 8 week tolerance study, mice were treated for 5 days per week with up to 100 mg/kg clindamycin phosphate by applying up to 0.2 ml of the 1% gel. Some animals were also treated with 0.2 ml of the placebo gel or were left untreated. Treated and untreated animals were then

Animals were irradiated on the same five days per week that they were treated with drug or placebo. The test articles were applied after the daily UV exposure On Mon., Wed. and Fri. and before daily UV exposure on Tues. and Thurs. Some animals were also treated with the test articles and not irradiated. Skin thickening occurred in all male mice in untreated, placebo treated and clindamycin treated groups. Skin thickening also occurred in some female mice in each of these groups. All clinical findings were considered unrelated to the test articles. Therefore, the 100 mg/kg dose of clindamycin phosphate was selected for the 52 week photococarcinogenicity study.

Study Design Table:

Group	Test article	Volume of test article applied (ml/mouse)	Dose of clindamycin phosphate (mg/kg)	RBU/week
1	Untreated	0	0	600
2	Untreated	0	0	1200
3	Placebo gel	0.2	0	600
7	1% clindamycin phosphate gel	0.2	100	600

Note: groups 4, 5, and 6 were treated with products containing 5% benzoyl peroxide.

- Radiation source:

- Relation to Clinical Use: The drug product will be used topically on sun exposed skin so evaluation of its photocarcinogenicity is appropriate. The formulation used in the study is slightly different from the proposed formulation.

- Route of Administration: The test articles were applied topically to an approximately 20 cm^2 area of skin on the backs of the animals.

- Frequency of Drug Administration: Once daily Monday through Friday. On Monday, Wednesday and Friday test article was applied after irradiation and on Tuesdays and Thursdays test article was applied before irradiation. Treatment was continued for 40 weeks.

- Unscheduled Sacrifices or Deaths: Mice found dead were necropsied. Mice *in extremis* and mice with tumors greater than 10 mm planar diameter were sacrificed and necropsied. All mice in a dosage group were sacrificed if less than one-half of the mice in the group survived and more than one-half of the surviving mice in the group had tumors of at least 4 mm planar diameter.

