CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Key words:
Reviewer Name: Kumar D. Mainigi
Division Name: Dermatologic and Dental drug Products, HFD-540
Review completion date: 08-14-2000
Electronic file number:
NDA 50-741 AZ original amendment/ 03-06-2000
Information to sponsor: Yes
Sponsor: Stiefel Laboratories, Inc.
255 Alhambra Circle, Coral Gables, FL 33134
Manufacturers: Clindamycin phosphate

1. [redacted]

2. [redacted]

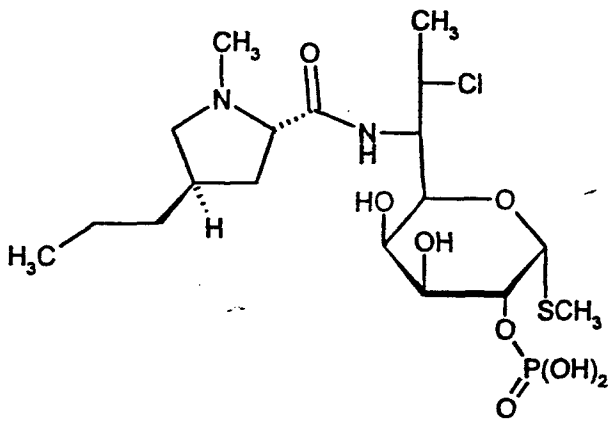
Benzoyl peroxide

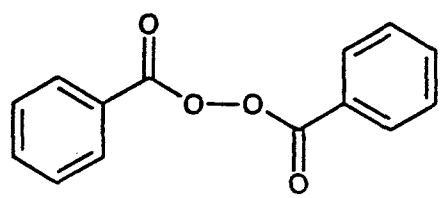
[redacted]

Drug: Clindoxyl™ Gel (Clindamycin phosphate 1%+Benzoyl Peroxide 5%)

Chemical Names of Active Ingredients:

Clindamycin phosphate: Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*theo*-α-D-*galacto*-octopyranoside-2-(dihydrogen phosphate) (CAS# 24729-96-2)
Benzoyl peroxide: Dibenzoyl peroxide (CAS# 94-36-0)
Molecular Formula/Molecular weight: Benzoyl peroxide: $C_{14}H_{10}O_4$/242.23
Clindamycin phosphatre:$C_{18}H_{34}ClN_2O_8PS$/504.97





Drug class: Antibacterial
Indication: Treatment of Acne vulgaris

Relevant submissions: INDs: —

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NDA: 50-756 (Dermik)

Composition:

Ingredients	Quantity(% w/w)	Function
Benzoyl Peroxide	(	Active agent
Clindamycin Phosphate	**	Active agent
Carbomer 940	:	Gelling agent
Dimethicone		Slip agent
Disodium Lauryl Sulfosuccinate		Wetting agent
Edetate Disodium		Chelating agent
Glycerin		Emollient
Silicone Dioxide		Thickner/slip agent
Methylparaben ***		Preservative
Poloxamer		Slip agent
Sodium Hydroxide		For pH adjustment
Purified Water	—	
Total	100.00	

* To provide 5.0% w/w benzoyl peroxide in the gel (when benzoyl peroxide is 75% active). The actual quantity used to be adjusted based on the lot activity and quantity of water adjusted accordingly.
** To provide — w/w Clindamycin in the gel (2% manufacturing overage) in finished product (when Clindamycin phosphate purity is —). The actual quantity used to be adjusted based on the lot activity and quantity of water adjusted accordingly.
*** In the original NDA submission, the quantity was —. The studies reviewed in this report were conducted with the new formulation containing —, Methylparaben.

Route of administration: Topical

Disclaimer: The information submitted by the sponsor was utilized to prepare this review.

Proposed use: Clindoxyl Gel is indicated for the treatment of acne vulgaris. It is proposed that the drug product should be applied once daily in the evening to the affected sites. The use of sunscreen is recommended if the subject is going out in the open.

Previous clinical experience: The safety, tolerance and efficacy of clindoxyl gel in the treatment of facial acne vulgaris have been evaluated in 5 vehicle-controlled double blind parallel group clinical studies. These 11 days long studies were conducted in a total of 1319 mostly Caucasians (males 688, females 631) ranging in age from 12 to 31 years. According to the sponsor, clindoxyl gel was more effective than either of the active agents (5% benzoyl peroxide gel or 1% clindamycin phosphate gel) and more effective than the vehicle gel in once daily topical treatment of acne vulgaris. In addition, four

standard clinical patch studies (n=283) were conducted to evaluate the potential of clindoxyl gel to cause phototoxicity, photo contact sensitization, or contact sensitization. In the main clinical studies, the adverse effects observed in 1.8% of patients treated with clindoxyl gel included mild worsening of acne, mild or moderate pruritus, mild paraesthesia, moderate erythema, and mild or moderate dry skin.

Introduction and drug history: For over two decades, both clindamycin and benzoyl peroxide (BZPO) have been used as individual drugs to treat acne vulgaris. BZPO is also available in various over-the-counter formulations. Clindamycin is an approved prescription drug, and its topical formulation for the treatment of acne is available in solution, gel, or lotion forms (CLEOCIN T).

Mechanism: BZPO has been shown to be effective against *Propionibacterium acnes*, the organism involved in the pathogenesis of acne vulgaris and found in sebaceous follicles and comedones. The antibacterial action of BZPO is linked to its potent oxidizing properties; its degradation to benzoic acid in the skin generates free radicals. Additionally, BZPO may also act as a keratolytic and keratogenic agent. Its antiacne activity is also believed to derive from its irritant properties. It induces proliferation of epithelial cells, leading to sloughing and repair.

Clindamycin is a semisynthetic antibiotic, which primarily affects the inflammation of acne through its activity against *P. acnes*. It is proposed that inhibition of leukocyte movement may be a major mechanism by which certain antibiotics (e.g., clindamycin, erythromycin, tetracycline) suppress inflammatory skin diseases. However, the topical antibiotic therapy has been associated with the development of resistant bacterial strains. According to the literature reports quoted by the sponsor, the topical use of clindamycin may result in clindamycin-resistant *P. acnes*. It has also been observed that erythromycin-resistant *P. acnes* may also develop cross-resistance to clindamycin. A combined erythromycin BZPO gel (BENZAMYCIN) is marketed for the treatment of acne. Reportedly, it is superior to either agent alone (Goodman and Gilman, 1996). The proposed combination of clindamycin and BZPO is based on the same logic, and it is expected that two drugs would not interfere with each other's activity.

Nonclinical studies: The active ingredients BZPO and clindamycin had been individually evaluated in a large number of animal studies. The original submission (05-14-1996) included individual summaries of published pharmacologic and toxicologic profiles of both the active agents. To support the combination product (Clindoxyl™ Gel), the sponsor had conducted three animal studies listed below.

1. *Four-week dermal toxicity study in rats.
2. Twelve-week dermal toxicity study in minipigs.
3. Ocular irritation test in rabbits.

*This study was reviewed under the original review dated 10-18-1996

1. 90-Day Dermal Toxicity Study of Clindoxyl Gel in Minipigs (0470PS50.001; August-November 1998).

