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APPLICATION NUMBER:
50-819

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW
(ADDENDUM)**

NDA	50-819
Submission Letter Date(s)	12/21/2007, 2/19/2008
PDUFA Due Date	10/26/08
Brand Name	Acanya Gel (pending brand name approval)
Generic Name	Aqueous gel containing clindamycin phosphate 1.2% and benzoyl peroxide 2.5%
Primary Reviewer	Jang-Ik Lee, Pharm.D., Ph.D.
Primary Review Team Leader	Lydia Velazquez, Pharm.D.
OCP Division	DCP 3
OND Division	ODE3/DDDP
Sponsor	Dow Pharmaceutical Sciences, Inc.
Relevant IND(s)	IND 41,733
Submission Type	505(b)(2)
Formulation; Strength(s)	Aqueous gel; clindamycin phosphate 1.2%, benzoyl peroxide 2.5% in 50 g jar
Proposed indication	Topical treatment of acne vulgaris in patients 12 years or older
Proposed Dosage and Administration	Applied to the affected areas on the face once daily.

ADDENDUM

In the clinical pharmacology review dated September 29, 2008 in DFS, the clinical pharmacology reviewer team recommended a maximum use systemic exposure (MUSE) bioavailability study in the targeted patient population under maximal use conditions in comparison to the listed product, BenzaClin Gel[®] as a Phase IV commitment.

The purpose of the MUSE study in comparison to the listed product is to aid in establishment of a bridge between the proposed and listed products in clinical and pharmacology/toxicology information required under the provision of 505(b)(2) of the Food, Drug and Cosmetic Act. Such a bridge would allow using the information from the listed product (BenzaClin Gel[®]) toward the approval of the proposed product.

In subsequent discussions with the clinical and the pharmacology/toxicology review teams, it has been determined that the bridge is not necessary since the pertinent information will come from the literature. Therefore, the applicant may conduct the MUSE study as a Phase IV commitment without the listed product as a comparator.

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/s/

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

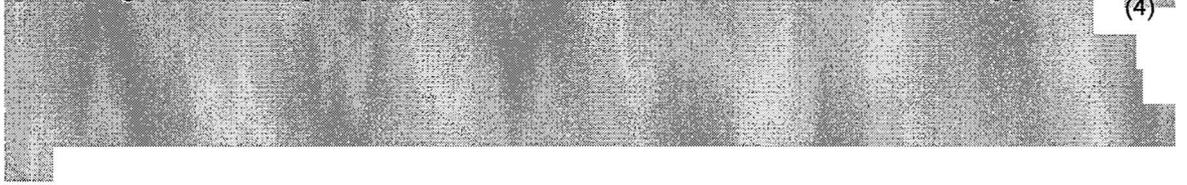
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1 EXECUTIVE SUMMARY

Acanya Gel[®] is a combination product with two active ingredients of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% in an aqueous gel formulation. This submission is a 505(b)(2) application referencing BenzaClin Topical Gel[®] (NDA 50-756 approved in September 20, 2000) containing clindamycin phosphate 1.2% and benzoyl peroxide 5% as a listed drug product. (b) (4)



The applicant has requested a waiver for pediatric studies (see Section 2.3.2.2 *Pediatric Patients*). In terms of in vivo bioavailability, the applicant has submitted study report 2104-047-051-053-056, entitled “In Vitro Percutaneous Absorption of Clindamycin and Benzoyl Peroxide from BenzaClin, (b) (4) (1/2.5), (b) (4), and Duac Topical Gel Using Intact Human Skin from Two Healthy Donors”, in order to obtain a waiver of the in vivo bioavailability study requirement. In vitro bioavailability studies are allowed under the provisions §320.24 but only when the tests have been shown to correlate with in vivo bioavailability ((b)(1)(ii)) or the test is such that it ensures human in vivo bioavailability ((b)(5)) neither of which conditions are met by this study.

