

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-782

MICROBIOLOGY REVIEW(S)

APR 20 2000

Consultative Review for HFD-540
Division of Dermatologic and Dental Drug Products
Clinical Microbiology Review

Requester: Indira Kumar

Date of Request: 2-2-00

Date Received by DAIDP: 2-3-00

Reason for Request: Clinical Microbiology Review of an original NDA

IND/NDA Number: ~~000000~~, 50782 (new #)

Review Date: 2-4-00

Submission/Type: Original NDA

Document Date: 1-27-00

Assigned Date: 2-7-00

Applicant: Clindagel, LLC
4189 Chaparral Court
Santa Rosa, CA 95409

Authorized U.S. Agent: Target Research Associates
554 Central Avenue
New Providence, NJ 07974

Contact Person: Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs
Target Research Associates
554 Central Avenue
New Providence, NJ 07974
Phone: (908) 464-7500

Drug Product Name:

Proprietary: Clindagel™

Nonproprietary/USAN: Clindamycin Phosphate ——— gel

Code Names/ #'s:

Therapeutic Class: Antimicrobial

Pharmacological Category/Indication:
Clindagel™ 1% topical gel is: ~~indicated~~ for treatment of acne vulgaris.

~~50782~~ (new #) Clindagel™ 1% topical gel

Clindagel, LLC

Authorized U.S. Agent: Target Research Associates

Clindagel™, the subject of this NDA, is a topical anti-infective drug product containing 1% clindamycin phosphate in a gel vehicle. Clindamycin phosphate is inactive in vitro however, rapid in vivo hydrolysis converts this compound to clindamycin which has antimicrobial activity against gram positive aerobic (except *Enterococcus faecalis*), and gram negative and gram positive anaerobic microorganisms. Clindamycin phosphate solution for intramuscular and intravenous injection, as well as clindamycin topical solution, gel and lotion formulations have been previously approved and marketed in the U.S.

The sponsor has not submitted any new microbiology data to support the proposed labeling. In addition, a study comparing absorption of topical daily application of Clindagel™ versus twice-daily application of the previously marketed topical gel, Cleocin T®, for five days in patients with acne vulgaris, has not been completed and results are not available at this time. However, the data from previous applications indicates that following multiple topical applications of clindamycin phosphate (at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution) very low levels of clindamycin is present in the serum (0-3 ng/mL) and less than 0.2% of the dose is recovered in urine as clindamycin. Data from previous applications also indicates that clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of clindamycin in extracted comedones after application of topical Cleocin T® solution for 4 weeks was 597 µg/g of comedonal material.

After some discussion with Dr. Dennis Bashaw, the Biopharmacology supervisor, and the Biopharmacology review officer Dr. Abimbola Adebowale, this reviewer was assured that the ADME profile of the new formulation, Clindagel™, is unlikely to be significantly different from that of the previously marketed topical formulation, Cleocin T®. Given the current circumstances it is the belief of this reviewer that the microbiology section of the product insert should be written for a topical antimicrobial agent rather than a systemic agent. Thus the Microbiology subsection of CLINICAL PHARMACOLOGY section of the product insert should read as follows:

Microbiology: Although clindamycin phosphate is inactive in vitro, rapid in vitro hydrolysis converts this compound to clindamycin, which has antibacterial activity. Clindamycin inhibits bacteria protein synthesis at the ribosomal level by binding to the 50S ribosomal subunit and affecting the process of peptide chain initiation. In vitro studies indicated that clindamycin inhibited all tested *Propionibacterium acnes* cultures at a minimum inhibitory concentration (MIC) of 0.4 µg/mL. Cross-resistance has been demonstrated

CONCLUSION & RECOMMENDATIONS:

From microbiology point of view the application is approvable when the Microbiology subsection of the label is revised to read as:

██████████) 50782 (new #) Clindagel™ 1% topical gel

Clindagel, LLC

Authorized U.S. Agent: Target Research Associates

Microbiology: Although clindamycin phosphate is inactive in vitro, rapid in-
hydrolysis converts this compound to clindamycin which has antibacterial activity
Clindamycin inhibits bacteria protein synthesis at the ribosomal level by binding to the
50S ribosomal subunit and affecting the process of peptide chain initiation. In vitro
studies indicated that clindamycin inhibited all tested *Propionibacterium acnes* cultures
at a minimum inhibitory concentration (MIC) of 0.4 mg/mL. Cross-resistance has been
demonstrated. ██████████

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Sousan Sayahtheri Altaie, Ph. D.
Clinical Microbiology Review Officer

- HFD-540/Division File
- HFD-520/Division File
- HFD-520/Micro/S. S. Altaie
- HFD-540/MO/P. Huene
- HFD-540/Chem/J. Vidra
- HFD-540/PharmTox/P. Brown
- HFD-540/TL BioPharm /D. Bashaw
- HFD-540/Biopharm/A. Adebowale
- HFD-540/Stat/V. Freidlin
- HFD-540/PM /I. Kumar

Concurrence Only:

- HFD-540/Dir/J. Wilkin
- HFD-520/TL Micro/A. T. Sheldon

RD and Final Initialed 4/13/00 AJP

[/S/] 4513500 [/S/] 4/14/00

**APPEARS THIS WAY
ON ORIGINAL**