2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

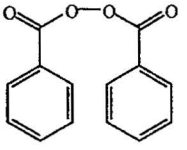
NDA number: 50-819
Review number: 1
Sequence number/date/type of submission: 000 / 12/21/2007 / Original submission
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Dow Pharmaceutical Sciences
Manufacturer for drug substance: Clindamycin phosphate, [redacted] b(4)
[redacted]. Benzoyl peroxide hydrous, [redacted]
[redacted].

Reviewer name: Jiaqin Yao
Division name: Dermatology and Dental products
HFD #: 540
Review completion date: 9-25-08

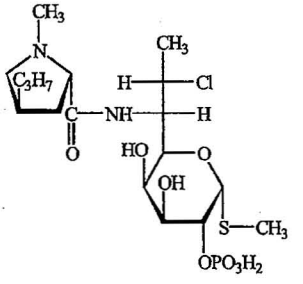
Drug:

Trade name: Acanya [redacted] Gel b(4)
(1.2% clindamycin phosphate, 2.5% benzoyl peroxide)
Generic name: IDP-110 Gel, [redacted] Gel
Code name: [redacted] Admixture Active Gel
Chemical name: Benzoyl peroxide (BPO): Dibenzoyl peroxide
Clindamycin phosphate: 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)
CAS registry number: Benzoyl peroxide: 94-36-0;
Clindamycin phosphate: 24729-96-2
Molecular formula/molecular weight: Benzoyl peroxide: $C_{14}H_{10}O_4$/242.23
Clindamycin phosphate: $C_{18}H_{34}ClN_2O_8PS$/504.97

Structure:



Benzoyl peroxide



Clindamycin phosphate

Relevant INDs/NDAs/DMFs: INDs 41,733, 44,492, ——— and ———, NDAs 50-741 and 50-756

Drug class: Anti-acne

Indication: Acne Vulgaris

Clinical formulation: The product is a two-component product consisting of a benzoyl peroxide gel and clindamycin phosphate concentrate. The components are mixed by the pharmacist at time of dispensing. The composition of the mixture is as follows.

Table 2.3.P.1.2.1. Quantitative Composition of IDP-110Gel

Ingredient	%w/w	Quantity per ——— Jar (g)
Clindamycin Phosphate, USP	1.20[1]	
Hydrous Benzoyl Peroxide, USP	2.50[2]	
Propylene Glycol, USP		
Carbomer 980		
Potassium Hydroxide, NF (q.s. ad pH 4.5 - 6.5)		
Purified Water, USP		

[1] Equivalent to 1% w/w clindamycin
[2] Based on ——— benzoyl peroxide
[3] Average of quantities present in three registration batches

b(4)

Note: This formulation appears to differ from the one used in nonclinical studies including the carcinogenicity and photocarcinogenicity studies as the following

Ingredient	% w/w	
	Admixture Active Gel	Placebo Gel
Clindamycin phosphate		0
Benzoyl peroxide		0
Propylene glycol, USP		
Carbomer ———, USP		
Potassium hydroxide		
Purified water, USP		

b(4)

Route of administration: Topical

Proposed use: Acanya ——— Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older. Acanya ——— Gel should be applied to the affected areas once daily or as directed by the physician.

b(4)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Introduction and drug history: The original IND (41,733) was submitted by Glaxo Dermatology and then was transferred to the current Sponsor. The Sponsor submitted an ANDA [65,443, ——— (1/5)] using the already marketed BenzaClin Topical Gel (clindamycin 1% - benzoyl peroxide 5%) as the reference drug. The formulations for Acanya ——— Gel (1/2.5) and the final-to-be marketed ——— Gel (1/5) in ANDA 65,443 are similar with respect to excipients and excipient levels except for the reduced concentration of BPO from 5% to 2.5%, the ——— concentration of propylene glycol from ——— , and the corresponding adjustment of purified water. However, the ——— Gel (Admixture Active Gel) tested in all nonclinical studies contained ——— , and carbomer ——— (see the table above), instead of Carbomer 980 in the final-to-be marketed ——— Gel (1/5) in ANDA 65,443. The Sponsor planed to rely on a clinical bridge with BenzaClin and ——— (1/5) and the safety data generated from the ——— Gel (Admixture Active Gel) to support this NDA filing [505(b)(2)] for the Acanya ——— Gel (1/2.5). It was determined that the sponsor did not generate an adequate clinical bridge. Therefore, the sponsor will rely on literature data for some of the nonclinical information needed for clindamycin and benzoyl peroxide. b(4)

