

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

PHARMACOLOGY REVIEW(S)

MAR 17 1999

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

NDA 50-756 (Original submission 04-10-1998)

Drug: _____ **Topical Gel** (Clindamycin 1% and benzoyl peroxide 5%)

Sponsor: Dermik Laboratories, Inc.
500 Arcola Road
Collegetown, PA 19426-0107
Ronald F. Panner
(610) 454-3026

Number of Volumes: Six (6)

Date CDER Received: 04-13-1998

Date Assigned: 04-22-1998

Date of Review: 11-27-1998

Category: Antibacterial

Indication: Treatment of acne vulgaris

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Related submissions:

INDs:

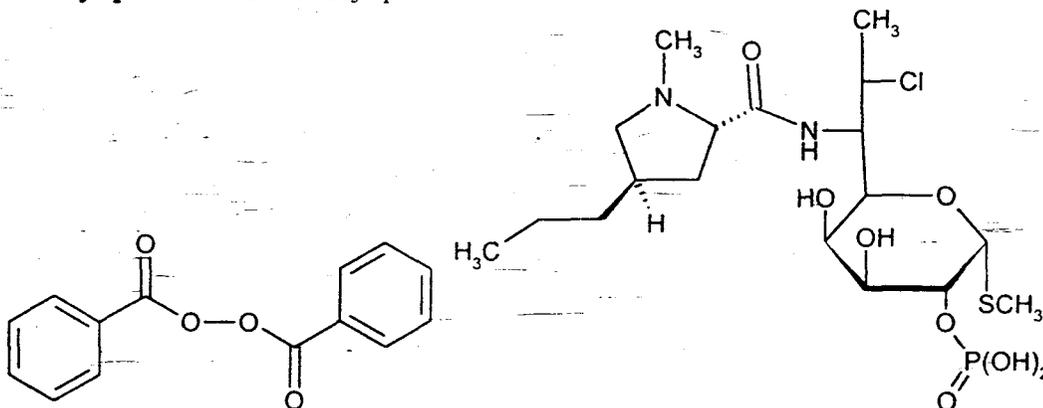
(Dermik)

NDA: 50-741 (Stiefel)

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



Drug Product: _____ Topical Gel will be marketed as a two component package, a jar containing benzoyl peroxide gel (BZPO) and a vial containing clindamycin phosphate powder (CP). Before dispensing, the pharmacist will dissolve the CP powder in distilled water and then mix it with BZPO gel in the jar.

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Quantitative Formulation of Dispensed Clinoxin Topical Gel

<u>Ingredient</u>	<u>mg/g</u>
Clindamycin phosphate, USP	[]
Hydrous benzoyl peroxide — USP	
Carbomer — NF	
Sodium hydroxide, NF	
Diocetyl sodium sulfosuccinate —	
Purified water, USP	

Background Information and Scientific Rationale: 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, 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 Safety Evaluation of Combination Drug Product: In a pre-NDA meeting on July 29, 1996, it was recommended to the sponsor that the *in vivo* genotoxicity of [redacted] product of clindamycin phosphate] found in the combination product as an impurity should be evaluated. In addition, although the active ingredients clindamycin phosphate and benzoyl peroxide had been individually tested in a large number of animal studies, these compounds had never been tested in combination. Therefore, the formulation need to be evaluated for its potential toxicity in two animal species. The sponsor had conducted all the recommended studies. These studies were reviewed under submission number 020 on 12-17-1997.

- In the Mouse Micronucleus assay, clindamycin phosphate sulfoxide was found to be nonclastogenic.
- In 3-month long dermal studies in rat and rabbit, the combination product as well as BZPO were tested as mild irritants.

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Labeling: Except for three studies mentioned above, _____ Topical Gel has never been tested in any other *in vivo* or *in vitro* study. Long-term photocarcinogenicity/carcinogenicity studies conducted for the _____ have not been evaluated. Only after the results of these studies are evaluated and presented to appropriate committees, will an official policy regarding use of BZPO be established. Therefore at this stage, 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, and the recommended phase IV studies have been evaluated.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Pregnancy Category C

References:

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, P., Linnainma, K. and Sorosa, M (1984). SCE induction in CHO cells by peroxides 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 mouse. Toxicol. Appl. Pharmacol. 23: 288-325.

Regulatory conclusion: In order to file this NDA, the sponsor agreed to conduct a few non-clinical studies. These studies were properly conducted and the evaluation of reported data in December 1997 supported the safety of the combination product. Therefore, from the non-clinical safety viewpoint, this NDA is approvable. In the meantime, the Investigations and the Pre-Approval Compliance Branch after observing some serious deficiencies in the manufacturing of _____ has recommended "to withhold approval of this NDA" (Appendices I-II). In addition, the review chemist has pointed out several major impurities in clindamycin phosphate (Appendix III). The sponsor has yet to answer some queries from the review chemist, including the identification of a single unknown impurity _____. It is possible that some of these impure preparations were used to conduct the recommended subchronic studies, however, at this stage this fact has not been properly established.

Regulatory Recommendations:

1. In case the two subchronic animal studies were not conducted with the unknown _____ impurity, the sponsor will need to qualify that impurity by conducting at least one subchronic study with the marketed drug product. Alternatively, this impurity could be qualified in conjunction with a dose-range finding study that needs to be conducted for dermal carcinogenicity study mentioned under #2 (below).
2. Acne is considered to be a chronic condition requiring long-term treatment. In phase IV, the sponsor should conduct a dermal carcinogenicity study and study effects on UV-induced skin carcinogenicity.

/S/ 3/12/99

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

CC: Original NDA 50-756
HFD-82
HFD-540
MO/Huene
Chem/Vidra
Pharm/Mainigi
Pharm/Jacobs
CSO/White

Concurrence:
A.Jacobs, TL, HFD-540
J.Wilkin, Dir, HFD-540

/S/ 3/11/99
/S/ 3/12/99

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Message to be conveyed to the sponsor

1. In case the two subchronic animal studies were not conducted with the unknown impurity, the sponsor will need to qualify that impurity by conducting at least one subchronic study with the marketed drug product. Alternatively, this impurity could be qualified in conjunction with a dose-range finding study that needs to be conducted for dermal carcinogenicity study mentioned under #2 (below).
2. Acne is considered to be a chronic condition requiring long-term treatment. In phase IV, the sponsor should conduct a dermal carcinogenicity study and study effects on UV-induced skin carcinogenicity.

**APPEARS THIS WAY
ON ORIGINAL**