CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-801

MICROBIOLOGY REVIEW

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
NDA 21-709 Date review completed: 17 February 2004

Date company submitted: 2 Dec 2003 Date received by CDER: 24 Dec 2003

Reviewer: Fred Marsik, Ph.D. Date assigned: 6 Feb 04

NAME AND ADDRESS OF APPLICANT

Connetics
3290 West Bayshore Rd.
Palo Alto, CA 94303

CONTACT PERSON

Sharon L Hill
Senior Director, Regulatory Affairs
650-843-2858

DRUG PRODUCT NAME

Proprietary: [redacted]
Established name: Clindamycin phosphate
Code name/number: None
Chemical name: Methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thi-L-threo-D-galacto-octopyranoside 2-(dihydrogen phosphate)
Chemical formula: $C_{18}H_{34}ClN_2O_8PS$

PROPOSED INDICATION

Treatment of acne vulgaris

PROPOSED DOSAGE FORM, DOSAGE, STRENGTH, ROUTE OF ADMINISTRATION, AND DURATION OF TREATMENT

Proposed dosage form: Foam
Strength and dosage: 1% clindamycin phosphate applied topically once daily
Route of administration: Topical
Duration of treatment: 12 weeks.

DISPENSED

Rx

RELATED DOCUMENTS

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
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IND 64,577

REMARKS

The applicant submitted an original NDA for Clindamycin Phosphate Foam, 1% for topical application to treat acne vulgaris. Clindamycin Phosphate Foam was developed as a change in dosage form of the reference listed drug, Clindagel® (clindamycin phosphate) topical gel, 1%.

Microbiological studies have not been conducted by Connetics for clindamycin phosphate and clindamycin. Clindamycin Phosphate Foam is the subject of a 505(b)(2) New Drug Application, which relies on the reference listed drug (RLD) Clindagel® (clindamycin phosphate gel) topical gel, 1%. Microbiology related information is located in section 2.4.2 of this submission.

Dermatology (HFD-540) has requested an assessment of the microbiology section and the proposed draft labeling with regards to the proposed microbiology & clinical pharmacology sections.

CONCLUSION

The applicant provided sufficient microbiology information from the literature to support the fact that clindamycin when tested in vitro at a concentration of 0.4 µg/mL inhibits the growth of the majority of the *Propionibacterium acnes* isolates tested. *Propionibacterium acnes* is an organism associated with acne vulgaris. This in vitro data suggests that clindamycin phosphate used in the proposed 1% concentration in a topical preparation may inhibit the growth of *P. acnes* at the site of its application. The literature indicates that clindamycin phosphate 1% applied topically is a recognized standard of care for mild to moderate acne vulgaris. The results of the clinical studies that the applicant performed suggest that their Clindamycin Phosphate Foam, 1% is not inferior to the reference-listed drug, Clindagel® for the treatment of acne vulgaris. The studies also showed that both products are not inferior in their treatment of acne vulgaris to the respective vehicles of the products. Microbiology studies were not performed during the clinical studies.

From a microbiology perspective the product is approvable with the following changes to the "Indication" and "Microbiology" sections of the package insert (See Agency's proposed "INDICATION" and "MICROBIOLOGY" sections of package insert below).