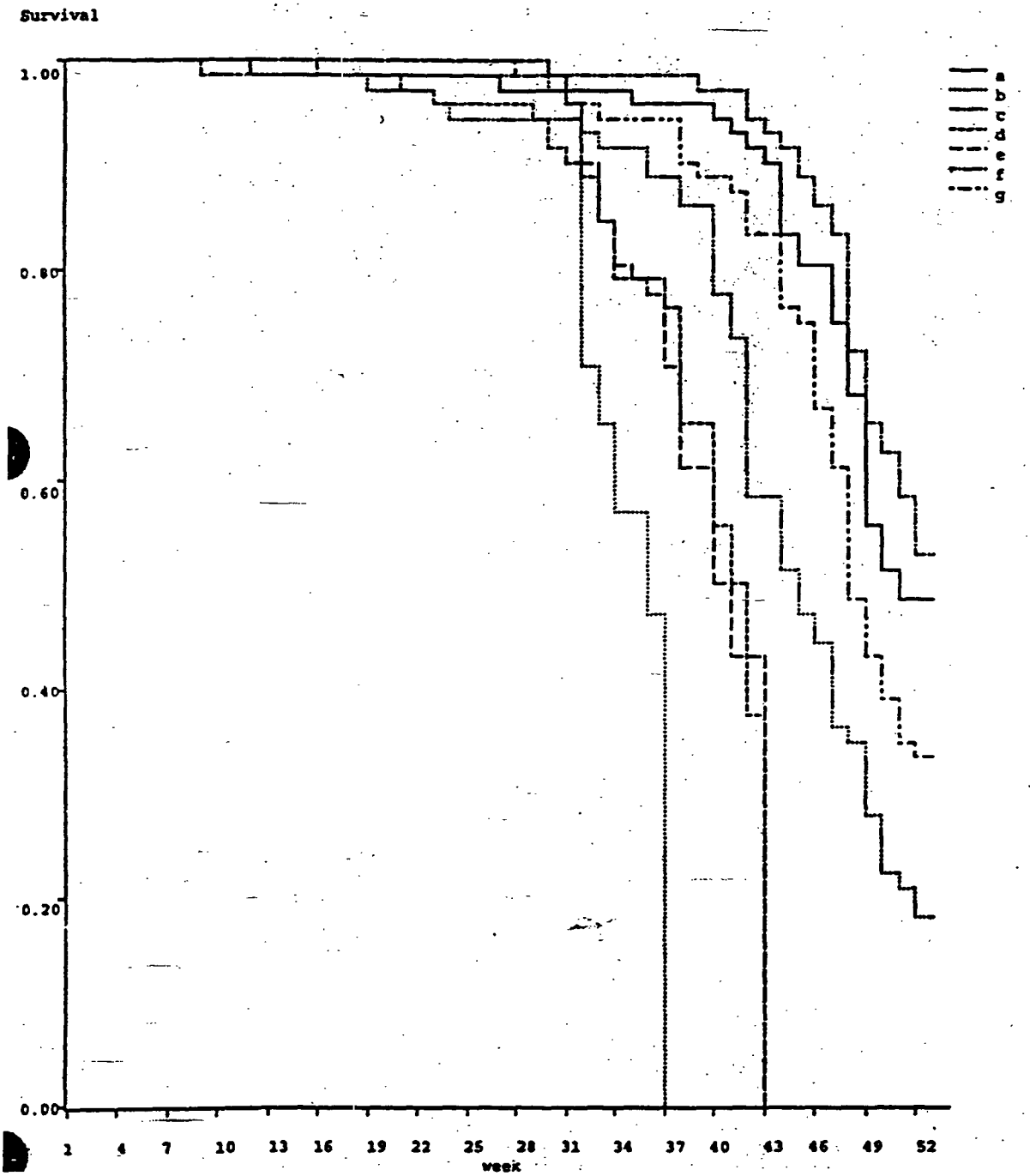
Study Results and Frequency of Monitoring:

- Clinical Observations: Clinical signs were evaluated at least once a week.

  No treatment related clinical findings were noted other than the cutaneous responses. Greater incidences of erythema and flaking of the skin were observed in male and female mice treated with clindamycin phosphate compared to the untreated animals receiving 600 RBU/week. The severity of these skin reactions was greater in the male mice than in female mice. The placebo gel did not produce any increase in skin reactions when compared to the untreated animals. The skin reactions observed in clindamycin treated mice generally did not exceed the incidence and severity of reactions observed in the untreated mice receiving 1200 RBU/week.

- Mortality: Mice were observed for viability twice daily.

  The figure below shows survival of the animals throughout the 52 weeks of the study. The letters a through g correspond to the group numbers 1 to 7. The untreated group receiving 600 RBU/week is group a, the untreated group receiving 1200 RBU/week is group b, the placebo gel group is group c and the clindamycin phosphate group is group g. It can be seen that the high dose of radiation produced the largest decrease in survival (b). The survival of the clindamycin phosphate treated animals was slightly lower than the untreated and placebo gel treated animals receiving 600 RBU/week. Most of the deaths were due to early sacrifice due to tumor burden.