Background: In a communication dated March 9, 1998, it was recommended that the sponsor should conduct a 12-week dermal toxicity study, preferably in minipigs, with the final formulation stored for the allowed storage period (shelf life) of 60 days. The sponsor has conducted the recommended study.

Facility: ———

GLP compliance: A signed GLP statement is included.

MATERIALS AND METHODS

Test article 1: Aged Clindoxyl Gel (stored for 60 days at room temperature), Lot numbers D0048/A D0048/C, and D0048/E
Test article 2: Non-aged Clindoxyl Gel, Lot number D0048
Control article/vehicle: Vehicle Gel, Lot number D0781
Animals: Approximately 2-4 months old (9-14 kg) Minipig-Yu^{R} Yucan;
3 animals /sex/dose group
Dose groups (mg/kg): Vehicle Gel (500), Non-aged Clindoxyl Gel (500), Aged Clindoxyl Gel (50 and 500)
Procedures: Animals received once daily application of the respective test article on a pre-shaved site (10x25cm) on the back for 90 consecutive days. Each day, after six hours of exposure, the application sites were gently cleaned with a gauge soaked in the warm water.
Parameters evaluated:
Clinical observations and Draize's scoring of dermal lesions: Daily through the study period
Body weight: Prior to initiation of dosing, and weekly thereafter
Ophthalmoscopy: Ophthalmic examinations were conducted by indirect ophthalmoscopy and slit lamp biomicroscopy.
Clinical pathology: Blood samples collected prior to study initiation and terminal sacrifice on day 91, were used to evaluate hematologic (9 parameters) and serum chemistry parameters (19 parameters).
Gross pathology and Organ weights: At necropsy, all animals were examined for any internal or external gross lesions. The following organs were weighed: adrenals, brain, kidneys, liver, testes, and ovaries.
Histopathology: All the gross lesions and approximately 42 tissues/organs from all the animals were subjected to complete microscopic examination.

Statistical analysis: Analysis of variance and Dunnett's procedure were used to screen the statistical significance and degree of significance, respectively.

Results:

- No deaths or drug-related clinical signs of local or systemic toxicity were observed during the treatment period. A few animals in each group including controls exhibited some sloughing of dry skin (12/24) and redness (5/24) at the treated sites. These lesions were not considered drug related.
- No inter-group differences in body weights and food consumption were recorded.
- No drug-related ocular lesions developed during the treatment period.
- There were no drug or dose-related changes in any of the hematologic or serum chemistry parameters. A few statistically significant ($p<0.05$) changes such as decreased levels of Hb and Hct in the non-aged gel group, were still within the range of normal values for this strain.
- No gross lesions or inter-group differences in the absolute and relative organ weights were observed.
- Inflammation due to focal granulomas observed in the lungs of one control female and one female of 500mg aged clindoxyl gel group was not considered to be drug-related. Some foreign material was found in the center of at least one small granuloma.

Conclusion: The treatment with the fresh and aged Clindoxyl Gels for 13 weeks did not produce any systemic or local toxicity in minipigs.

2. Evaluation of the Ocular Irritation Index of CLINDOXYL™Gel (1% Clindamycin as Phosphate, and 5% Benzoyl peroxide) and of PanOxyl® Aquagel (5% Benzoyl Peroxide) in Rabbits (R & D Report SCI-99-R01; September 1999).

Facility: I

MATERIALS AND METHODS

Test system: Six albino rabbits (strain, sex, age and body weights not reported); 3 animals per test article.
Test articles: Clindoxyl Gel (lot # E0320)
PanOxyl Aquagel 5% (lot #90060)

One eye of each rabbit received application of 100mg of the test article, the other eye remained as untreated control. At 1, 4, 24, 48, and 72 hours post-application, the eyes were examined for opacity and ulceration of the cornea, inflammation of the iris, and erythema, edema and discharge from the conjunctiva. The ocular lesions were graded using method of Kay and Calandra.

Results: At no observation period, any of the test articles exhibited any reaction on the cornea and iris. In case of clindoxyl gel, minor erythema of the conjunctiva was observed in all the rabbits at one hour and one rabbit at 24 hour, thereafter no ocular lesions were observed. No edema or discharge from the conjunctiva were observed at any time point. Based on the scores for ocular lesions, clindoxyl gel was graded as very slightly irritant.

Following the application of PanOxyl Aquagel, minor erythema and edema of the conjunctiva were observed in all rabbits throughout the study. This formulation was graded as slightly irritant.

Overall Summary of Pharmacology and Toxicology of clindoxyl gel, benzoyl peroxide, and clindamycin: No pharmacology or pharmacokinetic studies were conducted with the combination drug product. To support the clinical safety of clindoxyl gel, the sponsor has conducted three basic toxicology studies.

In a 28-day dermal toxicity study in rats at the highest dose level of 2 grams clindoxyl gel/kg (~200 times the proposed clinical dose), mild erythema occurred in a time and dose-dependent fashion. In a 90-day dermal toxicity study in minipigs, clindoxyl gel (50 and 500mg/kg) did not produce any local or systemic toxicity. In a primary eye irritation assay in rabbits, the drug product was established as a very weak irritant.

The safety of clindoxyl gel is primarily based on the individual safety profiles of benzoyl peroxide and clindamycin. Both antibacterial compounds have been used as single entity agents in topical treatment of acne vulgaris. However, both operate through different mechanisms. *In vitro,* clindamycin HCl inhibited the chemotactic activity of human leukocytes. It is suggested that inhibition of leukocyte movement may be the principal mechanism to suppress the inflammatory skin diseases. The antibacterial action of BZPO is linked to its potent oxidizing properties; its degradation to benzoic acid in the skin generates free radicals. Additionally, BZPO may also act as a keratolytic and keratogenic agent. Its antiacne activity is also believed to derive from its irritant properties. It induces proliferation of epithelial cells, leading to sloughing and repair.

The oral LD_{50} for BZPO in mice ranged from 1.4 to 2.1 g/kg. The acute doses in the mice caused depression in the central nervous system and deaths. In rodents, the acute oral toxicity seems to be formulation and species dependent. An oral dose of 3g BZPO/kg to

rats from a 10% BZPO lotion did not produce any adverse effects. However, mice receiving 1.25-2.5g BZPO/kg from another 10% BZPO formulation, were lethargic, prostrate, and exhibited labored respiration within four hours of dosing. In a single dose dermal study in guinea pigs, doses up to 1g/kg produced a dose-related loss in body weight.

The absorption and biodisposition of ^{14}C-BZPO were assessed *in vitro* using excised human skin, and *in vivo* in the rhesus monkeys (Nacht et al., 1981). In the skin, BZPO penetrated through the stratum corneum, follicular openings, or both, and was recovered as benzoic acid at the dermal side. In monkeys, following the topical or intramuscular administration of ^{14}C-BZPO, up to 98% of the radioactivity in the urine was present in benzoic acid. It is suggested that BZPO penetrated into the skin layers is metabolized to benzoic acid, which then enters the systemic circulation. Since no hippuric acid was found in monkey urine, it was inferred that renal clearance of BZPO was sufficiently rapid as to preclude its hepatic conjugation with glycine.

