

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-819

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 24, 2008, Revised October 6, 2008
From	Markham C. Luke, M.D., Ph.D., Lead Medical Officer, Dermatology
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	50-819
Applicant	Dow Pharmaceutical Sciences, Inc.
Date of Submission	December 26, 2007
PDUFA Goal Date	October 26, 2008
Proprietary Name / Established (USAN) names	Acanya Gel
Dosage forms / Strength	Acanya (clindamycin phosphate 1.2%, benzoyl peroxide 2.5%) Topical Gel
Proposed Indication(s)	For the topical treatment of acne vulgaris in patients 12 years or older.
Recommended:	<i>Approval</i>

1. Introduction

Combining benzoyl peroxide with an antibiotic, such as clindamycin, in a topical formulation for the treatment of acne vulgaris is not novel. Other topical formulations of such a combination product have been previously approved and labeled for this indication. The current product utilizes a concentration of benzoyl peroxide that is lower than previously approved combination products (2.5%) together with clindamycin in its phosphate form (1.2%). The product comes to the pharmacist with the two active ingredients separated and requires mixing prior to dispensing to the patient. Due to stability, the combined product has a short shelf life.

Perceived benefits for combination products for acne treatment such as ease of use and improved compliance come with this product together with potential problems such as lack of stability of the active ingredients due to incompatibility (e.g. oxidative nature of benzoyl peroxide) and potential for irritation due to the combination of active ingredients.

2. Background

Key focal regulatory issues during review of this application for a combination product includes (1) 21 CFR 300.50 or the need to demonstrate the contribution of each of the active ingredients and (2) the 505(b)(2) nature of the application where the sponsor is borrowing the

Agency's finding for safety for at least one of the active ingredients by not performing all of the required pre-clinical studies. The initial submission references an unapproved ANDA product that is 5% Benzoyl peroxide and _____ clindamycin phosphate, which in turn had applied to be bioequivalent to Benzaclin gel.

b(4)

3. CMC/Device

- General product quality considerations

As discussed in the CMC review by the primary reviewer, Rajiv Agarwal, the product comes as a kit consisting of two separate component products, clindamycin phosphate _____, and benzoyl peroxide _____. The clindamycin phosphate _____ is provided as a 10 gram _____ f _____. The benzoyl peroxide _____ is provided as a forty gram _____ f _____. When dispensing, the pharmacist mixes the clindamycin solution into the _____ containing benzoyl peroxide _____ using a _____ spatula that is provided as part of the kit.

b(4)

Of note, both components contain propylene glycol, which can lend itself to enhanced penetration of certain ingredients when used on human skin. Such formula differences result in the need for individual assessments of bioavailability as is discussed under Clinical Pharmacology/Biopharmaceutics below.

The CMC reviewer recommends that an 18 month expiration date be granted for the unmixed trade components. For the admixed drug product, 2 months of expiration dating at room temperature is granted.

- Facilities review/inspection

The manufacturing sites for both drug substances have been recommended as Acceptable based on profile per Rajiv Argawal, the CMC reviewer.

- Other notable issues:

Physician's Samples

A notable issue is the need for specific labeling to address the sample size, which comes pre-mixed from the manufacturer. While in general samples of tablets are not usually described in labeling, sample sizes of topical drugs, especially where the use or product design is different from the reference product are recommended to be included. Further, the expiration dating and storage conditions are different for the Acanya samples. The labeled storage conditions for the sample will be refrigerated until dispensing to physician, at which time, the product can be used for up to 3 months (3 month expiry dating).

This reviewer recommends that the unique storage and product specifications for the samples be included in the package insert that accompanies the samples if they are to be part of the approval for this drug. Otherwise it is not clear how information regarding samples is to

be disseminated to the patients who use the samples. However, the regulations do not address labeling for samples as this was discussed in detail with Bronwyn Collier, the acting Chief Project Manager with regard to regulatory approach for this matter.

Topical ' — ' gel

The original submission included referencing the product as a "topical ' — gel". The type of gel is not specified according to CDER CMC standards, therefore, referring to this product as a "gel" or "topical gel" should be sufficient. This will be changed in the labeling.

b(4)

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Jiaqin Yao, indicated that this application did not have any approvability issues, however, the labeling will be written in a manner consistent with the lack of a clinical bridge to any other Listed Drug.