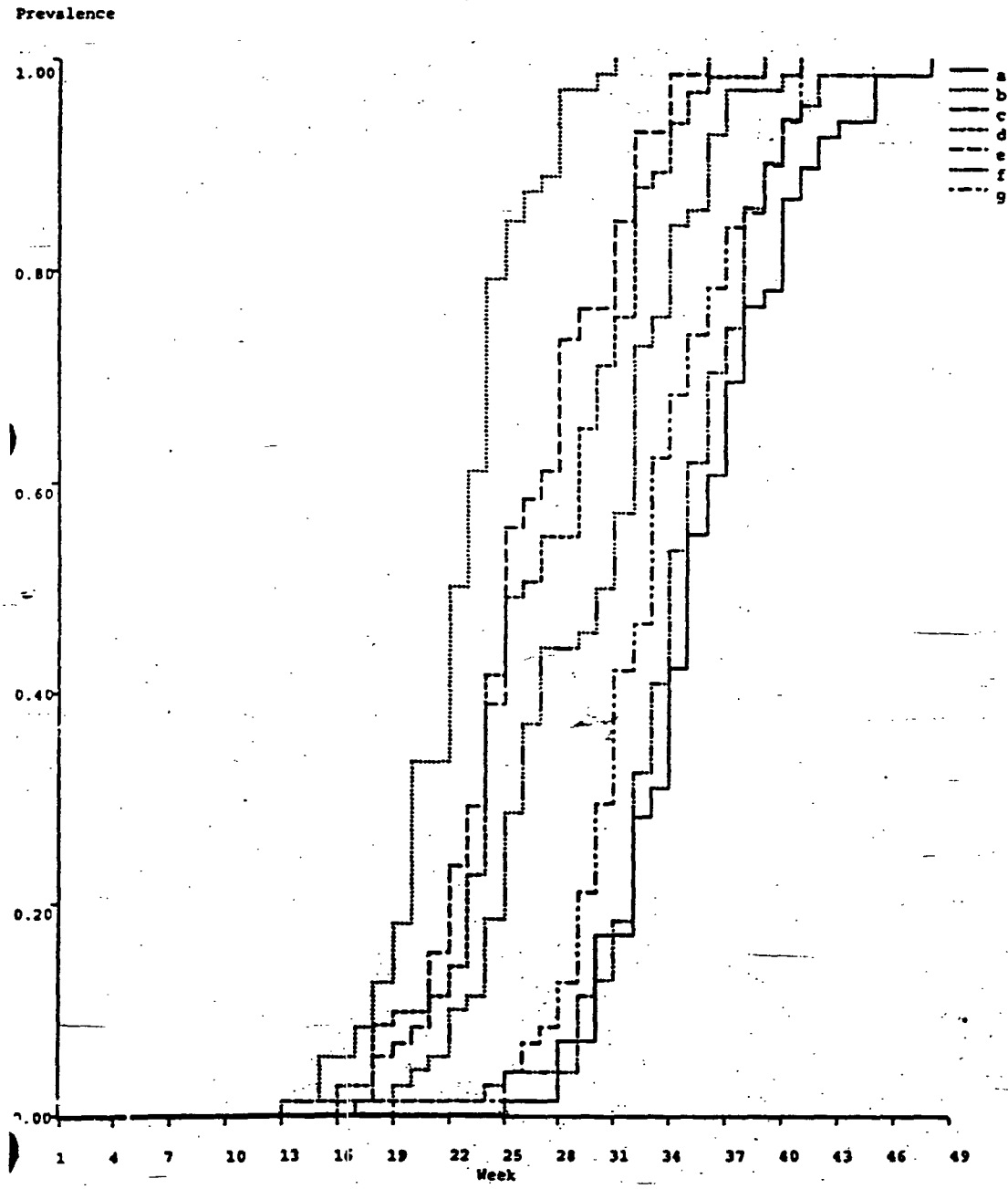
- Body Weight: Body weights were recorded weekly.

  Clindamycin phosphate and placebo gel treatment did not produce any significant effects on final body weight or body weight gain.

- Tumor data: Each mouse was examined weekly for tumor development.

  Topical application of clindamycin phosphate 1% gel was associated with a slight enhancement of photocarcinogenesis. There was an increased prevalence in all

tumor size categories. The figure below is for perceptible tumors but figures for other tumor sizes are similar. The clindamycin phosphate group in the figure is group g and is represented by a line composed of a long dash followed by two short dashes. It can be seen that the tumor prevalence for this group increased more rapidly than for either the low UV dose control group (a) or for the placebo gel treated group (c).



