

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**50-819**

**PHARMACOLOGY REVIEW(S)**

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A  
NEW NDA/BLA**

NDA Number: 50-819

Applicant: Dow Pharmaceutical

Stamp Date: Dec. 21, 2007

Drug Name: Clindaben Gel

NDA/BLA Type: 505(b)(1)

b(4)

(  , Gel)

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A  
NEW NDA/BLA**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			NA
11	Has the applicant addressed any abuse potential issues in the submission?			NA
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jiaqin Yao Feb. 13, 2008  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

\_\_\_\_\_  
 Team Leader/Supervisor Date

## Pharmacology/Toxicology Supervisory Memorandum

**NDA number:** 50-819  
**Sequence number/date/type of submission:** 000 / December 26, 2007 / original submission  
**Sponsor and/or agent:** Dow Pharmaceutical Sciences, Inc.  
**Supervisor name:** Barbara Hill  
**Division name:** Division of Dermatology and Dental Products  
**Date:** October 3, 2008  
**Drug:** Acanya (clindamycin 1%/benzoyl peroxide 2.5%) gel  
**Drug class:** Anti-acne  
**Indication:** Topical treatment of acne vulgaris in patients 12 years and older

### Introduction and discussion:

This application was submitted under section 505(b)(2) of the FD&C Act. Originally the sponsor believed that they had generated an adequate clinical bridge to the listed drug product BenzaClin which contains clindamycin 1%/benzoyl peroxide 5%. The sponsor conducted a clinical bridging study with a different concentration of their drug product (i.e., \_\_\_\_\_) and the listed drug BenzaClin. However, it was determined that the sponsor did not conduct an adequate clinical bridging study with Acanya gel (clindamycin 1%/benzoyl peroxide 2.5%) since the Acanya gel formulation was not tested in a clinical bridging study with the listed drug BenzaClin. Therefore, it was determined that this NDA would be a 505(b)(2) application based on the conducted nonclinical toxicology studies and submitted literature references.

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The sponsor conducted two phase 3 clinical studies comparing the combination product (a dyad; clindamycin 1%/benzoyl peroxide 2.5% gel) to its monads (clindamycin 1% gel and benzoyl peroxide 2.5% gel) and vehicle gel in the treatment of moderate to severe acne vulgaris. The duration of treatment in both clinical studies was 12 weeks with once daily administration of the drug product to the face only. Dr. Brenda Vaughan, the clinical reviewer, determined that efficacy was sufficiently demonstrated to allow for approval from a clinical perspective.

The clinical pharmacology reviewer, Dr. Jang-Ik Lee has determined that "the application does not contain adequate in vivo bioavailability information required by 21 CFS 320." The sponsor had been previously informed during both the End of Phase 2 and pre-NDA meetings that a maximal use systemic bioavailability study should be conducted with their drug product. Dr. Jang-Ik Lee recommends that the sponsor 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." It has been determined by the clinical review team that it would be acceptable to conduct this study as a post-marketing commitment.

The sponsor conducted several nonclinical toxicology studies to support the safety of Acanya gel. Information on these studies can be found in the review by Dr. Jiaqin Yao. The pivotal toxicology studies include the following:

- 1) 35-Day Dermal Toxicity study in Rats with \_\_\_\_\_ (91 GLA P007 S016)
- 2) 35-Day Dermal Toxicity Study in Rabbits with \_\_\_\_\_ (91 GLA P007 S005)
- 3) 90-Day Gavage Toxicity Study of an Admixture Active Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) in Rats (91 GLA P007 S032)
- 4) Study title: In Vitro Mammalian Chromosome Aberration Test (7001-U5HP-01-07)
- 5) Dermal Carcinogenicity Study of an Admixture Active Gel (\_\_\_\_\_ - Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and its Components in Mice (92 GLA P007 S034)
- 6) 2 Year Oral (Gavage) Carcinogenicity Study of an Admixture Active Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and its Components in Rats (92 GLA P007 S033)
- 7) Primary Skin Irritation Study in Rabbits with \_\_\_\_\_ (91 GLA P007 S007)
- 8) Primary Eye Irritation Study in Rabbits with \_\_\_\_\_ (91 GLA P007 S006)
- 9) Dermal Sensitization Study in Guinea Pigs with \_\_\_\_\_ (91 GLA P007 S008)
- 10) Photoirritation Study in Rabbits with \_\_\_\_\_ (91 GLA P007 S009)