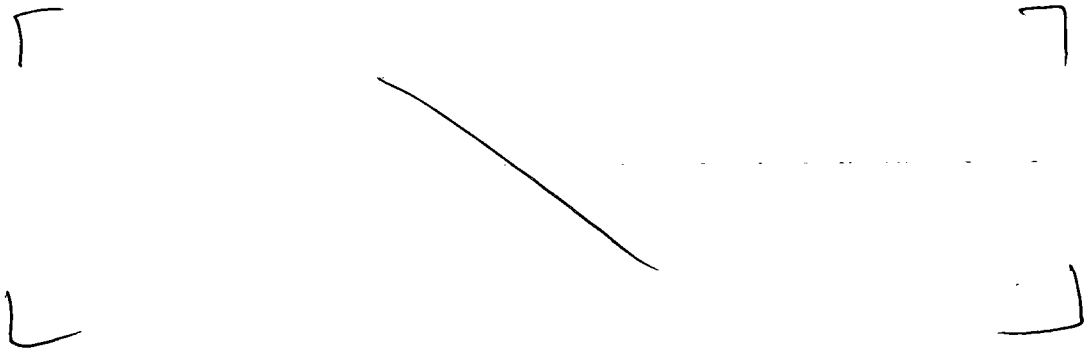
APPLICANT'S PROPOSED MICROBIOLOGY SECTION OF THE PACKAGE INSERT

MICROBIOLOGY SECTION

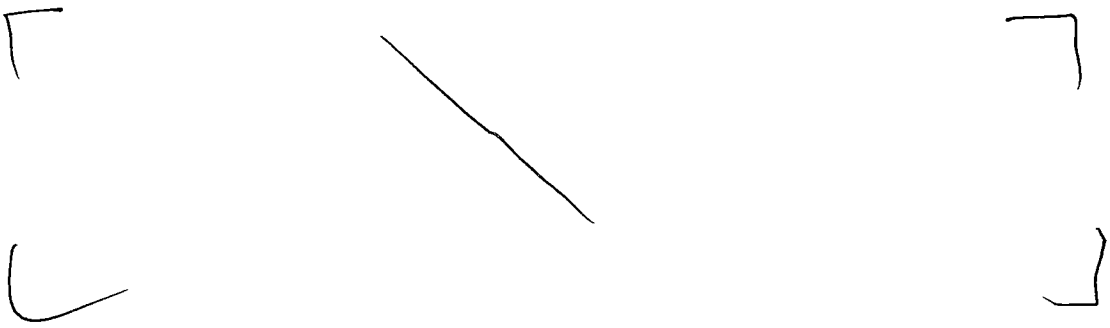
Microbiology: Although clindamycin phosphate is inactive in vitro, rapid in vitro hydrolysis converts this compound to clindamycin, which has antibacterial activity. Clindamycin inhibits bacteria protein synthesis at the ribosomal level by binding to the 50S ribosomal subunit and affecting the process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

AGENCY'S PROPOSED CHANGE TO THE "MICROBIOLOGY" SECTION OF THE PACKAGE INSERT

MICROBIOLOGY SECTION



Microbiology: The clindamycin component has been shown to have in vitro activity against *Propionibacterium acnes*, an organism which is associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product. Cross-resistance between clindamycin and erythromycin has been demonstrated.



DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
NDA 21-709 Date review completed: 17 February 2004

INTRODUCTION

Background and Summary:

Connetics Corporation (Connetics) submitted this New Drug Application (NDA), in the Common Technical Document (CTD) format, for Clindamycin Phosphate Foam, 1% (Clindamycin Phosphate Foam) under section 505(b)(2) of the Food, Drug and Cosmetic Act.

Clindamycin Phosphate Foam was developed as a change in dosage form of the reference listed drug (RLD) Clindagel® (clindamycin phosphate topical gel, 1%) for once daily topical application in the treatment of acne vulgaris under an investigational new drug application, IND 64,577. Connetics plans to rely upon the Agency's previous finding of safety and effectiveness for Clindagel and new information generated on the foam formulation.

The applicant states that Clindamycin Phosphate Foam is a non-greasy, non-residue topical dosage form of clindamycin phosphate, delivered in VersaFoam™. VersaFoam is Connetics Corporation's quickbreaking, temperature sensitive, foam vehicle platform. When VersaFoam is applied to the skin, body heat causes the foam structure to breakdown depositing the active ingredient directly at the application site. The applicant states that they feel there will be better patient compliance with the foam formulation because of the improved cosmetic advantage over the older dosage forms.