The table below shows the median time to tumor onset for tumors ≥1 mm in each group. Group 7 is the clindamycin phosphate treated group. It can be seen that the time to tumor onset in the clindamycin phosphate treated group is shorter than for the

Females

Group	1	2	3	7
Test article dosage (mg/kg)	None	None	0 Placebo	100
UVR exposure (RBU/week)	600	1200	600	600
	C	+++	N.S.	N.S.
		C	---	---
			C	N.S.

Sexes Combined

Group	1	2	3	7
Test article dosage (mg/kg)	None	None	0 Placebo	100
UVR exposure (RBU/week)	600	1200	600	600
	C	+++	N.S.	+
		C	---	---
			C	N.S.

a. Codes relate to level of statistical significance based on two-tailed p-values. Note that the comparison group is indicated by a C on the same line. Plus signs indicate the group specified has a risk greater than that with which it is being compared; minus signs indicate the group specified has a risk less than that with which it is being compared.

+++, --- = P<0.001
++, -- = P<0.01
+, - = P<0.05
N.S. = Not Significant

- Gross Pathology: All mice, whether found dead, euthanized *in extremis* or sacrificed at the end of the study were subjected to a gross examination of the external surfaces of the body and all internal tissues.

The group treated with clindamycin phosphate had a slightly increased incidence of enlarged and mottled livers and a statistically significant enlargement of lymph nodes. This does not appear to be a specific effect of clindamycin phosphate since it was also observed in the untreated high UV dose group and in groups treated with benzoyl peroxide. The report suggests that these effects may be related to the increased skin reaction and tumor burden in these groups. There was a significant increase in the number of male mice with enlarged preputial glands in the clindamycin phosphate treated group. Again, this may not be a specific effect of clindamycin phosphate treatment since the same effect was observed in those

animals receiving only benzoyl peroxide and not in those receiving the mixture of benzoyl peroxide and clindamycin phosphate.

Overall Interpretation and Evaluation:

- Adequacy of the carcinogenicity study and appropriateness of the test model: Photococarcinogenesis studies conducted by [redacted] often use an [redacted]. Often the drug is applied [redacted] The reason for this difference is not explained. However, the fact that an enhancement was observed suggests that the design was adequate in this case.

Clindagel and the 1% clindamycin gel formula used in the photococarcinogenicity study absorb very little light at 290 nm and above (see absorption spectra attached as appendix). Therefore, it is unlikely that the drug product would be photochemically activated by simulated solar radiation. The observed enhancement of UV carcinogenicity was probably due to some other mechanism such as tumor promotion or thinning of the protective layers of the skin. These mechanisms may not require that the drug be applied immediately prior to daily irradiation.

Summary Conclusions and Recommendations:
The photococarcinogenicity study shows that the 1% clindamycin phosphate gel formulation tested was able to cause a slight enhancement of UV induced skin tumor formation in the hairless mouse model. The vehicle gel also appeared to cause a slight enhancement of UV induced skin tumors although this effect was not statistically significant. The increase in skin tumorigenesis observed in the clindamycin phosphate treated animals was not statistically greater than the placebo gel treated animals. Some of the enhancement of skin tumor formation by the clindamycin phosphate containing gel may be due to effects of the vehicle.

IMMUNOTOXICOLOGY:
As noted above, one study entitled Delayed Contact Hypersensitivity in Guinea Pigs (Study 0424XC52.002) was conducted with the to-be-marketed formulation. This study was previously submitted and reviewed in SN 000 of IND 56,487. Briefly, none of the animals treated with Clindagel or Clindagel vehicle showed any irritation after the induction or challenge phases of the study and so Clindagel showed no tendency to induce delayed contact hypersensitivity.

REPRODUCTIVE TOXICOLOGY:
The teratogenic potential of clindamycin phosphate has been previously investigated in SD rats and IR and CF1 mice. Each species was injected subcutaneously with 100 and 180 mg/kg on gestation days 6 through 15. There was no indication of teratogenic effects and no detrimental effect on reproduction.