Studies reviewed within this submission:

1. **90-Day Gavage Toxicity Study of an Admixture Active Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) in Rats** (91 GLA P007 S032)
2. **Study title: In Vitro Mammalian Chromosome Aberration Test** (7001-U5HP-01-07) b(4)
3. **Dermal Carcinogenicity Study of an Admixture Active Gel (——— - Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and its Components in Mice** (92 GLA P007 S034)
4. **2 Year Oral (Gavage) Carcinogenicity Study of an Admixture Active Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and its Components in Rats** (92 GLA P007 S033)

Studies <u>not</u> reviewed within this submission:

The following studies were reviewed by Dr. S. R. Joshi in IND 41,733.

1. **Acute oral toxicity study in mice with ———Gel** (91 GLA P007 S003)
2. **Acute oral toxicity study in rats with ——— Gel** (91 GLA P007 S001)
3. **Acute dermal toxicity study in rats with ——— Gel** (91 GLA P007 S004)
4. **35-Day Dermal Toxicity study in Rats with ———** 1 GLA P007 S016) b(4)
5. **35-Day Dermal Toxicity Study in Rabbits with ———** (91 GLA P007 S005)
6. **Primary Skin Irritation Study in Rabbits with ———** (91 GLA P007 S007)
7. **Primary Eve Irritation Study in Rabbits with ———** (91 GLA P007 S006)
8. **Dermal Sensitization Study in Guinea Pigs with ———** (91 GLA P007 S008)
9. **Photoirritation Study in Rabbits with ———** (91 GLA P007 S009)

The following study was reviewed by Dr. Jiaqin Yao in IND 41,733.

1. **A Photocarcinogenesis Study of An Admixture Active Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and Its Components in Albino Hairless Mice** (92 GLA P007 S035)

2.6.2 PHARMACOLOGY

No pharmacology studies have been conducted with IDP-110 Gel, which is a combination product of 1% clindamycin (1.2% clindamycin phosphate) and 2.5% benzoyl peroxide (BPO). Clindamycin is an antibiotic that decreases Propionibacterium acnes (P. acnes) colonization of skin follicles and reduces the inflammatory aspect of acne. BPO is an antibacterial agent effective against P. acnes through oxidation. Additionally, BPO reduces non-inflammatory lesions, comedones, through induction of keratolysis and desquamation.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

NA

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

See the individual study reports in the Toxicology section.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

NA

2.6.6 TOXICOLOGY

2.6.6.1 Single-dose toxicity

1. **Acute oral toxicity study in mice with ——— Gel** (3242.25, 91 *GLA P007 S003*) b(4)
2. **Acute oral toxicity study in rats with ——— Gel** (3242.24, 91 *GLA P007 S001*)
3. **Acute dermal toxicity study in rats with ——— Gel** (3242.26, *91 GLA P007 S004*)

These 3 single-dose toxicity studies were reviewed by Dr. S. R. Joshi within the original submission of IND 41,733 in 1993.

In both mice and rats, the oral LD_{50}s of ——— (1% clindamycin and 5% BPO) were >5000 mg/kg (corresponding to >250 mg/kg BPO and >50 mg/kg clindamycin). The derma LD_{50} of ——— (1% clindamycin and 5% BPO) in rats was >5000 mg/kg (corresponding to >250 mg/kg BPO and >50 mg/kg clindamycin). The ——— gel tested in the three studies was from Lot 110A-110A. b(4)

2.6.6.2 Repeat-dose toxicity

The following information on the two 35-day toxicity studies was duplicated from the review by Dr. S. R. Joshi within the original submission of IND 41,733 in 1993.

4. 35-Day Dermal Toxicity study in Rats with [redacted] b(4)

SLS Study No. 3242.33 (*91 GLA P007 S016*)

Materials Tested: Placebo Gel Combination (*Lot 113P-111P*), 5% Benzoyl Peroxide gel (*Lot 110A-111P*), 1% Clindamycin gel (*Lot 113P-110A*), [redacted]™ gel (*Lot 110A-110A*).

Animals: Sprague-Dawley rats; 10/sex/group.

