

Gram-negative aerobic bacteria. Clindamycin is indicated for the treatment of wide-range of infections including lower respiratory tract infections, skin and skin structures infections, bone and joint infections and intraabdominal infections.

During the drug development the sponsor was asked to collect specimens for culture of *P. acnes* from inflammatory and non-inflammatory lesions of patients who do not respond to treatment with 1% clindamycin/2.5% benzoyl peroxide. All isolates were to be tested against clindamycin and benzoyl peroxide to determine the concentrations of these products individually and combined required to inhibit the growth of *P. acnes*. In addition, the sponsor was asked to provide information on in vitro activity of clindamycin and benzoyl peroxide against *P. acnes*.

The proposed labeling does not include any antibacterial claim and the applicant did not conduct studies to determine the role of clindamycin and benzoyl peroxide in preventing or reducing antimicrobial resistance in pathogens associated with acne or present on the skin.

I concur with the conclusions reached by the clinical microbiology reviewer.

7. Clinical/Statistical-Efficacy

To support safety and efficacy of ACANYA Gel for the treatment of moderate to severe acne vulgaris, the applicant has submitted data from two Phase 3 trials (DPSI-06-22-2006-012 and DPSI-06-22-2006-017) and one Phase 2 dose-ranging study. The two pivotal trials were 4-arm, multi-center, double-blind, randomized, active- and vehicle-controlled. Specifically, these studies evaluated the combination product (1% clindamycin/2.5 benzoyl peroxide), clindamycin phosphate 1.2%, benzoyl peroxide 2.5%, and the vehicle alone. Patients between the ages of 12 and 70 who had moderate to severe acne at baseline were enrolled into these studies. The evaluation of efficacy was based on Evaluator's Global Severity Score (EGSS), Lesion Counts and Visual Analog Sore (VAS) and included ITT population (all randomized patients who received study medication).

The efficacy was based on co-primary endpoints that included EGSS and acne lesion counts. The primary efficacy was demonstrated if 1% clindamycin/2.5% benzoyl peroxide combination product was superior to vehicle for dichotomized Evaluator's Global Severity Score and absolute changes in inflammatory and non-inflammatory lesion count from baseline at week 12 and if the combination product was superior to the monads, clindamycin and benzoyl peroxide for dichotomized Evaluator's Global Severity Score and absolute changes from baseline at week 12 in inflammatory lesion count. Success on the Evaluator's Global Severity Score was defined as at least a 2 grade improvement from baseline at week 12. Although a 2 grade improvement on the Evaluator's Global Severity Score was a predefined endpoint and acceptable definition of success, especially for the moderate to severe disease, a response "clear or "almost clear" would provide clinically important information for the prescribers.

Efficacy results are presented below:

Study 012

	Tradename Gel N=399	Clindamycin N=408	Benzoyl Peroxide N=406	Vehicle Gel N=201
EGSS - 2 grade reduction from baseline	131 (33%)	100 (25%)	96 (24%)	38 (19%)
EGSS - Clear or Almost Clear	115 (29%)	84 (21%)	76 (19%)	29 (14%)
Inflammatory Lesions*	15	12	13	9
Noninflammatory Lesions*	22	18	21	13

*Mean absolute change

Study 017

	Tradename Gel N=398	Clindamycin N=404	Benzoyl Peroxide N=403	Vehicle Gel N=194
EGSS-2 grade reduction from baseline	147 (37%)	114 (28%)	114 (28%)	27 (14%)
EGSS - Clear or Almost Clear	113 (28%)	94 (23%)	94 (23%)	21 (11%)
Inflammatory Lesions*	14	11	11	6
Noninflammatory Lesions*	19	15	15	8

*Mean absolute change

In both studies, a combination product (1% clindamycin/2.5% benzoyl peroxide) was superior to vehicle based on the mean absolute reduction in inflammatory and non-inflammatory lesion counts and at least 2-grade improvement on the EGSS scale at week 12. In addition, 1% clindamycin/2.5% benzoyl peroxide gel was superior to clindamycin gel alone and benzoyl peroxide gel alone in reducing the mean absolute count of inflammatory lesions and at least 2-grade improvement on the EGSS scale at week 12.

8. Safety

The safety population consisted of all randomized patients who applied study treatment and for whom one safety evaluation is available. The safety database for 1% clindamycin/2.5% benzoyl peroxide included 872 patients, ages 12 years and older, who applied a study treatment at least once. The mean duration of exposure was 83 days in controlled clinical studies. Seven hundred ninety seven patients with acne vulgaris received ACANYA gel in phase 3 trials. The majority of patients were Caucasians and the mean age across groups was 19. Adverse events and local signs and symptoms were monitored throughout the study.