Reproductive toxicity studies have also been conducted in rats and mice with oral clindamycin hydrochloride and clindamycin palmitate. Rats dosed with up to 200 mg/kg clindamycin hydrochloride and 600 mg/kg clindamycin palmitate during days 6 to 15 of gestation did not show any signs of teratogenicity.

Rats treated orally with up to 60 mg/kg clindamycin hydrochloride and 300 mg/kg clindamycin palmitate showed no impairment of reproductive performance. In these studies, treatment was started in male rats at 40 days of age and in the females, 14 days before breeding. Reproductive performance was not affected in these studies.

GENETIC TOXICOLOGY:

The sponsor has not included any information on the genetic toxicology of clindamycin. The label for Cleocin Phosphate Sterile Solution contains the following statement:

> Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

SPECIAL TOXICOLOGY STUDIES:

As mentioned above, two additional studies were conducted by the sponsor with the to-be-marketed formulation. One was an acute irritation study in rabbits and the other is an acute eye irritation study in rabbits. Both of these studies were previously submitted and reviewed in SN 000 of IND 56,487.

Briefly, Clindagel was considered to be nonirritating to the rabbit eye and no signs of irritation were observed in rabbit skin treated with Clindagel under partial occlusion for four hours.

OVERALL SUMMARY AND EVALUATION:

The three nonclinical studies conducted with Clindagel suggest that it is not a primary dermal or ocular irritant in rabbits nor does it induce hypersensitivity in the guinea pig. There does not appear to be any reason to expect Clindagel to have greater toxicity than previously approved formulations of Clindamycin phosphate.

Clindamycin phosphate is found in a number of approved drug products including several topical formulations for acne vulgaris. The most significant toxicity associated with the use of clindamycin phosphate has been the induction of colitis. This is believed to be caused by the overgrowth of a toxin-producing *Clostridium difficile.* Absorption of clindamycin phosphate from topical application may be sufficient to cause colitis. A warning about this adverse effect is included in the labels of currently approved formulations of clindamycin and in the proposed label for Clindagel.

The label for Cleocin T Gel states that reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day. These studies have not revealed evidence of impaired fertility or harm to the fetus. Cleocin T Gel is listed as a pregnancy category B drug. The proposed label of Clindagel contains this information and maintains this category.

The label for Cleocin phosphate IV solution states that the genotoxicity of clindamycin phosphate was evaluated by a rat micronucleus test and an Ames test. Both tests were negative. This information is not in the proposed Clindagel label but could be added.

The acrylic acid polymer used in the drug product is listed as [redacted] This ingredient does not have a monograph in the USP/NF but the sponsor claims that it is equivalent to and qualifies under the chemical name of Carbomer 941, NF. [redacted] is the same polymer as Carbomer 941 but [redacted] and is therefore considered to be the preferable ingredient. Carbomer 941 has been used previously in approved topical drug products and so there are no safety concerns from using [redacted] in the current product.

Conclusions:
This NDA is approvable from a pharmacology/toxicology perspective. Some changes to the label are recommended.

Communication Review:
- Labeling Review (NDA):
  The current proposed label for Clindagel does not contain a Carcinogenesis, Mutagenesis and Impairment of Fertility section. Since dermal carcinogenicity and photococarcinogenicity studies have been submitted in the NDA, it is recommended that this information be incorporated into the label. Mutagenesis information from the Cleocin Phosphate Sterile Solution label could also be included. Fertility information in the Cleocin label should be included in this section of the label, also.

  The following wording can serve as an example for the Carcinogenesis, Mutagenesis and Impairment of Fertility section of the label.

  > The carcinogenicity of a 1% clindamycin phosphate gel similar to Clindagel was evaluated by daily application to mice for two years. The daily doses used in this study were approximately 3 and 15 times higher than the human dose of clindamycin phosphate from 5 milliliters of Clindagel, assuming complete absorption and based on a body surface area comparison. No significant increase in tumors was noted in the treated animals.
  >
  > A 1% clindamycin phosphate gel similar to Clindagel caused a statistically significant shortening of the median time to tumor onset in a study in hairless mice in which tumors were induced by exposure to simulated sunlight.
  >
  > Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.
  >
  > Reproduction studies in rats using oral doses of clindamycin hydrochloride and clindamycin palmitate hydrochloride have revealed no evidence of impaired fertility.