Percutaneous penetration and metabolism of BZPO were assessed *in vitro* using human skin and *in vivo* in 5 patients with leg ulcers (Morsches and Holzmann, 1982). In the excised skin, BZPO was metabolized to benzoic acid primarily in the dermis. The portion that penetrated the intact skin was benzoic acid only.

Following topical application of ^{14}C-BZPO 10% gel on the skin of hairless Sprague Dawley M rats, distribution and dissociation were determined at 3, 8, and 24 hours. Most of the applied dose was retained in the hornylayer where metabolic conversion to benzoic acid was low. The reservoir effect of the stratum corneum produced slow, sustained diffusion of radioactivity toward the living layers of skin down to the deeper dermis that justifies the localized action of BZPO. In the dermis, conversion to benzoic acid increased sharply and the metabolite was taken up by the systemic circulation (Wepierre et al., 1986).

The majority of *in vitro* studies based on the Ames test have been almost equally uniform in suggesting that BZPO is not a mutagen. However, Matula et al. (1987) attributed these negative results to the difficulty of dissolving BZPO in DMSO at an adequate concentration. However, when dissolved in acetone, BZPO exhibited weak mutagenic activity in Ames assay. In addition, this compound has also been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, cause DNA-protein cross-links in the human cells, and neoplastic transformation in mouse epidermal cells (Saladino et al., 1985; Hartley et al., 1985; Gensler and Bowden, 1983; Gindhart et al, 1985). It was also reported that BZPO induced a dose-dependent increase in the incidence of sister chromatid exchanges in Chinese hamster ovary cells (Jarventaus et al., 1984).

A single teratology study in white Leghorn chicken eggs indicated that at all dose levels, BZPO increased malformations at a moderate frequency, and except for the lowest dose, there was a dose-related increase in embryonic deaths (Korhonen et al., 1984).

The status of BZPO as a generator of free radicals is well established. There is also strong evidence to suggest that the free radical generating ability of BZPO is responsible for its tumor promotional effects. These include an increase in dark basal keratinocytes, epidermal hyperplasia, increased terminal differentiation and ornithine decarboxylase level, and inhibition of intercellular communication in mouse, hamster, and human cells (Slaga et al., 1981; Klein-Szanto and Slaga, 1982; Lawrence et al., 1984; Saladino et al., 1985; Binder and Volpenhein, 1988).

BZPO not only shares most of the tumor-promoting features of well-known tumor promoter TPA (Tetradecanoyl phorbol acetate), but also exhibits several properties of a complete carcinogen not shared by TPA. These include resistance to inhibition by retinoic acid, and induction of a high ratio of carcinomas to papilomas (Klein-Szanto and Slaga, 1982; Slaga et al., 1982, 1983).

Most long-term topical studies with BZPO were conducted with SENCAR (i.e., sensitive to carcinogens) mice. While promotion was observed almost in all studies, the potential for carcinogenicity was observed in a select few. However, it must be mentioned that most of these studies were of academic interest only, and were not conducted to meet any regulatory requirements. Procedural deficiencies found in these studies included inadequate number of animals, selection of doses without conducting any dose range-finding studies, inadequate data on animal survival, and lack of adequate controls. In one series of studies, the purity, stability and accuracy of dosing was questionable. In some published reports, data for both sexes were pooled for analysis. In one case, report was published only in the abstract form, and the study was further faulted by not counting all the tumors that developed. The most critical deficiency in all of these topical studies was the short duration of treatment.

In view of the inadequate information available about the carcinogenic/photocarcinogenic potentials of BZPO, the agency in 1992 recommended to the Nonprescription Drug Manufactures Association (NDMA) to conduct lifetime carcinogenicity studies in two species of rodents. It was also recommended that in a separate study, BZPO should also be evaluated for photo co-carcinogenicity. The studies conducted for NDMA are still in progress, and only interim reports have been received. Only after the complete reports are evaluated and results are presented to the appropriate committees, an official opinion regarding the carcinogenicity and photo co-carcinogenicity of BZPO will be established.

A number of over-the-counter and prescription drugs for topical applications contain BZPO in concentration ranging from 2.5 to 10 percent. In animals and humans, BZPO is

degraded in the upper layer of the epidermis to benzoic acid, and the trace amounts of parent drug, if at all absorbed, are rapidly excreted in the urine. No systemic toxicity has ever been reported in subjects treated with BZPO; however, dermal reactions (local irritation, contact allergy) have occurred in 10% of the patients using this drug for treatment of acne.

Most of the animal studies for clindamycin were conducted with clindamycin hydrochloride. The oral LD_{50} for clindamycin HCl in rats was 2618mg/kg; the intraperitoneal LD_{50} in mice was 361mg/kg. In mice, the intreaperitoneal dose around LD_{50} led to depression, whereas deaths occurred within minutes of intravenous dosing. The subcutaneous LD_{50} for clindamycin phosphate was 179mg/kg in the neonatal and >2,000mg/kg for the adult rats.

Five daily oral doses of 500mg clindamycin HCl/kg produced diarrhea in rats. A similar observation was made in dogs. In one-year oral study (0, 30, 100, and 300mg clindamycin HCl/kg/day) in rats, the inflammation of lacrimal and salivary glands (29/80) was the major adverse effect observed during the first week of treatment. After six months of treatment, rales, weight loss, and mortality associated with murine pneumonia occurred with increased frequency. At study termination, compared to controls, the weights of kidneys and liver were slightly increased in the drug treated rats. Seven deaths in the high-dose group were related to the drug treatment. In one-year dog study, the MTD for clindamycin HCl was considered to be greater than 300mg/kg/day but less than 600mg/kg/day. In the 300mg-dose group, sporadic elevation in serum transaminases was observed.

In 22-day dermal toxicity studies conducted with clindamycin HCl in pigs, and with clindamycin phosphate in rats; two daily applications in pigs varied from 7.33 to 10.26 mg clindamycin/kg, while three daily applications in rats varied from 50 to 70mg clindamycin/kg/day. In both species, no gross or microscopic lesions for irritation were observed.

The adverse local and systemic effects of clindamycin in humans are well known. In severe infections, patients are administered intravenous or intramuscular doses of 600 to 1200 mg drug per day. At these dose levels, the incidence of gastrointestinal disturbance (abdominal pain, diarrhea) has been reported in 2 to 20% of patients; 0.01 to 10% patients developed psuedomembraneous colitis (abdominal pain, diarrhea, fever, mucus and blood in the stools) caused by the toxin released by *Clostridium difficle*. Dermal reactions (contact dermatitis, irritation, oily skin, Gram-negative folliculitis) have been reported in approximately 10% of patients treated with 1% clindamycin phosphate.