Acne vulgaris

Acne vulgaris is a skin disorder of the sebaceous follicles that commonly occurs in adolescence and in young adulthood. While the exact cause of acne vulgaris is not understood some factors that may contribute to the condition have been identified. Acne vulgaris lesions may occur because local metabolism of sex hormones stimulates an increase in the size of the sebaceous glands resulting in the production of excess sebum, the lipid rich secretion of the sebaceous gland. Sebum is believed to be a pivotal player in acne pathogenesis and provides a growth medium for *Propionibacterium acnes*. The major pathogenic factors involved are hyper keratinazation, obstruction of sebaceous follicles resulting from abnormal keratinization of the infundibular epithelium, stimulation of sebaceous gland secretion by androgens, and microbial colonization of pilosebaceous units by the anaerobic bacterium *P. acnes*, which promotes perifollicular inflammation (**1,2,3**). The increased activity of sebaceous glands, elicited by androgen, causes proliferation of *P. acnes* in the pilosebaceous ducts. The organism possesses a ribosome-rich cytoplasm and a relatively thick cell wall and produces several biologically active mediators that may contribute to inflammation, for instance, by promoting leukocyte migration and follicular rupture. In inflamed lesions, numerous neutrophils and macrophages infiltrate around hair follicles and sometimes phagocytosis *P. acnes* (**4**). The immunologic response to *P. acnes* involves the humoral, cell-mediated, and

complement pathways (*3*). The suppression of *P. acnes* has been shown to be associated with clinical improvement although absolute numbers of *P. acnes* do no correlate with the severity of acne (**5**).

Topical clindamycin phosphate is prescribed for the treatment of mild to moderate acne vulgaris (**6**). Clindamycin phosphate is a lincosamide antibiotic with activity against a variety of gram-positive bacteria as well as gram-positive and gram-negative anaerobes. Clindamycin binds to the 50S subunit of the bacterial ribosome and inhibits early stages of protein synthesis. It is primarily a bacteriostatic agent. Clindamycin phosphate is biologically inactive being hydrolyzed to the active form of free clindamycin. This hydrolyzation occurs following oral, parenteral and topical administration (**7**). The literature indicates that the MIC_{90} range for clindamycin against *P. acnes* is in the range of $\leq$0.06 to 0.125 µg/mL (**8,9**). Studies of the use of clindamycin and erythromycin for the treatment of acne vulgaris have documented the development of resistance to both antimicrobials between 6 to 18 weeks (**4,10,11**). Resistance to clindamycin is associated with cross-resistance to erythromycin (**10**).

Microbiology Studies

Section 5.3.5.4 (Other Study reports)

The applicant notes that microbiology studies have not been conducted by Connetics for clindamycin phosphate and clindamycin. Clindamycin Phosphate Foam is the subject of a 505(b)(2) New Drug Application which relies on the reference listed drug (RLD) Clindagel® (clindamycin phosphate gel) Topical Gel, 1%. The microbiology related information for this application is located in Module 2, Section 2.4.2 Pharmacology and Section 2.6.2 Pharmacology written summary. The applicant states (section 2.4.2, pg. 2) that in accordance with agreement from the Agency that this application is deemed appropriate for 505(b)(2) submission, no new nonclinical pharmacology or toxicology studies are needed in support of this application for Clindamycin Phosphate Foam, 1%. Under the Federal Food, Drug & Cosmetic (FD&C) Act section 505(b)(2) and 21 CFR 314.54, the basis for approval for Clindamycin Phosphate Foam will rely on nonclinical animal studies on clindamycin phosphate that supported the reference listed drug (RLD) Clindagel™ (**12**) and relevant publications in the literature.

In section 2.4.2 of this submission the Applicant provides a literature summary of the chemical properties of clindamycin, its mechanism of action against bacteria, its activity against bacteria including *P. acnes*, an organism associated with acne vulgaris, and its use as a topical treatment for acne vulgaris. See the "Acne vulgaris" section of this review for a summary of this information.

CONCLUSION

In the opinion of this review the applicant has provided an appropriate literature summary on the characteristics of clindamycin, it activity against bacteria including *P. acnes* and the use of clindamycin for the treatment of acne vulgaris.