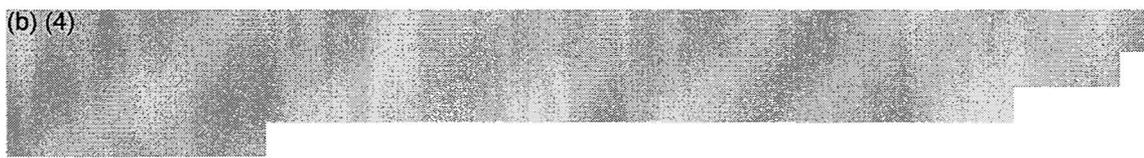
The applicant also submitted the study report DPS 07-07-2005-001, “A Phase 3 Bioequivalence Study of (b) (4) Gel to BenzaClin”, to support the clinical bridge for 505(b)(2) application purpose. The study does not compare in vivo bioavailability of the active ingredients; but instead assesses clinical outcomes between (b) (4) Gel (clindamycin phosphate 1.2%/benzoyl peroxide 5%), (b) (4) and BenzaClin Topical Gel[®], the listed product. It should be noted that the proposed product is not a pharmaceutical equivalent of either of these “reference” products as is it contains a (b) (4) amount of benzoyl peroxide than either (b) (4) Gel[®] or BenzaClin[®] (2.5% vs. 5%)

At the present time the proposed brand name, ‘Acanya Gel[®]’ has not been approved. In this submission, the applicant used other unapproved product names for Acanya Gel[®] such as (b) (4) Gel, (b) (4) (1/2.5) Gel and IDP-110 Gel.

1.1 Recommendation

The clinical pharmacology information included in this application is not adequate to support the approval of the proposed product, Acanya Gel[®]. Specifically, the application does not contain adequate in vivo bioavailability information required by 21 CFR §320. The clinical pharmacology review team reminded the applicant of such requirement during the End-of-Phase-2 and pre-NDA meetings.

(b) (4)



In order for NDA 50-819 to be approved, the applicant is required 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[®] in comparison to the listed drug BenzaClin Gel[®]. Elements of the said study should include:

- a) Highest frequency of dosing in the proposed label for Acanya[®] Gel and BenzaClin[®] 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).

Should the Division of Dermatological and Dental Drug Products (DDDDP) determine that there is sufficient safety and efficacy information in the clinical studies database for approval we would still recommend that the study outlined above be conducted as a Phase IV post marketing commitment. This is in keeping with previous precedent and underscores the need for such information in drug development.

This recommendation should be communicated to the clinical division and subsequently to the applicant.

1.2 Phase 4 Commitments

The clinical pharmacology information submitted in this application is not adequate to support the approval of the proposed product. However, if as a result of overall regulatory determination by the DDDDP based on the efficacy and safety of the submitted clinical study results, a decision is made to approve the application, an in vivo bioavailability study will be required to be conducted post approval. Under these circumstances just described, the clinical pharmacology review team recommends conducting a 'maximum use systemic exposure (MUSE)' bioavailability study in the targeted patient population under maximal use conditions in comparison to the listed product, BenzaClin Gel[®] as a Phase IV commitment.

1.3 Summary of Clinical Pharmacology Findings

The applicant did not assess the characteristics of clindamycin or benzoyl peroxide absorption in subjects with acne vulgaris. Instead, the applicant performed an in vitro skin permeation study (2104-047-051-053-056) using dermatomed healthy human abdominal skin mounted to Bronaugh flow-through diffusion cells. The amount of drug in the receptor fluid, the dermis and the epidermis was measured after a single application (5 mg/cm²) of the proposed (Acanya Gel[®]) or listed drug products (BenzaClin Topical Gel[®], Duac Gel[®]) using a high performance liquid chromatographic (HPLC) method.

Although **clindamycin** concentrations could not be quantified (below the limit of quantitation [LOQ]) and compared in dermis samples and receptor solutions, the concentrations in epidermis samples were consistently above the LOQ (200 ng/sample) for all compared products. However,

due to large cell-to-cell (coefficient of variation [CV] up to 133%) and donor-to-donor (difference up to 3.5 fold) variability, and small number of skin donors (n = 2), the clindamycin recovery in the epidermis could not be reliably compared between the proposed and listed drug products.

Benzoyl peroxide was not detectable in the receptor solution or the dermis for any of the products. Although benzoyl peroxide was detected in a few epidermis samples, benzoyl peroxide concentrations were not quantifiable (lower than the LOQ, 40 µg/sample). Because benzoyl peroxide concentrations were not detectable or quantifiable, the extent of benzoyl peroxide absorption could not be compared between the proposed and listed drug products.

Benzoic acid was not detectable in dermis samples. Although benzoic acid was detected in receptor solutions and epidermis samples, benzoic acid concentrations were not quantifiable due to the LOQ. The LOQ of benzoic acid in receptor solution (400 ng/mL) is approximately 3% of applied dose when the solution is collected for 6 hours. Thus, by detecting benzoic acid in the samples, the extent of benzoyl peroxide absorption could not be compared between the proposed and listed drug products.

The HPLC method used in the study showed poor recovery of all analytes from receptor solutions (as low as 30% in benzoyl peroxide recovery).