References:

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15. Slaga, T.J., Solanke, V., and Logani, M. (1983). Studies on the mechanism of action of antitumor promoting agents: Suggestive evidence for the involvement of free radicals in promotion. *Radioprotectors and Anticarcinogens* 471-485.
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Interpretation of safety data:

Clindamycin phosphate in the body is rapidly hydrolyzed to clindamycin, and about 90% of it is converted into two inactive excretory bilary metabolites, N- demethylclindamycin and clindamycin sulfoxide. Accumulation of clindamycin has been reported only in patients with severe hepatic damage.

A number of over-the-counter and prescription drugs for topical applications contain BZPO in concentration ranging from 2.5 to 10 percent. In animals and humans, BZPO is oxidized in the upper layer of the epidermis to benzoic acid, and the trace amounts of parent drug, if at all absorbed, are rapidly excreted in the urine. No systemic toxicity has ever been reported in subjects treated with BZPO; however, dermal reactions (local irritation, contact allergy) have occurred in 10% of the patients using this drug for treatment of acne.

In dermal studies in rats (4 weeks) and minipigs (13 weeks) conducted at dose levels 32 and 47 times (mg/m^2) the human dose, except for some mild erythema in rats, no other signs of local or systemic toxicity were observed in either of the species. In the clinical studies, the mild to moderate dermal lesions were observed only in 1.8% of the patients treated with Clindoxyl Gel.

The level of clindamycin in Clindaoxyl Gel is several hundred folds lower than that can cause systemic toxicity. The proposed clinical dose of 0.5g /day contains 5 and 25 mg of clindamycin and BZPO, respectively. At such low dose levels, no serious local or systemic adverse effects are expected.

Labeling: Clindoxyl Gel and clindamycin have never been tested in lifetime studies. Long-term photocarcinogenicity/carcinogenicity studies of BZPO conducted for the Nonprescription Drug Manufacturers Association are still in progress. To date only interim reports of these studies are available. Only after the results of the completed studies are evaluated and presented to the appropriate committees, will an official policy regarding use of BZPO be established. Till then, the agency's existing policy regarding labeling of BZPO products needs to be followed. Although the proposed dosing regimen for Clindoxyl Gel involves single daily application in the evening, the compliance among teenagers regarding exposure to sun has always been doubtful. Therefore, a statement

warning the user to avoid sun exposure following drug application should be included in the label, as it is currently required for drug products containing BZPO.

At this stage, the following tentative draft for labeling is proposed. This draft shall be revised after the agency has established the final rules regarding labeling of products containing BZPO.

Carcinogenesis, Mutagenesis and Impairment of Fertility

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Regulatory conclusions/recommendations: This new drug application is approvable, provided the sponsor agrees to the recommended changes in the labeling.

/S/ 08/14/00

Kumar D. Mainigi, Ph.D., M.P.H., D.A.B.T.

INDFS
8/22/00

CC: Original NDA 50-741
HFD-82
HFD-540
MO/Huene
Pharm/Mainigi
Chem/Vidra
CSO/Cintron

Concurrence:
A.Jacobs,TL/HFD-540 O.g in DFS 8/22/00
J.Wilkin, Dir/HFD-540 could not locate in DFS on 9/5/00
9/5/00

APPEARS THIS WAY
ON ORIGINAL

REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Division of Dermatologic and Dental Drug Products, HFD-540

NDA 50-741 (Original submission 05-14-1996)
DRUG: Clindoxyl™ Gel (Clindamycin phosphate 1%+Benzoyl Peroxide 5%)
SPONSOR: Stiefel Laboratories, Inc.
Route 145, Oak Hill, NY 12460
William A. Carr, Jr. (518-239-6901)

OCT 31 1996

Number of Volumes: Two (2)
Date CDER Received: 05-14-1996
Date Assigned: 05-17-1996
Date Review Started: 09-16-1996
Date Review Completed: 10-18-1996

Dosage and Route of Administration: Gel, topical
Category: Antibacterial
Indication: For the treatment of Acne Vulgaris
Review Objective: To evaluate the safety of two long approved and used antiacne drugs in combination.

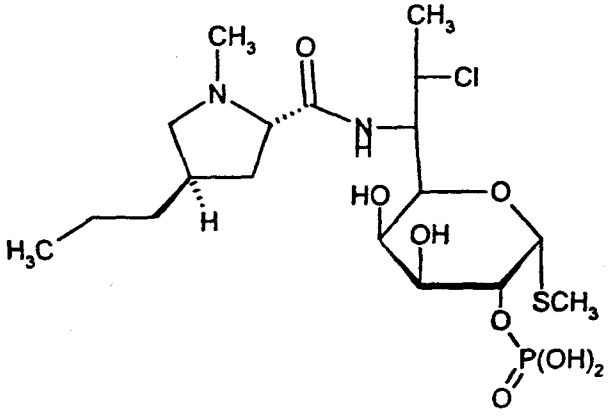
Chemical Names of Active Ingredients:

Clindamycin phosphate: Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*theo*-α-D-*galacto*-octopyranoside-2-(dihydrogen phosphate)

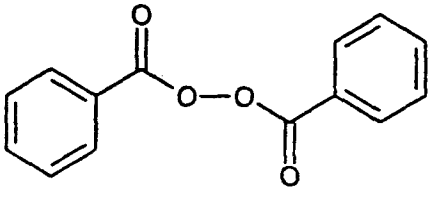
Benzoyl peroxide: Dibenzoyl peroxide

Chemical Structures:

Clindamycin phosphate



Benzoyl peroxide



Related INDs: [redacted]

Composition:

Active Ingredients	**Quantity (% w/w)**
Benzoyl peroxide	*
Clindamycin phosphate	**
Inactive Ingredients	
Carbomer 940	
Dimethicone	
Disodium Lauryl Sulfosuccinate	
Edetate Disodium	
Glycerin	
[redacted]	
Methylparaben	
Poloxamer	
Purified Water	
Sodium Hydroxide	
Total	100.00

* To provide 5.0% w/w benzoyl peroxide in the gel (when benzoyl peroxide is 75% active). The actual quantity needed to be adjusted based on the lot activity.
** To provide [redacted] w/w Clindamycin in the gel (when Clindamycin phosphate purity is 80%). The actual quantity needed to be adjusted based on the lot activity.

Background Information and Proposed Formulation: For over two decades, both clindamycin and benzoyl peroxide (BZPO) have been used as individual drugs to treat *acne vulgaris*. BZPO has been shown to be effective against *Propionibacterium acnes*, the organism involved in the pathogenesis of *acne vulgaris* and found in sebaceous follicles and comedones.The antibacterial action of BZPO is linked to its potent oxidizing properties, its oxidation to benzoic acid in the skin generates free radicals. Additionally, BZPO may also act as a keratolytic and keratogenic agent. Its antiacne activity is also believed to derive from its irritant properties. It induces proliferation of epithelial cells, leading to sloughing and repair.

Clindamycin is a semisynthetic antibiotic which primarily affects the inflammation of acne through its activity against *P. acnes*. It is an approved prescription drug for the topical treatment of acne and is available in solution, gel, or lotion forms (CLEOCIN T). It is proposed that inhibition of leukocyte movement may be a major mechanism by which certain antibiotics (e.g., clindamycin, erythromycin, tetracyclin) suppress inflammatory skin diseases. However, the topical antibiotic therapy has been associated with the development of resistant bacterial strains. A combined erythromycin BZPO gel (BENZAMYCIN) is marketed for the treatment of acne. Reportedly, it is superior to either agent alone (Goodman and Gilman, 1996). The proposed combination of clindamycin and BZPO is based on the same logic, and it is expected that two drugs would not interfere with each other's activity.