No studies were conducted to evaluate animal reproductive/developmental toxicity. No carcinogenicity, mutagenicity, and impairment of fertility testing with Acanya gel have been conducted. Information from literature is gleaned and provided in the label as per the Pharmacology/Toxicology review.

Rat oral carcinogenicity and mouse dermal carcinogenicity studies were conducted with a different formulation of clindamycin plus benzoyl peroxide. Both of these studies were deemed "acceptable, but not optimal" by the Executive CAC as noted in the meeting memo by the Executive CAC Chair, David Jacobson-Kram, Ph.D.

The toxicology of both of the active ingredients and that of the excipients are well known and are described in detail in the Pharmacology/Toxicology review. It was discussed amongst the Pharmacology/Toxicology review team that this 505(b)2 application could be supported from the literature, together with the submitted nonclinical studies conducted by the applicant.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer, Dr. Jang-Ik Lee, recommends that the "clinical pharmacology information included in this application is not adequate to support the approval of the proposed product" in that "the application does not contain adequate in vivo bioavailability information required by 21 CFR 320." Of note, the applicant was reminded of this need at both the End-of-Phase 2 and the pre-NDA meetings.

The Clinical Pharmacology reviewer recommends that the applicant conduct "a maximal use systemic exposure bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients of Acanya Gel in comparison to the listed drug BenzaClin Gel."

While such a comparative study may be needed for a 505(b)2 application that seeks to reference an already marketed product in order to bridge to Agency's findings of safety and efficacy, this is not the case for Acanya Gel as discussed in the Pharmacology/Toxicology section above and in the pertinent discipline reviews.

However, though the comparator is not necessary, the maximal use systemic exposure bioavailability study is still required for — as per 21 CFR 320. A post-marketing commitment to address the requirement for the maximal use study was sent to the sponsor.

b(4)

6. Clinical Microbiology

While both clindamycin and benzoyl peroxide have anti-microbial effects, the relevance of that effect on acne vulgaris treatment is not clear (for example, Koch's postulates have not been fulfilled for any microbial organism, including *P. acnes*). The proposed labeling from the sponsor for this section is overly promotional and will need to be modified. The labeling as modified from what the applicant sent in was discussed and agreed upon with the Clinical Microbiology reviewer.

7. Clinical/Statistical - Efficacy

The applicant conducted two phase 3 studies comparing the combination product (a dyad) to its monads (clindamycin and benzoyl peroxide) and vehicle in the treatment of moderate to severe acne vulgaris. The two studies 012 and 017 had randomized 1414 and 1399 patients, respectively, to either the combination product, clindamycin, benzoyl peroxide, or vehicle in a 2:2:2:1 ratio. After 12 weeks of treatment, efficacy was evaluated at week 12 for the following primary endpoints: (1) a two grade improvement from baseline to 12 weeks in the Evaluator's Global Severity Score (EGSS) and (2) mean absolute change from baseline in inflammatory and non-inflammatory lesion counts. Study 012 had 33 investigative sites and Study 017 had 35 investigative sites.

For the EGSS evaluation, use of the two grade improvement results in greater percentages of success than with clear or almost clear. Clear or almost clear is the preferred representation of the EGSS evaluation as it is more clinically relevant. Most patients would prefer to be clear or almost clear of their acne rather than just improve from say severe to mild. Labeling will need to incorporate both information or can include only the clear or almost clear numbers with acknowledgement that primary success was determined via two grade improvement.

Table 1 below reflects the statistical analysis of the two grade improvement as success in EGSS from baseline. Table two shows the absolute change in lesion counts from baseline. The Biostatistics reviewers were Drs. Clara Kim and Mat Soukop.

Table 1: Primary Efficacy Results - Number (%) of Successes on EGSS at Week 12 (ITT)

	Study 012			
	IDP-110 n=399	Clindamycin n=408	BPO n=406	Vehicle n=201
Number of successes (%)	131 (32.8%)	100 (24.5%)	96 (23.6%)	38 (18.9%)
p-value [†]	NA	0.002	0.001	<0.0001

	Study 017			
	IDP-110 n=398	Clindamycin n=404	BPO n=403	Vehicle n=194
Number of successes (%)	147 (36.9%)	114 (28.2%)	114 (28.3%)	27 (13.9%)
p-value [†]	NA	0.009	0.009	<0.0001

[†] P-values were calculated using logistic regression with treatment, analysis center, dichotomized skin type, and baseline severity as factors.