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The nonclinical toxicology studies were conducted with a gel formulation that contained a higher concentration of benzoyl peroxide (\_\_\_\_\_ gel; clindamycin 1%/benzoyl peroxide 5%) compared to Acanya gel (clindamycin 1%/benzoyl peroxide 2.5%). The sponsor also submitted literature data to provide additional nonclinical toxicology data to support the safety of Acanya gel. The Pharmacology/Toxicology reviewer, Dr. Jiaqin Yao, reviewed the submitted literature data and nonclinical toxicology studies. Dr. Jiaqin Yao initially determined that in the absence of a clinical bridge, that data from two genotoxicity studies for clindamycin (an Ames test and in vivo micronucleus assay) were not provided in the NDA since the submitted literature article (Snyder RD and Green JW, A review of the genotoxicity of marketed pharmaceuticals, Mutation Research, 488:151-169, 2001) refers to marketed pharmaceuticals.

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Dr. Abby Jacobs, Pharmacology/Toxicology Associated Director, informed me during a discussion concerning this NDA on September 17, 2008 that the missing data for clindamycin (i.e., the Ames test and in vivo micronucleus assay) is not an approvability issue for NDA 50-819. This decision to not require providing an ICH battery of genotoxicity data for clindamycin is unique to Acanya gel approval and may not be broadly applicable to other drug products. The reason for this decision is that the sponsor has conducted oral and dermal carcinogenicity studies with their drug product with negative results. The sponsor conducted an in vitro mammalian chromosomal aberration assay with clindamycin in human lymphocytes which was negative. In addition, information will be incorporated into the label describing the genotoxicity of benzoyl peroxide based on submitted literature data. Since one active moiety of the drug product is genotoxic, then it is presumed the entire drug product is genotoxic and the missing genotoxicity data for clindamycin is not critical. However, it was determined that it would be appropriate to conduct a tele-conference with the sponsor to ask them if they could submit literature that did not refer to a marketed drug product.

A tele-conference was conducted with the sponsor on September 18, 2008. The sponsor was informed that it has been determined that they do not have an adequate clinical bridge. We informed the sponsor that the submitted literature reference that referred to a marketed drug

product was not acceptable in the absence of a clinical bridge. We asked the sponsor if they could submit literature for the Ames test and in vivo micronucleus assay conducted with clindamycin that did not refer to a marketed drug product. The sponsor indicated that there was no such data. We asked the sponsor to submit this information to the NDA to document that no such data was available in the literature. The sponsor asked if this was an approvability issue and we informed the sponsor that this is not an approvability issue but that data from the Ames test and in vivo micronucleus assay conducted with clindamycin based on literature that refers to a marketed drug product can not be included in the Acanya gel label. The sponsor said this was acceptable.

**Conclusion:**

The literature information along with the nonclinical studies conducted by the sponsor are adequate to support the safety of Acanya gel, from a pharmacology and toxicology perspective. The labeling of Acanya gel should use the information from the nonclinical studies conducted by the sponsor and from the literature as outlined in the review by Dr. Jiaqin Yao.

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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Barbara Hill  
10/7/2008 07:51:57 AM  
PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 50-819  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 12/26/2007  
DRUG NAME: Acanya ——— Gel  
INDICATION: Acne  
SPONSOR: Dow Pharmaceutical  
REVIEW DIVISION: Dermatology and Dental Products  
PHARM/TOX REVIEWER: Jiaqin Yao  
PHARM/TOX SUPERVISOR: Barbara Hill  
DIVISION DIRECTOR: Susan Walker  
PROJECT MANAGER: Tamika White

b(4)