Nonclinical Safety Evaluation: The sponsor has conducted only one subchronic study to evaluate the safety of the proposed formulation. Prior to this submission, Clindoxyl™ Gel has never been tested in animals. The current submission also includes individual summaries of published pharmacologic and toxicologic profiles of benzoyl peroxide and clindamycin or clindamycin hydrochloride.

Twenty-eight-Day Repeated Dose Dermal Toxicity Study of Clindoxyl Gel in Sprague Dawley Rats (93G-2325; November-December 1993).

Facility: —
GLP Declaration: A signed statement is enclosed

Study Objective: This study aimed to investigate the local and systemic adverse effects of the proposed formulation resulting from interaction (if any) of two active components.

Study Design

Test Substances/ Dose Levels: Clindamycin Gel (Lot # 292313)-- 80, 400, and 2,000 mg / kg
Vehicle Gel (Lot # 237316)--2,000 mg / kg

Test Animals: Six to eight weeks old male and female Sprague-Dawley rats (150-250 g).
10 rats / sex / dose level.

Procedures: Animals received daily applications of test material on preshaved sites (~ 10% of body surface) under occlusion for 28 consecutive days. Following 6 hours of daily exposure to drug or vehicle, sites were rinsed with water and scored for dermal reactions according to Draize. Body weights and food consumption were determined weekly. Prior to necropsy, blood samples collected from all animals were used to determine hematologic (6 tests) and clinical chemistry (13 tests) parameters. Absolute and relative weights of liver, kidneys, and gonads were determined. Histopathologic examinations were conducted on all gross lesions and about 25 tissues / organs taken from all the control and high dose animals.

Results / Conclusions: No drug related deaths or clinical signs of toxicity were observed at any dose level; the highest dose used was about 200 times the proposed clinical dose. A few sporadically distributed but statistically significant changes in hematologic (increased neutrophils) and clinical chemistry (increased glucose and aspartate aminotransferase) parameters were not considered toxicologically significant. Necropsy examination did not reveal any drug related gross lesions, nor were any intergroup differences in organ weights and histopathologic lesions observed. Dose and time dependent slight to mild erythema was observed in drug treated animals; however, there were no signs of edema at any dose level.

Labeling: Except for one subchronic toxicity study reviewed above, Clindoxyl Gel has never been tested in any other *in vivo* or *in vitro* study. Long-term photocarcinogenicity / carcinogenicity studies of BZPO conducted for the Nonprescription Drug Manufacturers Association are still in progress and reports are expected by the end of 1996. Only after the results of these studies are evaluated and presented to the appropriate committees, will an official policy regarding use of BZPO be established. Till then, the agency's existing policy regarding labeling of BZPO products needs to be followed. Although the proposed dosing regimen for Clindoxyl Gel involves single daily application in the evening, the compliance among teenagers regarding exposure to sun has always been doubtful. Therefore, a statement warning the user to avoid sun exposure following drug application should be included in the label, as it is currently required for drug products containing BZPO.

At this stage, the following tentative draft for labeling is proposed. This draft shall be revised after the agency has established the final rules regarding labeling of products containing BZPO.

ay

Refeences:

Matula, T.I., Downie, R.H. and Barrett, N (1987). Mutagenicity studies of benzoyl peroxide in bacteria. Environmental Mutagenicity Society:Abstract # 177.
Jarventaus, H., Norpa, ., Linnainma, K. And Sorosa, M (1984). SCE induction in CHO cells by peroxies used in the plastic industry. Mut. Res. 130, 249 (Abstract 11-3C-8).
Epstein, S.S., Arnold, E., Andrea, J., Bass, Y. And Bishop, Y (1972). Detection of chemical mutagens by the dominant lethal assay in the mous. Toxicol. Appl. Pharmacol. 23: 288-325.

TOXICOLOGIST'S DISCUSSION AND INTERPRETATION OF SAFETY DATA

Both active ingredients of Clindoxyl™ Gel have been evaluated as independent entities and used widely for the treatment of acne vulgaris. The adverse local and systemic effects of clindamycin are well known. In severe infections, patients are administered intravenous or intramuscular doses of 600 to 1200 mg drug per day. At these dose levels, the incidence of gastrointestinal disturbance (abdominal pain, diarrhea) has been reported in 2 to 20% of patients; 0.01 to 10% patients developed psuedomembraneous colitis (abdominal pain, diarrhea, fever, mucus and blood in the stools) caused by the toxin releasd by *Clostridium difficle*. Dermal reactions (contact dermatitis, irritation, oily skin, Gram-negative folliculitis) have been reported in approximately 10% of patients treated with 1% clindamycin phosphate. The drug in the body is rapidly hydrolyzed to clindamycin, and about 90% of it is converted into two inactive excretory bilary metabolites, N- demethylclindamycin and clindamycin sulfoxide. Accumulation of clindamycin has been reported only in patients with severe hepatic damage.

A number of over-the-counter and prescription drugs for topical applications contain BZPO in concentration ranging from 2.5 to 10 percent. BZPO is oxidized in the upper layer of the epidermis to benzoic acid, and the trace amounts of parent drug, if at all absorbed, are rapidly excreted in the urine. No systemic toxicity has ever been reported in subjects treated with BZPO; however, dermal reactions (local irritation, contact allergy) have occurred in 10% of the patients using this drug for treatment of acne. The level of clindamycin in Clindaoxyl Gel is several hundred folds lower than that can cause systemic toxicity. The proposed clinical dose of 0.5g / day contains 5 and 25 mg of clindamycin and BZPO, respectively. At such low dose levels, no serious local or systemic adverse effects are expected.

Drug interaction is a critical issue. Looking into the chemical reactivity of BZPO, it is expected that this compound could damage the structure and / or function of clindamycin in several ways. First, their interaction might promote the adverse effects of clindamycin otherwise not observed at the nontoxic dose level. Second, free radicals generated from BZPO might break the antibiotic molecule into some toxic degradation products. Third, the interaction could also adversly modulate the antiacne activity of both agents.

In a rat subchronic dermal toxicity study conducted at a dose level 200 times the human dose, except for some mild erythema, no other signs of toxicity were observed. Benzamycin, a combined erythromycin BZPO gel has been marketed since 1984. This product is known to be more effective in the treatment of acne vulgaris than either components used as single entity drugs. Reportedly, clindamycin and erythromycin share a common mechanism for their antiacne activity. In addition, clindamycin probably will not interfere with the free radical generation from BZPO, and the latter will not inhibit the hydrolysis of clindamycin phosphate to clindamycin, since these are completely different and independent chemical reactions. It is also assumed that because of the lack of any interaction, the concurrent use of BZPO and clindamycin should not cause any change in the pharmacokinetic behavior of either agent.