Missing values were imputed using LOCF

Source: Study Report DPSI-06-22-2006-012, pg. 67; Study Report DPSI-06-22-2006-017, pg. 65; and reviewer analysis.

Table 2: Primary Efficacy Results - Mean Absolute Change in Lesion Counts at Week 12 (ITT)

	Study 012			
	IDP-110 n=399	Clindamycin n=408	BPO n=406	Vehicle n=201
Inflammatory lesions				
Mean absolute change (sd)	14.8 (10.8)	12.2 (11.6)	13.0 (10.4)	9.0 (11.9)
p-value [†]	NA	<0.001	0.012	<0.001
Non-inflammatory lesions				
Mean absolute change (sd)	22.1 (21.2)	17.9 (19.9)	20.6 (22.0)	13.2 (20.4)
p-value [†]	NA	0.005	0.134	<0.001

	Study 017			
	IDP-110 n=398	Clindamycin n=404	BPO n=403	Vehicle n=194
Inflammatory lesions				
Mean absolute change (sd)	13.7 (10.5)	11.3 (11.7)	11.2 (10.6)	5.7 (12.6)
p-value [†]	NA	0.003	0.001	<0.001
Non-inflammatory lesions				
Mean absolute change (sd)	19.0 (19.9)	14.9 (18.8)	15.2 (19.0)	8.3 (19.8)
p-value [†]	NA	0.007	0.016	<0.001

[†] P-values were calculated using ANCOVA with the baseline inflammatory count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

Missing values were imputed using LOCF.

Source: Reviewer analysis.

Dr. Brenda Vaughan, the primary clinical reviewer discusses in her review that “Statistical superiority of the combination drug product Acanya gel has been demonstrated over its monads, clindamycin and BPO [benzoyl peroxide], and its vehicle in two well-controlled, phase 3, multi-center, randomized, double-blind, vehicle controlled, 12 week clinical studies (012 and 017). The clinical relevance of the efficacy benefit seen appears to be sufficient to allow that about 5% to 7% more patients will achieve clear or almost clear while on this drug than if they were on one of the monads. Further, the point estimates show that the product allows for 15% to 17% more clear or almost clear from acne vulgaris than vehicle.

Study 1 (012)	Acanya Gel N=399	Clindamycin Gel N=408	Benzoyl Peroxide Gel N=406	Vehicle Gel N=201
EGSS – Clear or Almost Clear	115 (29%)	84 (21%)	76 (29%)	29 (14%)
2 grade reduction from baseline	131 (33%)	100 (25%)	96 (24%)	38 (19%)
Inflammatory Lesions – Mean absolute change	15	12	13	9
Non-Inflammatory Lesions - Mean absolute change	22	18	21	13

Study 2 (017)	Acanya Gel N=398	Clindamycin Gel N=404	Benzoyl Peroxide Gel N=403	Vehicle Gel N=194
EGSS Clear or Almost Clear	113 (28%)	94 (23%)	94 (23%)	21 (11%)
2 grade reduction from baseline	147 (37%)	114 (28%)	114 (28%)	27 (14%)
Inflammatory Lesions – Mean absolute change	14	11	11	6
Non-Inflammatory Lesions - Mean absolute change	19	15	15	8

The Clinical review team is in agreement that there is efficacy in the treatment of acne vulgaris albeit modest with this drug.

8. Safety

Systemic and topical clindamycin use have been associated with *Clostridium difficile* related colitis. As a class these topical clindamycin products include the following in the Warnings section of labeling:

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. When significant diarrhea occurs, Acanya Gel should be discontinued.

Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

No cases of colitis were noted during the conduct of the studies for this product, however.

The most characteristic safety concern of topical products for treatment of acne vulgaris is local irritation at the site of application. This was seen in the studies using Acanya. This information should be included in the labeling. Dermal safety studies were conducted with the higher concentration formulation containing 5% benzoyl peroxide instead of 2.5%. That information informs for this product as the sponsor did not conduct any dermal safety studies with the Acanya product by prior agreement. It was agreed with the sponsor that the results from the higher concentration product would provide the determination for dermal safety for the lower concentration product.