A waiver for a repeat photo-toxicity, photo-allergy study, and repeat insult patch testing was requested by the sponsor and the waiver was granted on the basis that the proposed to-be-marketed formulation and ~~the~~ formulation were similar enough based on individual excipients and excipients level. A 21-day cumulative irritation study of 1% clindamycin/2.5% benzoyl peroxide was previously review by the Agency in 2004. The phototoxicity/allergenicity was evaluated in two studies with ~~the~~ and it was also determined that 1% clindamycin/2.5% benzoyl peroxide formulation does not significantly absorb UV/Visible light between ~~the~~ nM.

b(4)

The most frequently reported systemic adverse events were nasopharyngitis and upper respiratory tract infection. The other reported adverse events were mostly related to local skin reactions. Sign and symptoms of skin irritation were comparable between treatment groups, mild and transient.

Safety concerns regarding clindamycin use are development of diarrhea associated with pseudomembranous colitis. The other adverse events reported with the use of clindamycin include abdominal pain, contact dermatitis, and skin irritation.

No new safety concerns were identified for clindamycin/benzoyl peroxide in this application. Relevant information for clindamycin already included in the clindamycin label for systemic use will be also included in this labeling for topical application of clindamycin/benzoyl peroxide as a class labeling.

9. Advisory Committee Meeting

None.

10. Pediatrics

The applicant has requested a waiver of the requirement to study pediatric patients younger than 12 years of age under the Pediatric Research equity Act of 2003, section 505B (a) of the Food, Drug, and Cosmetic Act. The request was based on the understanding that clindamycin/benzoyl peroxide is not likely to be used in a substantial number of pediatric patients and it does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients.

The partial waiver was granted for pediatric patients less than 12 years of age because there are too few children with the disease in that age group. This was presented at the Pediatric Review Committee meeting on September 24, 2008. The appropriate pediatric age group to be included in the clinical trials for acne is under discussion.

11. Other Relevant Regulatory Issues

The applicant is assuming that this application qualifies for three years of exclusivity under 21 CFR 314.108 since clinical investigation was conducted to support the proposed indication. However, clindamycin is an old antibiotic and does not qualify for marketing exclusivity based on the Section 507 of the Food, Drug and Cosmetic Act. The Federal Register notice 99N-3088, Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs issued January 24, 2000, lists the active drug substances, including any derivatives thereof, that are directly affected by the repeal of Section 507.

There are no other unresolved relevant regulatory issues.

12. Labeling

The applicant has proposed the tradename ~~_____~~ or Acanya for this topical gel. The first proposed name ~~_____~~ was not acceptable to DMETS because of the possibility of name confusion with the other approved products that could lead to medication errors. The second proposed name, Acanya was found to be acceptable. b(4)

Labeling discussions were focused on the description of efficacy data and the most appropriate presentation of such data in the labeling. It was decided to include response "clear" or "almost clear" in addition to 2 grade improvements on the Evaluator's Global Severity Score as this would be important information for the prescribers.

13. Decision/Action/Risk Benefit Assessment

The safety and efficacy of ACANYA Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%) for the treatment of acne vulgaris have been demonstrated in two Phase 3 trials. This topical product would provide once a day treatment for patients with acne vulgaris and because it contains 2.5% of benzoyl peroxide would be possibly less irritating than other products with higher concentrations of benzoyl peroxide.

This application was submitted under 505(b)(2) section of the Federal Food, Drug, and Cosmetic Act and it relies on the published literature to provide necessary nonclinical information regarding benzoyl peroxide and clindamycin.

The applicant intended to reference genotoxicity data for clindamycin in the BenzaClin label through establishing a clinical bridge that included clinical bioavailability study of ~~_____~~ (clindamycin phosphate ~~_____~~ and benzoyl peroxide ~~_____~~) and BenzaClin, an approved listed drug. The applicant did not include to-be-marketed formulation of clindamycin/benzoyl peroxide in the clinical bioavailability study and, therefore, cannot reference data in the BenzaClin label. However, the applicant has conducted carcinogenicity studies with the product, therefore, a clinical bridge or information from the literature regarding genotoxicity of clindamycin is not necessary for the approvability of this product. b(4)

During the development program for clindamycin phosphate 1.2% and benzoyl peroxide 2.5%, it was discussed that the in vivo bioavailability study under maximum use conditions would be needed and that an in vitro percutaneous absorption study alone would not be sufficient because non-viable normal skin has different permeation properties than diseased skin. The recommendation from clinical pharmacology is that the data from an in vivo bioavailability study under maximum use conditions for 1% clindamycin/2.5% benzoyl peroxide have to be provided preapproval or as a post-marketing commitment depending on the safety of this product.

Deputy Director Summary
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The applicant has agreed to conduct, as a post-marketing commitment, a maximum use systemic exposure bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients in ACANYA Gel.

Long-term safety studies are not recommended since the safety profile of clindamycin and benzoyl peroxide has been well described and well known. No safety signal was identified in the clinical trials. The frequency and severity of local skin reactions appears to be acceptable. No specific post-marketing risk management activities are needed for this product.

I am in agreement with the recommendation of the review team that this application should be approved.

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/s/

Stanka Kukich
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MEDICAL OFFICER