Irrespective of the claims made by the sponsor that BZPO is a not a carcinogen, the issue of potential carcinogenicity and / or photocarcinogenicity of BZPO has not been officially settled. Therefore at present, as with all other BZPO products, the label of Clindoxyl™ Gel should also contain the required warning about exposure to sun.

REGULATORY CONCLUSIONS: This new drug application is approvable, provided the sponsor agrees to the recommended changes in the labeling now and also in the future when the safety issues of BZPO are officially settled.

1st 10/23/96

Kumar D. Mainigi, Ph.D; M.P.H; D.A.B.T.
Toxicologist

CC: Original NDA 50-741
HFD-82
HFD-540
MO / Walker
Pharm / Mainigi
Chem / Rejali
CSO / White
Pharm / Jacobs

Concurrence:
A.Jacobs, TL, HFD-540 G. J. 10/23/96
J.Wilkin, Dir, HFD-540 GJ 10/31/96

APPEARS THIS WAY
ON ORIGINAL

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 50-741
Sequence number/date/type of submission: 000 / 22 February 2002 / AZ
Information to sponsor: No
Sponsor and/or agent: Stiefel Laboratories, Inc.
Manufacturer for drug substance:
Clindamycin phosphate: ———

Or ———

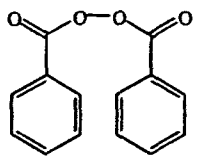
Benzoyl peroxide: ———

Reviewer name: Paul C. Brown
Division name: Division of Dermatologic and Dental Drug Products
HFD-540
Review completion date: August 1, 2002

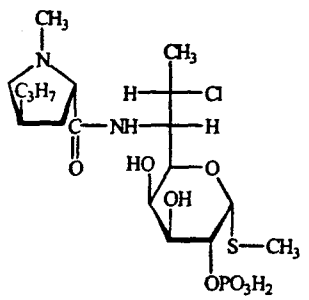
Drug:

Trade name: Clindoxyl Topical Gel
Generic name (list alphabetically): benzoyl peroxide and clindamycin phosphate
Chemical name: Benzoyl peroxide: Dibenzoyl peroxide
Clindamycin phosphate: Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*theo*-α-D-*galacto*-octopyranoside-2-(dihydrogen phosphate)

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
CAS registry number: Benzoyl peroxide: 94-36-0; Clindamycin phosphate: 24729-96-2
Structure:



Benzoyl peroxide



Clindamycin phosphate

Relevant INDs/NDAs/DMFs: ———

Drug class: antiacne

Indication: acne vulgaris

Clinical formulation: gel

Ingredients	Quantity (% w/w)
Benzoyl Peroxide	7*
Clindamycin Phosphate	**
Carbomer 940	
Dimethicone	
Disodium Lauryl Sulfosuccinate	
Edetate Disodium	
Glycerin	
Silicone Dioxide	
Methylparaben	
Poloxamer	
Sodium Hydroxide	
Purified Water	)

* To provide 5.0% w/w benzoyl peroxide in the gel (when benzoyl peroxide is 75% active). The actual quantity used to be adjusted based on the lot activity and quantity of water adjusted accordingly.

** To provide —— Clindamycin in the gel — manufacturing overage) in finished product (when Clindamycin phosphate purity is ——). The actual quantity used to be adjusted based on the lot activity and quantity of water adjusted accordingly.

Route of administration: topical to the skin

Proposed use:

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Introduction:
The sponsor was informed that this NDA was not approvable on September 6, 2000 due to clinical and CMC issues. The NDA was approvable from a pharm/tox perspective. The sponsor has submitted an amendment to the NDA to try to address the approvability issues. They have also submitted updated labeling.

Studies reviewed in the this submission:
None

Studies not reviewed in this submission:
None

Executive Summary

I. Recommendations

A. Recommendation on Approvability
The NDA is approvable from a pharm/tox perspective provided that certain phase 4 agreements are made and that the label is modified as detailed below.

B. Recommendation for Nonclinical Studies
It is recommended that the sponsor conduct a dermal carcinogenicity study and evaluate the effects of the drug on UV-induced skin cancer. These evaluations may be conducted after NDA approval.

C. Recommendations on Labeling
Several changes to the label are recommended. These are detailed in the review.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
No new nonclinical findings were presented in the current submission.

B. Pharmacologic Activity
No new information on the pharmacologic activity of the drug substances was presented in the current submission.

C. Nonclinical Safety Issues Relevant to Clinical Use
None

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
HFD-540/Pharm. Sup./Jacobs
HFD-540/MO/Huene
HFD-540/Clin. TL/Luke
HFD-540/PM/Lutwak
HFD-540/Chem/Vidra

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology summary:

BZPO has been shown to be effective against *Propionibacterium acnes*, the organism involved in the pathogenesis of acne vulgaris and found in sebaceous follicles and comedones. The antibacterial action of BZPO is linked to its potent oxidizing properties; its degradation to benzoic acid in the skin generates free radicals. Additionally, BZPO may also act as a keratolytic and keratogenic agent. It induces proliferation of epithelial cells, leading to sloughing and repair.

Clindamycin is a semisynthetic antibiotic, which may affect the inflammation of acne through its activity against *P. acnes*. It is proposed that inhibition of leukocyte movement may be a major mechanism by which certain antibiotics (e.g., clindamycin, erythromycin, tetracycline) suppress inflammatory skin diseases. The topical use of clindamycin may result in clindamycin-resistant *P. acnes*. It has also been observed that erythromycin-resistant *P. acnes* may also develop cross-resistance to clindamycin.

Pharmacology conclusions:

No new pharmacology information was included in the current submission.

III. SAFETY PHARMACOLOGY:

None

III. PHARMACOKINETICS/TOXICOKINETICS:

PK/TK summary:

Several published studies have shown that benzoyl peroxide is absorbed into the skin and is converted in the skin to benzoic acid. It appears that essentially all of the systemic exposure is to benzoic acid.

Studies in rats and dogs show that clindamycin is readily absorbed from the gastrointestinal tract and is excreted in the urine and feces. The products excreted in the urine include unchanged clindamycin, clindamycin sulfoxide and N-demethyl clindamycin. In dog, clindamycin is also glucuronidated. 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.

PK/TK conclusions:

No new nonclinical pharmacokinetics/toxicokinetics information is included in this submission.

IV. GENERAL TOXICOLOGY:

Toxicology summary:

The sponsor conducted two toxicology studies with the Clindoxyl gel. In a 28-day dermal toxicity study in rats at the highest dose level of 2 grams Clindoxyl gel/kg (~200 times the proposed clinical dose), mild erythema occurred in a time and dose-dependent fashion. In a 90-day dermal toxicity study in minipigs, Clindoxyl gel (50 and 500mg/kg) did not produce any local or systemic toxicity.