STUDY REPORTS OF CONTROLLED CLINICAL STUDIES PERTINENT TO THE CLAIMED INDICATION

Study CLN.C. 002 (Module 2, section 2.7.6.2)

This study is a Phase II Multicenter Randomized Investigator-Blinded Study to Evaluate the Safety and Efficacy of Clindamycin Phosphate Foam, 1% versus vehicle Foam and Clindagel™ (clindamycin phosphate gel) Topical Gel, 1% in Subjects with Acne Vulgaris

The objective of Study CLN.C.002 was to obtain safety and efficacy data on Clindamycin Phosphate Foam in the treatment of acne vulgaris and to use the data obtained to estimate the appropriate sample size for the pivotal Phase 3 Study CLN.C.003. No microbiology data was collected during this study.

Synopsis of Study

Study period: June 2002 to November 2002
Number of subjects enrolled: 130
Gender: 73 males, 57 females
Age: 12 – 50 years
Ethnicity: 99 Caucasians, 17 Black, 13 Hispanic, and 1 Asian

Criteria for Evaluation

Efficacy

Primary endpoints included the percent reduction in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12 (end of treatment) and the proportion of subjects who had an investigator's "Static Global Assessment" score of 0 or 1 at week 12. Secondary endpoints included the absolute reduction in lesion counts (total, inflammatory, and non-inflammatory) from baseline to week 12; and the change in the subject's "Global Assessment" from baseline to week 12.

Efficacy results:

The efficacy endpoints were not analyzed using statistical methods. Efficacy conclusions are limited to observations based on numerical differences between the treatment groups, as noted below for the ITT analyses.

From the primary and secondary efficacy endpoints, Clindamycin Foam and Clindagel generally yielded numerically more favorable results than the vehicle foam regimen, but no notable, consistent advantage was evident for either active group (Clindamycin Foam or Clindagel) over the other.

On the 5-point investigator's "Static Global Assessment Scale" (see below), a score of 0 or 1 at week 12 (end of treatment) was attained by more than twice the proportion of subjects in the active treatment groups as in the vehicle group (ITT analysis). The results were 57% (30/53) of subjects in the Clindamycin Foam treatment group, 64% (32/50) of subjects in the Clindagel group, and 26% (7/27) of subjects in the vehicle treatment group.

5-Point Investigator's Static Global Assessment

Score*	Definition
Grade 0	Clear – no evidence of acne vulgaris requiring treatment
Grade 1	Minimal – Few non-inflammatory lesions may be present, with rare small papules/pustules, and no nodulo-cystic lesions
Grade 2	Mild – non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and perhaps 1 small nodulo-cystic lesion
Grade 3	Moderate – inflammatory lesions are more apparent: many comedones and papules/pustules, perhaps a few nodulo-cystic lesions
Grade 4	Severe –highly inflammatory lesions predominate: variable number of comedones, several to many papules/pustules, several to many inflamed nodulo-cystic lesions

On the 6-point "Investigator's Global Assessment Scale" (see below) a score of 0 or 1 at week 12 (end of treatment) was attained by more subjects in the active treatment groups (ITT analysis) then in the vehicle group. The results were 28% (15/53) of subjects in the Clindamycin Foam group, 36% (18/50) of subjects in the Clindagel group, and 19% (5/26) of subjects in the vehicle foam group.

NOTE: The 5 point investigator's scale was originally used but was modified to a 6-point scale to better dichotomize the scale into two categories "Success" for subjects with scores of 0 to 1, and "failure" for subjects with scores of 2 or greater. The 6-point scale was used only to evaluate patients at the end of treatment while the 5-point scale was used to evaluate subjects at baseline and at the end of treatment.