The description of the reproductive toxicity studies in the Pregnancy: Teratogenic Effects sections of the Cleocin T Gel label and the proposed label for Clindagel do not contain [redacted]

[redacted] The proposed Clindagel label states:

[redacted]

This statement is based on reproductive toxicity studies that were conducted with clindamycin hydrochloride and clindamycin palmitate hydrochloride. Consequently, a direct comparison to clindamycin phosphate is not possible with out first converting the doses to equivalent clindamycin doses. An example of possible alternative wording for this section of the label is provided below based on dose comparison calculations outlined in the appendix.

[redacted]

RECOMMENDATIONS:

The NDA for Clindagel is approvable from a pharmacology and toxicology perspective. Changes to the label are recommended as outlined in the discussion above.

/S/

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

cc:
NDA 50-782
HFD-340
HFD-540
HFD-540/Pharm/Brown
HFD-540/TL/Jacobs
HFD-540/MO/Huene
HFD-540/ChemMidra
HFD-540/PM/Kumar

Concurrence Only:
HFD-540/DD/Wilkin /S/ 8/15/00

HFD-540/TL/Jacobs 6/21/00 in DFS

DFS ✓

Draft date (# of drafts): June 20, 2000 (1st draft); June 21, 2000 (2nd draft)
Appendix/attachments: Appendix 1: Dose multiple calculations.
Appendix 2: UV/visible absorption spectra of Clindagel and 1% clindamycin phosphate gel used in dermal carcinogenicity and photococarcinogenicity studies
Appendix 3: Executive CAC meeting minutes

(R)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

1 page

(R)

60	66
100	110
200	220

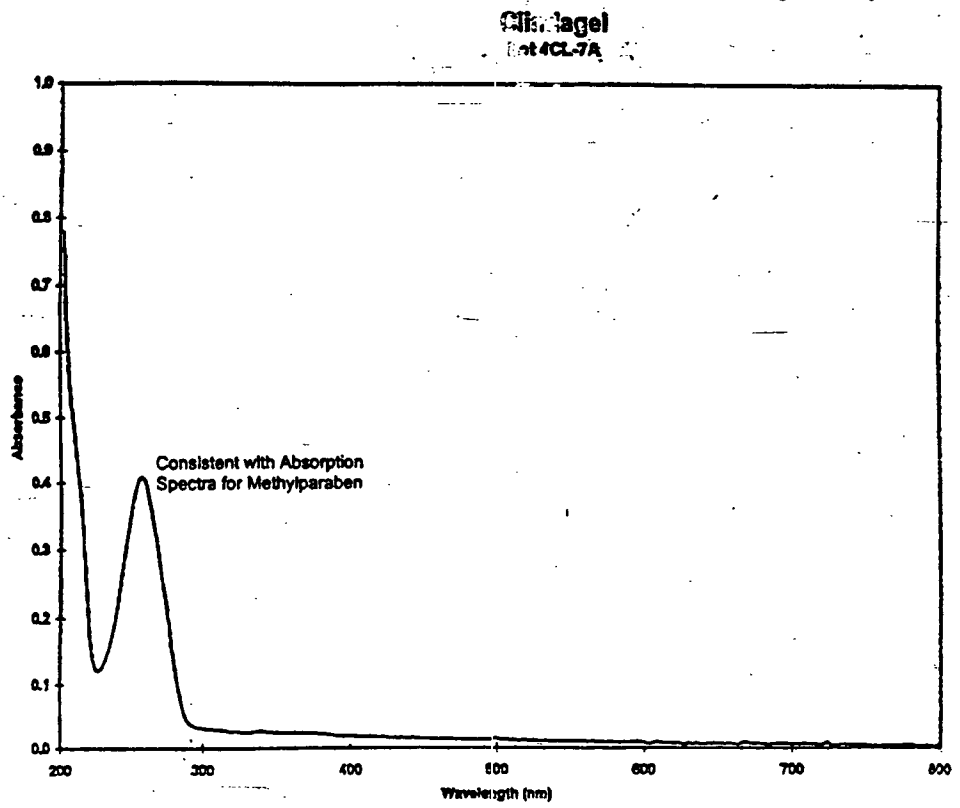
Clindamycin Palmitate HCl dose in mg/kg	Equivalent Clindamycin Phosphate dose in mg/kg (Clindamycin Palmitate HCl dose ÷ 1.39)
100	72
150	108
300	216
600	432