Date of review submission to DFS: 9-25-2008

## **TABLE OF CONTENTS**

<b>EXECUTIVE SUMMARY .....</b>	<b>1</b>
<b>2.6 PHARMACOLOGY/TOXICOLOGY REVIEW .....</b>	<b>4</b>
<b>2.6.1 INTRODUCTION AND DRUG HISTORY.....</b>	<b>4</b>
<b>2.6.2 PHARMACOLOGY.....</b>	<b>7</b>
<b>2.6.3 PHARMACOLOGY TABULATED SUMMARY.....</b>	<b>7</b>
<b>2.6.4 PHARMACOKINETICS/TOXICOKINETICS .....</b>	<b>7</b>
<b>2.6.5 PHARMACOKINETICS TABULATED SUMMARY.....</b>	<b>7</b>
<b>2.6.6 TOXICOLOGY.....</b>	<b>7</b>
2.6.6.1 Single-dose toxicity .....	7
2.6.6.2 Repeat-dose toxicity .....	7
2.6.6.3 Genetic toxicology.....	11
2.6.6.4 Carcinogenicity.....	13
2.6.6.5 Reproductive and developmental toxicology.....	40
2.6.6.6 Local tolerance .....	42
2.6.6.7 Special toxicology studies .....	44
<b>2.6.7 TOXICOLOGY TABULATED SUMMARY .....</b>	<b>45</b>
<b>OVERALL CONCLUSIONS AND RECOMMENDATIONS.....</b>	<b>45</b>
<b>APPENDIX/ATTACHMENTS .....</b>	<b>55</b>

## EXECUTIVE SUMMARY

### I. Recommendations

#### A. Recommendation on approvability

This NDA is approvable from a Pharmacology/Toxicology perspective

#### B. Recommendation for nonclinical studies

None

#### C. Recommendations on labeling

Since a sufficient clinical bridge has not been established to BenzaClin Topical Gel or any other drug product containing clindamycin and benzoyl peroxide, the following wording is recommended in the labeling of this NDA:

#### 8.1 Pregnancy

Pregnancy Category C.

There are no well-controlled trials in pregnant women treated with Acanya \_\_\_\_\_ Gel. It also is not known whether Acanya \_\_\_\_\_ Gel can cause fetal harm when administered to a pregnant woman. Acanya \_\_\_\_\_ Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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Animal reproductive/developmental toxicity studies have not been conducted with Acanya \_\_\_\_\_ Gel. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose of 2.5 g Acanya \_\_\_\_\_ Gel based on mg/m<sup>2</sup>, respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m<sup>2</sup>, respectively) revealed no evidence of teratogenicity.

b(4)

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility testing of Acanya \_\_\_\_\_ Gel have not been performed.

b(4)

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced squamous cell skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times amount of clindamycin and 3.6, 10.8, and 60 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g Acanya \_\_\_\_\_ Gel based on mg/m<sup>2</sup>, respectively) did not cause any increase in tumors.

However, topical treatment with another formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In a oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900, and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 2.4, 7.2, and 24 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g Acanya — Gel based on mg/m<sup>2</sup>, respectively) for up to 97 weeks did not cause any increase in tumors. In a 52 week dermal photocarcinogenicity study in hairless mice (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the gel formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation. b(4)

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g Acanya — Gel, based on mg/m<sup>2</sup>) revealed no effects on fertility or mating ability. b(4)

## II. Summary of nonclinical findings

### A. Brief overview of nonclinical findings

Acanya — Gel (IDP-110 Gel) is a combination product of 1% clindamycin (1.2% clindamycin phosphate) and 2.5% benzoyl peroxide (BPO). Nonclinical studies conducted with the ' ——— (Admixture Active Gel) containing 1% clindamycin and 5% benzoyl peroxide and literature data were submitted to support this NDA [(505(b)(2))]. Topical treatment with the ' ——— in rats and rabbits caused local effects at application sites including erythema, desquamation, and edema. Acanthosis and hyperkeratosis were also observed histopathologically in rats and rabbit after 35-day topical treatment. ' ——— was negative in the dermal sensitization test in guinea pigs. In addition, no photoirritating effects were noted in rabbits following topical treatment with the ' ——— and UVA light. b(4)

Although clindamycin phosphate was negative in the in vitro mammalian chromosome aberration assay, benzoyl peroxide was genotoxic. A dermal carcinogenicity study in mice, an oral carcinogenicity study in rat, and a photocarcinogenicity study in mice have been conducted with the ' ——— containing 1% clindamycin and 5% benzoyl peroxide; all of them were negative. However, benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice b(4)