The Warnings section, per discussion with the Pharmacology/Toxicology team and in looking at previous labels, will include a section on Ultraviolet Light and Environmental Exposure informing the patient to avoid sun exposure following application. Benzoyl peroxide has been found to be a dose-related tumor promoter.

9. Advisory Committee Meeting

No new Advisory Committee Meeting was held for this application. However, a previous Advisory Committee to address the endpoints and study design elements for clinical trials for drugs intended to treat acne vulgaris was held on November, 2002. Part of the discussion resulting from that and the current draft version of the *Guidance for Industry: Conducting*

Studies in Acne Vulgaris was to consider a 2 point reduction in a Physician's Global as an adequate assessment.

10. Pediatrics

The included pivotal studies had patients evaluated down to age 12 years. The applicant requested that the population less than 12 be waived and corresponding labeling only indicate the use of this product from age 12 and above. The reason for such a waiver would be because of insufficient patients to conduct studies.

A discussion of this issue was had with the PeRC (Pediatric Review Committee). The recommendation from the committee was to grant the waiver for further study for pediatric patients with acne vulgaris for less than 12 years. This would be a partial waiver. Future consideration would be to lower the age group after analysis of ICD-9 data and other disease epidemiology data together with the Pediatric and Maternal Health Staff. An ongoing consult to discuss this issue was initiated.

11. Other Relevant Regulatory Issues

505(b)2

As discussed briefly, above in the Background section (2), a major issue of concern with regard to the original submission is the putative clinical bridge to the listed drug product. In this case, the listed drug product is BenzaClin. The lack of any comparative clinical studies does not allow the Agency to bridge systemic safety to our findings for BenzaClin. Efficacy and topical safety are provided for in the conducted clinical study versus monads and vehicle that was provided in the submission.

While the required Pharmacology/Toxicology studies were thought not necessary for approval (see Pharm/Tox review), the Clinical Pharmacology reviewer and team maintained that the maximal use exposure study was still necessary, but not for approval given the circumstances for this specific product. No short-term systemic safety concerns were seen in the conducted clinical studies which included thousands of patients. This study could be conducted as a post-marketing commitment, but this should not be generalized for future applications. Systemic availability of topical products is needed prior-to-approval per 21 CFR 320.

Tradename

The original submitted Tradename of _____ was not accepted due to DDMAC and DMEPA concerns. _____ was thought to be too similar to the word "_____" which would imply claims of clarity.

A new proposed tradename of Acanya was accepted by DMEPA in OSE.

b(4)

12. Labeling

Please see the label, which is in PLR format and addresses the various use aspects of this medication. As noted elsewhere in this review, the proposed physician's sample size product is not described in the label.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is approval for this application with labeling that addresses adequately the issues described above.

- Risk Benefit Assessment

This topical formulation combining benzoyl peroxide and clindamycin is relatively low risk and the benefits are also relatively minimal in the treatment of acne vulgaris as seen in the clinical trial results at 12 weeks. The product has not been evaluated for longer use so the safety and efficacy of the product beyond 12 weeks is not known.

- Recommendation for Postmarketing Risk Management Activities

No special Postmarketing Risk Management Activities are recommended.

- Recommendation for other Postmarketing Study Commitments

A clinical pharmacology maximal use study is recommended to be conducted with Acanya gel. The wording of the request is as follows:

To conduct a 'maximum use systemic exposure (MUSE)' bioavailability study in the targeted patient population to determine the extent of systemic absorption of the active ingredients in Acanya™ Gel. Elements of the said study should include:

- a) Highest frequency of dosing in the proposed label for Acanya™ Gel
- b) Greatest duration of dosing in the above mentioned labels
- c) Use of to-be-marketed formulation
- d) Maximum total involved surface area to be treated at one time per labeling
- e) Amount applied per square centimeter to be documented
- f) Method of application/site preparation should be documented
- g) Sensitive and validated analytical method to measure active and potential metabolite(s).

Final study protocol submitted:	February 1, 2009
Patient accrual initiated:	May 1, 2009
Study completion:	August 1, 2009
Final report submission:	February 1, 2010

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

/s/

Markham Luke
10/15/2008 09:25:25 AM
MEDICAL OFFICER
CDTL for Acanya Gel.