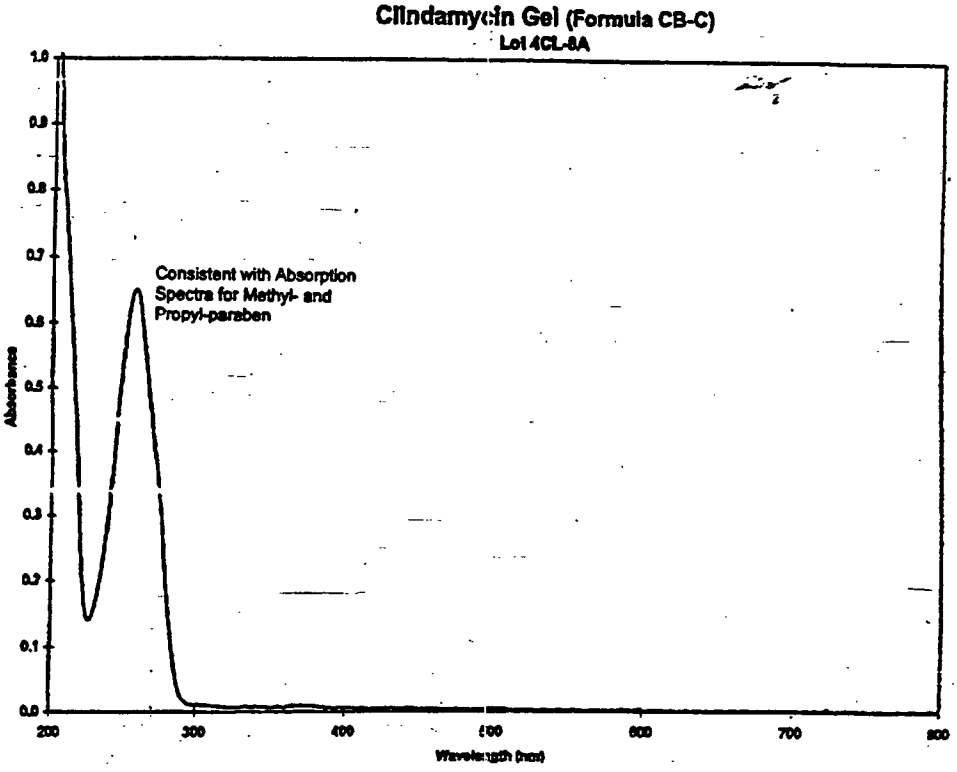
Human to animal dose comparison based on body surface area.

Dose in mg/kg	Dose in mg/m^2 (mg/kg × *km*)	Multiple of human dose (mg/m^2 ÷ 30.71 mg/m^2)
Mouse (*km* = 3)		
22	66	2.2
27	81	2.6
55	165	5.4
108	324	10.5
150	450	14.7
216	648	21.1
220	660	21.5
432	1296	42.2
Rat (*km*=6)		
33	198	6.4
55	330	10.7
66	396	12.9
72	432	14.1
110	660	21.5
216	1296	42.2
220	1320	43.0
432	2592	84.4

APPEARS THIS WAY
ON ORIGINAL

Appendix 2: UV/visible absorption spectra of Clindagel and 1% clindamycin phosphate gel used in dermal carcinogenicity and photococarcinogenicity studies





Appendix 3: Executive CAC meeting minutes

APPEARS THIS WAY
ON ORIGINAL