Experimental Design:

Group	Test Material	B.I.D		Size of treated area (cm^2)
		Dose (mg/kg)	Volume (ml/kg)	
1	Placebo gel combo	2500	2.40	20
2	1% Clindamycin gel	250	0.24	2
30	1% Clindamycin gel	750	0.73	6
4	1% Clindamycin gel	2500	2.40	20
5	5% Benzoyl Peroxide gel	250	0.24	2
6	5% Benzoyl Peroxide gel	750	0.73	6
7	5% Benzoyl Peroxide gel	2500	2.40	20
8	[redacted] gel	250	0.24	2
9	[redacted] gel	750	0.73	6
10	[redacted] gel	2500	2.40	20

b(4)

Procedure: Applied the formulation to the clipped dermal test site, 2x/day, 7 days/week for a minimum of 70 applications. Approximately 5 hours after the initial daily dose, the patches were removed and the animals received a second topical dose. Approximately 5 hours later the second patch was removed and the treated area of the skin was wiped clean with gauze moistened with distilled water.

Results:

Systemic Toxicity: There was no treatment related mortality during the study. There were no meaningful differences among the groups with respect to body weights, weight gain, food consumption, clinical pathology parameters (hematology and blood chemistry), gross necropsy findings or organ weights. No test article related histological changes were observed except for the local dermal reaction (see below).

b(4)

Local Dermal Reactions: Clinical signs were characterized by slight erythema and slight desquamation in the 1% clindamycin group and by slight to moderate erythema, slight desquamation occasional edema in the [redacted] gel and 5% benzoyl peroxide gel groups.

Histologically, dermal changes in the placebo gel combo and 1% clindamycin gel groups consisted of mild acanthosis and/or minimal hyperkeratosis in a few animals. Dermal

b(4)

changes were similar in 5% benzoyl peroxide gel and ——— gel groups and consisted of minimal to moderate acanthosis, minimal to moderate hyperkeratosis and occasional chronic dermatitis.

Plasma Concentrations: Samples were collected at necropsy (approx. 14 hours after last application).

Fifty plasma samples were analyzed for clindamycin content. No measurable amount of clindamycin was detected (Detection Limit: 50 ng/ml)

Thirteen plasma samples were analyzed for benzoic acid content as a measure of dermally absorbed benzoyl peroxide. No measurable amount of benzoic acid was detected (Detection Limit: 0.2 mcg/ml).

5. 35-Day Dermal Toxicity Study in Rabbits with ———

SLS Study No. 3242.23 (*91 GLA P007 S005*)

b(4)

Materials Tested: Placebo Gel Combination (*Lot 113P-111P*), 5% Benzoyl Peroxide gel (*Lot 110A-111P*), 1% Clindamycin gel (*Lot 113P-110A*), ——— gel (*Lot 110A-110A*).

Animals: New Zealand albino rabbits; 5/ sex/group.

Group	Test Material	B.I.D	
		Dose (g/kg)	Volume (ml/kg)
1	Placebo gel combo	2.5	2.5
2	1% Clindamycin gel	0.25	0.25
3	1% Clindamycin gel	1.25	1.25
4	1% Clindamycin gel	2.5	2.5
5	5% Benzoyl Peroxide gel	0.25	0.25
6	5% Benzoyl Peroxide gel	1.25	1.25
7	5% Benzoyl Peroxide gel	2.5	2.5
8	——— gel	0.25	0.25
9	——— gel	1.25	1.25
10	——— gel	2.5	2.5

b(4)

Procedure: Applied the formulation to the clipped dermal test site, 2x/day, 7 days/week for a minimum of 70 applications.

Two areas were clipped on each animal, one area in the right flank and the other area in the upper left flank. Approximately one-half of the total daily dose was applied equally to the two clipped areas; the remaining dose was similarly applied to the same two areas approximately 5 hours later. Approximately 5 hours later the second patch was removed and the treated area of the skin was wiped clean with gauze moistened with distilled water.

Results:

Systemic Toxicity: Orange colored urine was observed in the 5.0 g/kg/day 1% clindamycin gel group and in the 1.5- and 5.0 g/kg/day clindaben groups. The coloration of the urine was ascribed to excretion of clindamycin and an indication of toxicity.

No treatment related mortalities or clinical signs of toxicity occurred during the study. No apparent test article-related changes were noted among the groups with respect to clinical pathology, necropsy or organ weight data. Similarly, no treatment-related histopathological changes were observed in organs/tissues other than local dermal effects (see below).

Local Dermal Effects:

Placebo Gel combination: No dermal irritation in males or females.