Benzoyl peroxide:
Studies in animals and man have shown benzoyl peroxide to be a dermal irritant and possibly a contact sensitizer. It is not clear if standard chronic toxicity studies of benzoyl peroxide have been published. However, a variety of long term studies in various models have been conducted to investigate the possible carcinogenicity of benzoyl peroxide (see below). In addition, benzoyl peroxide has been used for a number of years at concentrations of up to 10% in OTC products for acne without any apparent significant systemic toxicity. Since benzoyl peroxide is converted to benzoic acid in the skin, this metabolite is likely to account for any systemic exposure. Benzoic acid is listed as GRAS substance for food and the World Health Organization has established an acceptable daily intake of benzoic acid of 5 mg/kg. A Cosmetic Ingredient Review (CIR) Expert Panel stated in a report published in 2001 that effects of benzoic acid in chronic exposure animal studies were limited to reduced feed consumption and reduced growth.

Clindamycin:
The most pronounced toxicity associated with clindamycin has been pseudomembranous 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. 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 warning about this adverse effect is included in the labels of currently approved formulations of clindamycin.

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.

Toxicology conclusions:
No new toxicology information was included in the current submission.

V. GENETIC TOXICOLOGY:

Genetic toxicology summary:

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 labels of two recently approved drug products containing benzoyl peroxide include the following wording.

> 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.

A rat micronucleus test and an Ames Salmonella reversion test have been performed with clindamycin. Both tests were negative.

Genetic toxicology conclusions:
No new genotoxicity information is included in the current submission.

Labeling recommendations:
It would be appropriate to include a description of the genotoxicity information mentioned above. The suggested wording is reviewed in section IX below.

VI. CARCINOGENICITY:

Carcinogenicity summary:
The carcinogenicity and photocarcinogenicity of the combination of benzoyl peroxide and clindamycin phosphate have not been evaluated.

The carcinogenicity and photocarcinogenicity of clindamycin phosphate were evaluated in topical studies submitted in an NDA for a different product. Apparently, no other studies of clindamycin carcinogenicity have been conducted or published.

The carcinogenicity of benzoyl peroxide has been investigated in a number of published studies; however, most of the studies have not been of two years duration and have not used daily application. In most studies, benzoyl peroxide applied alone did not produce skin tumors; however, in a study using SENCAR mice, benzoyl peroxide alone applied 2 times per week for 51 weeks produced skin tumors in 5 of 20 animals (Kurokawa et al., 1984). While the studies evaluating the carcinogenicity of benzoyl peroxide applied alone are limited, the studies clearly show that benzoyl peroxide is a tumor promoter and tumor progression agent in the skin in several animal models. The models in which benzoyl peroxide has shown activity include chemically or UV-initiated mice and hamsters. In one study conducted by the National Toxicology Program, benzoyl peroxide was shown to promote tumor formation initiated by dimethylbenzathracene or methyl-nitro-nitrosoguanidine in B6C3F_1, Swiss CD-1 and SENCAR mice (NTP TR 441, 1996). In this study the initiator was administered once and benzoyl peroxide was administered weekly for 52 weeks. Benzoyl peroxide by itself did not produce skin tumors in any strain in this study.

It has been argued that the tumor promoting ability of benzoyl peroxide in animal models is not relevant to humans (Binder et al., 1995; Kraus et al., 1995). Proponents of this view argue that induction of cellular proliferation is required in order for benzoyl peroxide to cause tumor promotion and that since this proliferation is not observed in humans, benzoyl peroxide is not a tumor promoter in humans. An alternative argument would be that benzoyl peroxide might be a tumor promoter in human skin if it were used at a high enough dose and duration. Also it is possible that other mechanisms may contribute to the tumor promoting ability of benzoyl peroxide. Several mechanisms have been proposed to explain the tumor promoting ability of benzoyl peroxide. Some of these mechanisms might occur even in the absence of cellular proliferation. A scientific consensus on which mechanisms are most relevant has not yet been established.

Human epidemiologic studies on the increased risk of skin cancer from benzoyl peroxide are limited in number and size but have not shown any association between benzoyl peroxide use and skin cancer. The largest and most relevant study was a retrospective study conducted in Canada, which examined acne treatments used by 966 facial skin cancer patients and 3864 age- and sex-matched controls over a period of 22 years. This study found no increased risk of skin cancer in individuals reporting benzoyl peroxide use for acne (Hogan et al., 1991).

The International Agency for Research on Cancer has reviewed the human and animal data on the carcinogenic potential of benzoyl peroxide (IARC monograph, 71:345-358, 1999). They concluded that there was limited evidence in animals and inadequate evidence in humans for the carcinogenicity of benzoyl peroxide. Overall, they concluded that benzoyl peroxide was not classifiable as to its carcinogenicity to humans.

In an evaluation of the safety of benzoyl peroxide in over-the-counter drug products, the agency stated in 1991 that the animal studies conducted were not adequate to evaluate the carcinogenicity of benzoyl peroxide (FR 56(102):37622, August 7, 1991). The agency was concerned that benzoyl peroxide might show complete carcinogenic effects with a long latency period since it possessed weak genotoxic potential. The Consumer Health Products Association (CHPA, formerly the NDMA) has conducting two-year dermal carcinogenicity studies in rats and mice with a benzoyl peroxide carbopol gel formulation to help address this concern. The CHPA is currently in the process of submitting these studies to the agency.

The Tg.AC transgenic mouse model is considered by the Agency to be an acceptable alternative model for the evaluation of carcinogenicity. Studies with Tg.AC mice are typically conducted using 20 weeks of treatment and compounds that are tumor promoters can be detected by this model. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in Tg.AC mice in a study with a total of 20 weeks of topical treatment (Spalding et al., 1993). This positive result should be included in the label.

In addition to studies in animals, several other studies have evaluated the impact of benzoyl peroxide treatment on intercellular communication in cultured cells. These assays are purported to identify nongenotoxic carcinogens. Results have been variable. Cases of decreased, increased or unchanged intercellular communication have been observed (for examples see Mikalson and Sanner, 1994; Jansen and Jongen, 1996 and Rivedal et al., 2000).

Benzoyl peroxide photocarcinogenicity:
A photococarcinogenicity study of 5% benzoyl peroxide has been conducted by the CHPA. This did not detect any increase in UV-induced tumor formation in hairless mice treated with a 10% benzoyl peroxide carbopol gel. On the other hand, a different study submitted to the Division of Dermatologic and Dental Drugs Products under a different NDA showed that application of a 5% benzoyl peroxide gel increased UV-induced tumor formation in hairless mice. These studies were conducted by the same laboratory using similar protocols. Results of photococarcinogenicity studies may vary from product to product since the vehicle can have pronounced effects on photocarcinogenesis. Several other published studies using varying UV and drug regimens have not shown an enhancement of UV induced tumors by benzoyl peroxide. However, another study submitted by the CHPA showed a weak promotion effect of benzoyl peroxide in UV initiated mice. Increased progression of UV-induced tumors from a benign to malignant phenotype has also been observed in mice treated topically with benzoyl peroxide (Athar et al., 1996).

Published studies indicate that repeated application of benzoyl peroxide on human skin may decrease the minimal erythema dose (Jeanmougin et al., 1983; Jeanmougin and Civatte, 1988). Benzoyl peroxide also increases UVA-induced plasma membrane damage and lipid oxidation in cultured cells by an unknown mechanism (Ibbotson et al., 1998). Benzoyl peroxide alone induces signs of chronic cutaneous damage in mouse skin similar to those induced by UVB light (Ibbotson et al., 1999). In this study, the effects of UVB and benzoyl peroxide together were additive.