6-Point Investigator's Static Global Assessment

Score*	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear: rare non-inflammatory lesions present, with rare non-inflamed papules (papules most be resolving and may be hyper-pigmented, though not pink) requiring no further treatment in the investigator's opinion
Grade 2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions)
Grade 3	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules and there may or may not be 1 small nodulo-cystic lesion
Grade 4	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions

*Overall assessment of subject's facial acne vulgaris

The mean percent reduction in total lesion counts from baseline to week 12 (end of treatment) was somewhat greater in the treatment groups than in the placebo group. The reduction percentages were 39% in the Clindamycin Foam group, 38% in the Clindagel group, and 35% in the vehicle foam group. The reduction was slightly greater for mean inflammatory lesion counts (45%, 49%, and 40%, respectively), and less pronounced for non-inflammatory lesion counts (36%, 31%, and 32%, respectively).

Mean absolute reductions in total lesion counts from baseline to week 12 (end of treatment) were somewhat greater in the ITT population in the Clindamycin Foam group than in the other treatment groups (25 lesions for Clindamycin Foam, 23 for Clindagel, and 21 for vehicle foam). This is because of a greater mean reduction in non-inflammatory lesions (13, 10, 11 in the respective treatment groups). Mean reduction in inflammatory lesions in the Clindamycin Foam group (12) and Clindagel group (13) were greater then in the vehicle foam group (10).

For the "Subject's Global Assessment" in the ITT population, the proportion of subjects with a score of 0 or 1 at week 12 (end of treatment) were highest in the Clindamycin Foam group (70% vs. 64%) in the Clindagel group and 52% in the vehicle foam group.

Conclusion

The applicant did not perform statistical analysis of the study results. Clindamycin Foam and Clindagel appear to have produced comparable results in this study. Clindamycin Foam appears to have better efficacy than vehicle foam at the end of treatment.

Study CLN.C.003 (Module 2, section 2.7.6.3)

This study is a Phase 3 multicenter (18 centers), randomized, double-blinded, double-dummy, vehicle-controlled safety and efficacy study to evaluate the safety and efficacy of Clindamycin Phosphate Foam versus Clindagel in subjects with acne vulgaris. Subjects were entered into the study and randomized to one of four parallel treatment groups in a 3:1:3:1 ratio of once daily treatment (morning or evening) with either Clindamycin Phosphate foam, vehicle foam, Clindagel or vehicle gel for 12 weeks. Microbiology data was not collected during this study.

The primary efficacy variables collected in study CLN.C.003 were similar to those collected in Study CLN.C.002. The 6 point "Investigator's Global Assessment Scale" (see above) was used for the entire study. All efficacy assessments were collected at all study visits (baseline/week0/day1, week 3, week 6, week 9, and week 12/end of treatment. Similarly the primary and secondary endpoints for CLN.C.003 were the same as for CLN.C.002.

Synopsis of Study

Study period: 12 September 200 to 5 August 2003
Number of subjects enrolled: 1026
Gender: 476 males, 550 females
Age: 12 – 55 years
Ethnicity: 657 Caucasians, 184 Black, 159 Hispanics, 13 Asians, and 13 others

Criteria for Evaluation

Efficacy

Primary endpoints included the proportion of subjects who had an "Investigator's Static Goal Assessment" score of 0 to1 at week 12/end of treatment (treatment success); and the percent reduction in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12. Secondary endpoints included the absolute reduction in lesion counts (total, inflammatory, non-inflammatory)) from baseline to week 12; the proportion of subjects who had a "Subjects Global Assessment" score of 0 to1 at week 12, and the change in the "Subject's Global Assessment" from baseline to week 12. Statistical analysis of study data was conducted.

Efficacy Results

Treatment Success: "Investigator's Static Global Assessment" score or 0 or 1 at Week 12

Clindamycin foam, 1% was non-inferior to Clindagel for the proportion of subjects with treatment success. For the ITT population, the proportions of subjects who attained treatment success at week 12 were 31% (120/386) for Clindamycin Foam, 27% (105/385) for Clindagel, 18% (23/127) for vehicle foam, and 20% (20/108) for vehicle gel. Analysis of treatment success by intrinsic characteristics (gender, race, and age) did not reveal any clinically meaningful differences in any treatment group.