1% Clindamycin Gel: No dermal irritation in males. Females showed slight erythema and slight desquamation during days 3 to 9. Exposure sites were normal from day 10 onwards.

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5% Benzoyl Peroxide Gel and ——— Gel: Notable dermal irritation in both males and females at all dose levels. This irritation consisted of slight to moderate erythema, slight edema, slight to moderate desquamation. Eschar formation and exfoliation were observed in several animals in each treatment group.

Histopathology (skin): Test article related changes were limited to the skin of the application site and occurred in most rabbits which received 5% Benzoyl Peroxide (all dose levels) or ——— (5% benzoyl peroxide + 1% clindamycinJ (also at all dose levels). No dermal irritation lesions occurred in 1% Clindamycin.

b(4)

The lesions were characterized by acanthosis, hyperkeratosis and chronic dermatitis. There was no meaningful difference in severity of the skin changes between the 5% Benzoyl Peroxide Gel and ——— Gel groups.

b(4)

According to the Pathologist, "Overall, the test article related changes in the 5% Benzoyl Peroxide Gel and ——— Gel groups were considered mild, were reflective of a normal physiologic response to the prolonged administration of a slight irritant under occlusion and would be expected to be quickly reversed following cessation of treatment. Since there was no test article related changes in the 1% Clindamycin Gel groups and no difference in type or severity of changes between the 5% Benzoyl Peroxide Gel and ———. Gel groups, it appears that the changes related to ——— Gel application were due to its benzoyl peroxide component."

b(4)

Plasma Levels: Samples were collected 5 hours after the second application of test article on days 9-10 and 30-31 of the study.

Fifty-two plasma samples were analyzed for clindamycin content. No measurable amount of clindamycin were detected (Detection Limit: 100 ng/ml).

One hundred-sixty plasma samples were analyzed for benzoic acid content as a measure of dermally absorbed benzoyl peroxide. The concentrations of endogenous benzoic acid in plasma samples were not affected by the daily administration of any of the gel-formulated test articles at doses as high as 5 g/kg/day.

6. 90-Day Gavage Toxicity Study of an Admixture Active Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) in Rats (3242.34, *91 GLA P007 S032*): Four groups of 12 male and 12 female SD rats received the Placebo Gel at10.0 g/kg/day or the Admixture Active Gel ( ) at 1.25, 5.0, or 10.0 g/kg/day orally by gavage for 93 or 94 consecutive days. The Admixture Active Gel contained clindamycin phosphate (1%), benzoyl peroxide (5%), propylene glycol ( ), carbomer ( ), and purified water, pH ( ) potassium hydroxide aqueous solution, and was from the Lots 3B217B216 and 3B217B216A. b(4)

There were no treatment-related effects on mortality, clinical signs, body weights, food consumption, clinical pathology, ophthalmology, necropsy, or organ weights. Minimal to mild periportal hepatocyte vacuolation was seen in 5 of 12 males at the 10.0 g/kg/day Admixture Active Gel level only. However, this finding was not observed in the females or in the males at the 1.25 and 5.0 g/kg/day doses.

In addition, blood samples were collected from four males and four females in the Satellite Control Group approximately two hours following dosing on Days 2, 29, and 94 and from four males and four females in the Satellite Treatment Groups (1.25, 5.0, and 10.0 g/kg/day) approximately two and five hours following dosing on Day 2 and approximately two hours following dosing on Days 8, 29, and 94 for analysis of active ingredients (clindamycin and benzoic acid as an indicator of benzoyl peroxide content). Urine samples were collected from four males and four females in the Satellite Control Group on Days 1/2, 28/29, and 93/94 and from four males and four females in the Satellite Treatment Groups on Days 1/2, 7/8, 28/29, and 93/94 for analysis of Clindamycin only. However, no data on the analysis of active ingredients was included in this study report.

6.6.6.3 Genetic toxicology

1. Study title: In Vitro Mammalian Chromosome Aberration Test

Key findings: Clindamycin phosphate was negative for the induction of structural and numerical chromosome aberrations in the in vitro mammalian chromosome aberration test using human peripheral blood lymphocytes.

Study no.: 7001-U5HP-01-07
Conducting laboratory and location: b(4)

Date of study initiation: 4-30-2007
GLP compliance: Yes
QA reports: Yes (X) no ()
Drug, lot #, and % purity: Clindamycin Phosphate, Lot 05050062P2, Purity 98%
Formulation/vehicle: Water

Methods:

Strains/species/cell line: Human peripheral blood lymphocytes (HPBL) from a healthy non-smoking 25 year old adult female.