Overall, the photococarcinogenicity studies conducted with benzoyl peroxide have provided mixed results. However, benzoyl peroxide decreases the human skin MED after repeated treatment and it has clear tumor promoting characteristics. Both of these mechanisms may contribute to an increased risk of photococarcinogenesis. Consequently, even with mixed results from photococarcinogenicity studies there is reason to be concerned about the potential for a photococarcinogenic effect from benzoyl peroxide containing products. It is possible that the sponsor's drug product could produce a positive result in a photococarcinogenicity study even though other studies may be negative.

Carcinogenicity conclusions:

Recommendations for further analysis:

It is recommended that the sponsor conduct a dermal carcinogenicity study and evaluate the effects of the drug on UV-induced skin cancer. These recommendations are made since the drug will be used chronically and because of the lack of carcinogenicity information on clindamycin phosphate and the combination of benzoyl peroxide with clindamycin phosphate. These evaluations could be conducted after approval of the NDA. These recommendations are consistent with phase 4 agreements made with other sponsors for similar combination drug products. For example, these same agreements were required for approval of a benzoyl peroxide/clindamycin phosphate topical gel product sponsored by Dermik Laboratories (approval letter dated 12/21/00).

Labeling Recommendations:
The label of Clindoxyl should contain information similar to the label for the benzoyl peroxide/clindamycin phosphate topical gel product sponsored by Dermik Laboratories, which

was recently approved. This includes a statement that benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The results of the Tg.AC mouse study should also be included in the label.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicology summary:
No reproductive or developmental toxicity studies have been conducted with Clindoxyl gel.

Benzoyl peroxide:
No reproductive or developmental toxicity studies have been conducted with benzoyl peroxide.

According to the 2001 CIR review, benzoic acid was associated with an increased number of resorptions and malformations in hamsters but there were no reproductive or developmental findings in two rat studies.

Clindamycin:
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.

Reproductive and developmental toxicology conclusions:

Labeling recommendations:
The label should include

VIII. SPECIAL TOXICOLOGY STUDIES:

Summary: In a primary eye irritation assay in rabbits, Clindoxyl gel was established as a very weak irritant.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Recommendation on approvability:
The NDA is approvable from a pharm/tox perspective provided that certain phase 4 agreements are made and that the label is modified as detailed below.

Recommendations on nonclinical studies:

It is recommended that the sponsor conduct a dermal carcinogenicity study and evaluate the effects of the drug product on UV-induced skin cancer. These evaluations could be conducted after NDA approval.

Review of labeling with basis for findings:
The Carcinogenesis, Mutagenesis, Impairment of Fertility and the Pregnancy section of the label submitted by Stiefel for Clindoxyl in the current amendment is essentially identical to the labeling of BenzaClin Topical Gel which is a product manufactured by Dermik Laboratories that also contains 1% clindamycin phosphate and 5% benzoyl peroxide. The NDA for BenzaClin was approved on 12/21/00.

The Carcinogenesis, Mutagenesis, Impairment of Fertility and the Pregnancy section of the label for Clindoxyl as proposed by Stiefel is reproduced below.

woman.

As noted above this label is the same as the label for BenzaClin except the name BenzaClin has been replaced with Clindoxyl. Several changes to these sections of the label are recommended. First, it is recommended . This study was conducted by Dermik in support of the NDA for BenzaClin. This study has not been published and it does not appear that Stiefel has the right to refer to this study. This study was recommended by the Division to help qualify the of Clindamycin phosphate found in BenzaClin.

The clindamycin [redacted] have been identified as [redacted] in Clindoxyl Topical Gel; however, Stiefel has established drug product specifications for the two [redacted] in Clindoxyl gel that are not more than 0.015% and 0.025%. According to the ICH Q3B guidance on Impurities in New Drug Products these are below the threshold requiring qualification. Therefore, removing the genotoxicity information on the clindamycin [redacted] from the Clindoxyl label is acceptable. BenzaClin had higher concentrations of these [redacted] and so qualification was recommended.

Additional genotoxicity studies of the clindamycin [redacted] are not recommended to support the Clindoxyl NDA because the levels of the [redacted] in the product are below the ICH Q3B threshold for qualification. In addition, there is no cause for concern to suggest that a genotoxicity study of the clindamycin [redacted], is necessary.

During discussions by the review team, it was suggested that the type of tumor be described for the TgAC study. The tumors induced in this study were squamous cell tumors. Therefore, it would be acceptable to add "squamous cell" before the words "skin tumors" in the sentence describing the results of this study.

Another change that is recommended is that the label should include the language for Pregnancy category C as prescribed in 21 CFR 201.57(f)(6)(i)(c). This section of 21 CFR states that if there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C: Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed."

The proposed label contains some limited information on developmental studies in rats and mice conducted with clindamycin but no studies have been conducted with Clindoxyl Topical Gel. This information can remain in the label but the specific wording for pregnancy category C should also be included.

Note: The label as proposed by the sponsor did not contain a precaution to patients to avoid sun exposure. Many other benzoyl peroxide-containing products have such a precaution. As noted above, benzoyl peroxide can increase the skin's sensitivity to sun and some photocarcinogenicity studies with benzoyl peroxide have given positive results. The Information to Patients section of the label for the approved product Benzamycin includes the following wording: "Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn." The lack of this type of warning in the proposed Clindoxyl label has been brought to the attention of the medical officer and clinical team leader.

Recommendations on labeling:

Note: The recommendations for labeling listed below have been incorporated into the draft label by the project manager during Division labeling meetings held for this NDA.

The following wording is recommended for the Carcinogenesis, Mutagenesis, Impairment of Fertility and the Pregnancy section of the label for Clindoxyl Topical Gel.

X. APPENDIX/ATTACHMENTS:

None

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Brown
8/1/02 10:23:03 AM
PHARMACOLOGIST

Abby Jacobs
8/1/02 10:50:09 AM
PHARMACOLOGIST

Jonathan Wilkin
8/4/02 04:36:32 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date September 5, 2000

From James D. Vidra, Ph.D., HFD-540

SEP 5 2000

Subject CMC Informational Requests for NDA 50-741/RS

To Wilson H. DeCamp, Ph.D.

Five CMC Informational Requests (IRs) were requested in a 5/14/97 Agency Letter. The two outstanding IRs should be submitted in the Project Management Letter with the previously discussed NDA deficiencies. The two IRs continue to remain outstanding:

1. Submit the justification for the hydrous benzoyl peroxide related substance specifications since none are included in the USP monograph for this bulk drug.

2. Provide a post-approval commitment statement to determine the viscosity for the first five production batches.

/S/

James D. Vidra, Ph.D.

Original NDA 50-741

HFD-540/Division File
HFD-540/DivDir/Wilkin 9/5/00
HFD-540/ChmRev/Vidra
HFD-540/ChmTL/DeCamp 9/5/00
HFD-540/ProjMgr/Cintron

File: N50741.RS.IR