Rates of treatment success for the per-protocol population were similar to those seen for the ITT population. In the per-protocol population, the proportions of subjects with treatment success were 35% (117/336) for Clindamycin Foam, 29% (99/236) for Clindagel, 21% (23/110) for vehicle foam, and 21% (23/108) for vehicle gel.

Clindamycin Foam was superior to vehicle foam for the proportion of subjects with treatment success in the ITT population, a significantly greater proportion of subjects attained treatment success in the Clindamycin Foam group (31%) than the vehicle foam group (185) [p = .0025, Cochran-Mantel-Haenszel (CMH) test]. The per-protocol results were consistent with the ITT results. The comparison of treatment success between Clindamycin Foam (35%), and vehicle foam (21%), also achieved statistical significance (p = .0030, CMH test) in the per-protocol analysis.

Percent Reduction in Lesion Counts at Week 12

Clindamycin Foam was non-inferior to Clindagel for the percent reduction in all three lesion counts (Total, inflammatory, non-inflammatory) from baseline to week 12 (end of treatment). In the ITT population, mean percent reduction in total lesion counts was 43% in the Clindamycin Foam group, 36% in the Clindagel group, 31% in the vehicle foam group, and 28% in the vehicle gel group. Mean percent reductions in inflammatory lesion counts were 49%, 45%, 35%, and 37%, and reductions in non-inflammatory lesions counts were 38%, 30%, 27%, and 21%, in the respective treatment groups. Analysis of the percent reduction in lesion counts by intrinsic characteristics (gender, race, and age) did not reveal any clinically meaningful differences in any treatment group. The results from the per-protocol analyses of this primary endpoint were similar to those seen in the ITT analysis.

Superiority of Clindamycin Foam to its vehicle was demonstrated for the mean percent reduction of all three lesion counts (total, inflammatory, and non-inflammatory). In the ITT population, mean percent reductions in all of the three lesion counts from baseline to 12 weeks were significantly greater in the Clindamycin Foam group than the vehicle foam group (all $p<0.05$, ANOVA model), parametric and non-parametric). Superiority of Clindamycin Foam to its vehicle was also demonstrated for the mean percent reduction of

all three lesion counts (total, inflammatory, non-inflammatory, all $p<0.05$) in the per-protocol population.

Secondary Efficacy Analyses

In the ITT population, the Clindamycin Foam group was not significantly different from the Clindagel group in the mean absolute reduction of total or inflammatory lesion counts ($p = 0.0607$ and $p = 0.1434$ respectively) from baseline to week 12. Mean absolute reduction of non-inflammatory lesion counts differed significantly ($p = 0.0319$) in favor of Clindamycin Foam over Clindagel. Clindamycin Foam demonstrated a significant difference (superiority) over its vehicle for all three lesion counts (all $p \leq 0.0163$) for both parametric and non-parametric analyzes.

The results of the per-protocol analyses of this secondary endpoint were similar to those seen in the ITT analyses, with the exception of the non-inflammatory lesion count comparison between Clindamycin Foam and Clindagel; which did not achieve statistical significance in the Per-Protocol analysis. Based on the non-parametric analyses, there were no significant differences between the Clindamycin Foam group and Clindagel group in the mean absolute reduction of all three lesion counts. Clindamycin Foam demonstrated a significant difference (superiority) over its vehicle for all three lesion counts for both parametric and non-parametric analyses.

Subject's Global Assessment at Week 12

Clindamycin Foam was superior to both Clindagel and vehicle foam for the proportion of subjects with a "Subject's Global Assessment" score of 0 to1 at week 12. In the ITT population, the success rate of the Clindamycin Foam group was significantly higher in the Clindagel group and the vehicle foam group. The results of the per-protocol analyses were similar to those seen in the ITT analyses.

Conclusion

The data provided by the applicant shows that Clindamycin foam is non-inferior to Clindagel in the treatment of acne vulgaris. The data also indicates that Clindamycin Foam offers superior clinical benefit to vehicle foam with statistical significance shown for all primary endpoints.