Dose selection criteria:

Basis of dose selection: A range finding study was performed at up to 5000 µg/mL.

Range finding studies: In the preliminary toxicity assay, the maximum dose tested was 5000 µg/mL. Human peripheral blood lymphocytes were treated in the absence and presence of S9 activation for 4 hours, and continuously for 20 hours in the absence of S9 activation. The test article was soluble in water and in the treatment medium at all concentrations tested at the beginning and conclusion of the treatment period. Substantial toxicity (at least 50% reduction in mitotic index relative to the solvent control) was not observed at any dose level in all three exposure groups. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 625 to 5000 µg/mL for all three treatment groups.

Doses used in definitive study: 625, 1250, 2500, and 5000 µg/mL for 4-hour treatment with or without S9 and for 20-hour treatment without S9.

Controls:

Vehicle: Water
Negative controls: Culture medium
Positive controls: Mitomycin C (MMC, 0.3 or 0.6 µg/mL) for nonactivation series and cyclophosphamide (CP, 20 µg/mL) for metabolic activation series.

Results:

Study validity: The study was considered valid since structural aberrations in the negative controls were within normal range and the positive control induced statistically significant increases in structural aberrations (17.0%, 19.0%, and 17.0% for MMC 0.6 µg/mL 4 hr -S9, CP 20 µg/mL 4 hr +S9, and MMC 0.3 µg/mL 20 hr -S9, respectively).

Study outcome: Mitotic inhibition was not reduced relative to the solvent control in any clindamycin phosphate-treated groups. A minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations in this study. However, no structural and/or numerical chromosome aberrations were seen in cells treated with 1250, 2500, or 5000 µg/mL clindamycin phosphate for 4-hour with or without S9 or for 20-hour treatment without S9.

2. Since a sufficient clinical bridge is not established to BenzaClin Topical Gel or another approved clindamycin/benzoyl peroxide product, additional nonclinical

information would be needed to support an NDA for Acanya [redacted] Gel. Alternatively, this required information may be provided by relying on data from available published literature that does not refer to any marketed pharmaceutical. Although the sponsor submitted a review article on the genotoxicity of clindamycin (Snyder RD and Green JW, A review of the genotoxicity of marketed pharmaceuticals, Mutation Research, 488:151-169, 2001), the information refers to marketed pharmaceuticals. Therefore, the statement, "Clindamycin phosphate was not genotoxic in Salmonella typhimurium or in a rat micronucleus test", can not be used to support this NDA. Data on the Ames test and in vivo micronucleus assay with clindamycin phosphate may be needed for this NDA, since a sufficient clinical bridge has not been established. b(4)

As stated in the review by Dr. Paul Brown in NDA 50-741 (Duac Gel), "A variety of genotoxicity studies have been conducted with benzoyl peroxide. Many of these studies are published. The results of these studies have sometimes been positive and sometimes negative. Several studies show that benzoyl peroxide can cause DNA strand breaks and oxidative DNA damage in cultured cells." The following wording in the labeling of some approved drug products containing benzoyl peroxide, "Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in Salmonella typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells", was based on literature data review (also see a review article, Kraus et al., Benzoyl peroxide: An integrated human safety assessment for carcinogenicity, Regulatory Toxicology and Pharmacology, 21:87-107, 1995). The same wording should be included in the label of this NDA.

[redacted]. This study has not been published and it does not appear that the current sponsor has the right to refer to this study. Therefore the statement, "Clindamycin phosphate sulfoxide, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test", which was shown in the labeling of BenzaClin Topical Gel, should not be included in the label of this NDA, since a sufficient clinical bridge has not been established to BenzaClin Topical Gel. b(4)

2.6.6.4 Carcinogenicity

1. Study Title: Dermal Carcinogenicity Study of an Admixture Active Gel ([redacted]- Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and its Components in Mice b(4)

Note: This study was reviewed in IND 56,487 by Dr. Paul Brown, in which the review primarily focused on the data from the control and clindamycin phosphate groups (Groups 1, 2, 8, and 9). The executive carcinogenicity assessment committee concluded that there was no significant increase in tumors in mice treated with 1% Clindamycin Phosphate Gel.