Based on the results of the in vitro study summarized above, the extent of percutaneous absorption of clindamycin and benzoyl peroxide can not be reliably compared between the proposed and listed drug products since the drug concentrations were unquantifiable or highly variable and there were only two skin donors. Furthermore, in diseases where there is a disruption of the skin, in vitro study result is not acceptable as a surrogate for in vivo bioavailability.

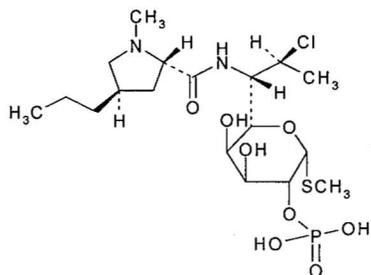
Note: The Optional Intra-Division Clinical Pharmacology Briefing was held on September 29, 2008. The attendees include Captain E. Dennis Bashaw, PharmD., Commander Lydia Velazquez, PharmD, and Jang-Ik Lee, Pharm.D., Ph.D.

2 QUESTION-BASED REVIEW

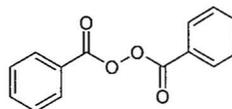
2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Acanya Gel is a topical combination product with two active ingredients of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% in an aqueous gel formulation. Clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo- α -D-galacto-octopyranoside 2-(dihydrogen phosphate). Benzoyl peroxide is an antibacterial and keratolytic agent. The structural formula for clindamycin phosphate and benzoyl peroxide are represented below:



Clindamycin phosphate
(molecular weight, 504.97)



Benzoyl peroxide
(molecular weight, 242.23)

The chemical composition of Acanya Gel is shown in the table below.

Ingredient	%w/w	Quantity per 50 g Jar (g)
Clindamycin Phosphate, USP	1.20 ¹	
██████████ Benzoyl Peroxide, USP	2.50 ²	
Propylene Glycol, USP		
Carbomer 980		
Potassium Hydroxide, NF		
Purified Water, USP		

¹Equivalent to 1% w/w clindamycin

²Based on ██████████ benzoyl peroxide

(b) (4)

(b) (4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis. The clinical relevance of this in the treatment of acne vulgaris is unknown. Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects.

Acne vulgaris is a multifactorial disease, resulting from interplay of keratinization abnormalities, excess sebaceous gland secretion, bacterial growth and inflammatory immune reactivity. Given the pathogenesis of acne, combination therapies affecting multiple etiologic factors have been shown to have significant benefit in acne treatment. This has been demonstrated with the combination of antibiotics (clindamycin or erythromycin) and keratolytic agents (tretinoin or benzoyl peroxide). In clinical practice, it is common for physicians to prescribe both topical benzoyl peroxide and a topical antibiotic for the treatment of acne. An example of combination products includes BenzaClin Gel (Sanofi Aventis, NDA 50-756).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Acanya Gel should be applied (b) (4) once daily (b) (4).
Acanya Gel is not for oral, ophthalmic or intravaginal use.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant has performed one Phase 2 study (DPS-07-12-2005-002) and two identical Phase 3 studies (DPSI-06-22-2006-012, DPSI-06-22-2006-017) which have provided clinical support for the efficacy of Acanya Gel. Male and female subjects 12 years or older were included in the studies. Dosing in the Phase 2 study was once or twice daily for 12 weeks, and in the 2 Phase 3 studies, it was once daily for 12 weeks. The gel was applied as a thin coating (a dab the size of a pea) that is gently rubbed into the skin on the face. All studies included subjects having between 17 and 40 acne inflammatory lesions, 20 and 100 non-inflammatory lesions, and 2 or fewer nodules.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoints were absolute change from baseline to Week 12 in mean inflammatory lesion counts and percent of subjects who achieve a two-point reduction at Week 12 in the Evaluator's Global Severity Score (EGSS) from baseline.

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure response relationships?

No blood sample was collected from study subjects enrolled in any clinical study to assess pharmacokinetics, pharmacodynamics or exposure-response relationships.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The exposure-efficacy response relationships have not been characterized in this 505(b)(2) application.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The exposure-safety response relationships have not been characterized in this 505(b)(2) application.

2.2.4.3 Does this drug prolong the QT or QTc interval?

No clinical study has been performed to determine the effect of Acanya Gel on QT interval.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dose is not based on a dose-concentration-response relationship but rather the approved dose of the listed product (BenzaClin Gel) and fixed dose studies conducted by the applicant.

2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

No clinical pharmacokinetic study has been conducted for this application.