OVERALL CONCLUSION

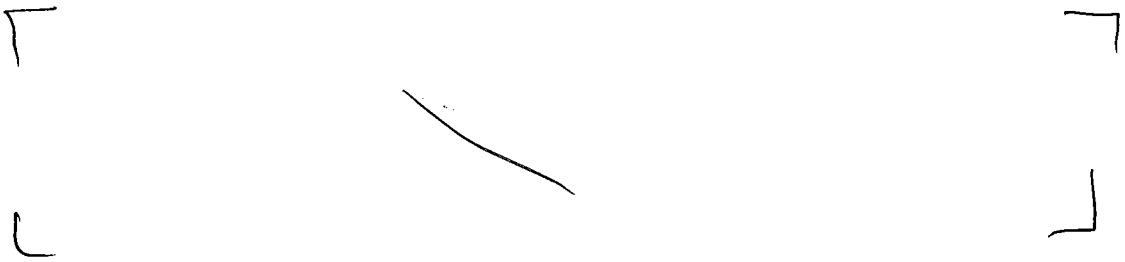
The applicant provided sufficient microbiology information from the literature to support the fact that clindamycin when tested in vitro at a concentration of 0.4 µg/mL inhibits the growth of the majority of the *Propionibacterium acnes* isolates tested. *Propionibacterium acnes* is an organism associated with acne vulgaris. This in vitro data suggests that clindamycin phosphate used in the proposed 1% concentration in a topical preparation may inhibit the growth of *P. acnes* at the site of its application. The literature indicates

that clindamycin phosphate 1% applied topically is a recognized standard of care for mild to moderate acne vulgaris. The results of the clinical studies that the applicant performed suggest that their Clindamycin Phosphate Foam, 1% is not inferior to the reference-listed drug, Clindagel® for the treatment of acne vulgaris. The studies also showed that both products are not inferior in their treatment of acne vulgaris to the respective vehicles of the products. Microbiology studies were not performed during the clinical studies.

From a microbiology perspective the product is approvable with the following changes to the "Indication" and "Microbiology" sections of the package insert (See Agency's proposed "INDICATION" and "MICROBIOLOGY" sections of package insert below).

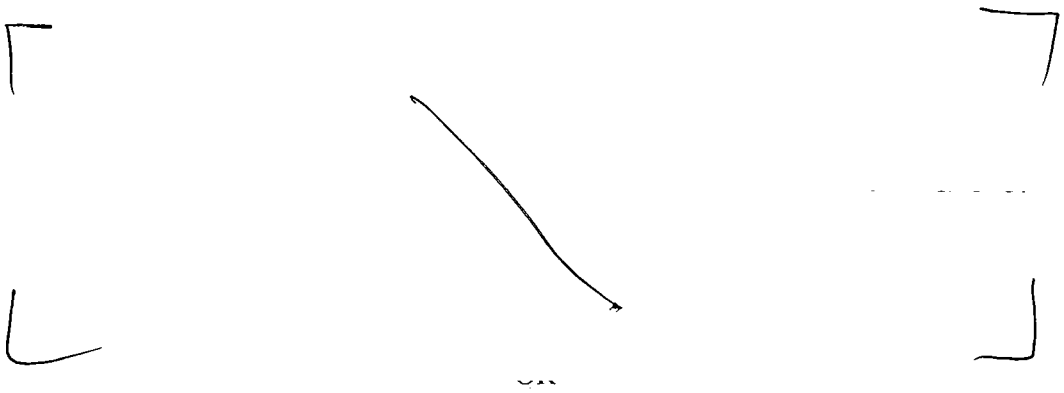
APPLICANT'S PROPOSED MICROBIOLOGY SECTION OF THE PACKAGE INSERT

MICROBIOLOGY SECTION



AGENCY'S PROPOSED CHANGE TO THE "MICROBIOLOGY" SECTION OF THE PACKAGE INSERT

MICROBIOLOGY SECTION



2. Microbiology: The clindamycin component has been shown to have in vitro activity against *Propionibacterium acnes*, an organism which is associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in

clinical trials with this product. Cross-resistance between clindamycin and erythromycin has been demonstrated.

ADDENDUM

At an Agency HFD-540 internal meeting on 19 Feb 04 the wording for the microbiology section of the package insert was discussed. It was felt that it would be preferable to have a microbiology section to the package insert. It was recognized that in the literature clindamycin has been shown to have in vitro activity against *P. acnes* and that the majority of the isolates were inhibited by a clindamycin concentration of 0.4µg/mL. However, because there was no in vitro susceptibility data for clindamycin against *P. acnes* isolates from subjects in the clinical studies conducted by the applicant there is no knowledge of the concentration of clindamycin that inhibits the majority of the *P. acnes* associated with the lesions of study subjects. Therefore, it was felt that no mention of a concentration of clindamycin that inhibits the majority of *P. acnes* can be made in the product package insert. It was agreed that cross-resistance between clindamycin and erythromycin does occur and that this should be mentioned in the microbiology section. The wording that was decided on was number 2.

REFERENCES

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3. Burkhart CG, CN Burkhart, PF Lehmann. 1999. Acne: a review of immunologic and microbiologic factors. *75*:328-331.
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11. Dreno B, A Reynaud, D Moyse. 2001. Erythromycin-resistance of cutaneous bacterial flora in acne. Eur J Dermatol *11*:549-553.
12. FDA. Approval letter for clindamycin phosphate gel, 1% (NDA 50-782), 2000.

_____ Date:_____
Frederic J Marsik, Ph.D.

CONCURRENCE ONLY

_RD#1 and Final Initialed 02/18/04 ATS
HFD-520/TLMicro/AT Sheldon, Jr., Ph.D.

_____ Date:_____
HFD-520/DepDir/L Gavrilovich, M.D.

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

/s/

Frederic Marsik
3/8/04 11:36:22 AM
MICROBIOLOGIST

Albert Sheldon
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MICROBIOLOGIST

Lillian Gavrilovich
3/8/04 03:12:13 PM
MEDICAL OFFICER

DIVISION OF ANTIINFECTIVES (HFD-520)
CLINICAL MICROBIOLOGY
DERMATOLOGY (HFD-540) CONSULT
NDA 21-709 FILEABILITY REVIEW
Reviewer: Fred Marsik, Ph.D. Date Review Completed: 12 Feb 04

1. Is the microbiology section organized in a manner to allow substantive review to begin? Not applicable*

2. Is the microbiology section indexed and paginated in a manner to allow substantive review to begin? Not applicable

3. Is the microbiology section and other microbiologically pertinent Sections of the NDA legible so that substantive review can begin? Not applicable

HAS THE APPLICANT SUBMITTED:

1. in vitro data in sufficient quantity, using necessary clinical and non-clinical strains and using necessary numbers of approved laboratories to meet current Divisional standards for approvability of the product based on submitted draft labeling? Not applicable

2. any required animal studies necessary for approvability of the product based on the submitted draft labeling? Not applicable

3. draft breakpoints and interpretive criteria in a manner consistent with contemporary standards, in a manner that attempts to correlate criteria with clinical results on NDA studies, and in a manner to allow substantive review to begin? Not applicable

4. all special studies/data requested by the Division during pre-submission discussions? Not applicable

5. draft labeling consistent with 201.56 and 201.57, current Divisional policy and the design of the development package. Yes

From a Microbiology perspective, is this NDA fileable? If NO give reasons below. Yes

*This application is being filed under 505(b)(2) no new microbiology data is required.

_____ Date: 12 Feb 04
Fred Marsik, Ph.D., Review Microbiologist
Concurrence Only:
Final Initialed 02/19/04 ATS
HFD-520/TLMicro/A T Sheldon, Jr., Ph.D.

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