CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-819

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 12, 2008
From	Stanka Kukich, M.D.
Subject	Deputy Director Summary Review
NDA/BLA #	NDA 50-819 IND 41,733
Applicant Name	Dow Pharmaceutical Sciences, Inc.
Date of Submission	December 21, 2007
PDUFA Goal Date	October 26, 2008
Proprietary Name / Established (USAN) Name	ACANYA™ Gel 1.2% clindamycin phosphate and 2.5% benzoyl peroxide
Dosage Forms / Strength	Topical Gel
Proposed Indication(s)	Topical Treatment of Acne Vulgaris in Patients 12 Years or Older
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Vaughan, M.D.
Statistical Review	Clara Kim, Ph.D.
Pharmacology Toxicology Review	Jiaqin Yao, Ph.D.
CMC Review/OBP Review	Rajiv Agarwal, Ph.D.
Microbiology Review	Kerry Snow
Clinical Pharmacology Review	Jang-Ik Lee, Ph.D.
DDMAC	Andrew Haffer, Pharm.D.
DSI	Roy Blay, Ph.D.
CDTL Review	Markham Luke, M.D.
OSE/DMETS	Jibril Abdus-Samad, Pharm. D.
OSE/DDRE	None
OSE/DSRCS	Sharon Mills, BSN, RN, CCRP
Other	-

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

ACANYA Gel is a combination product that contains 1% clindamycin (clindamycin phosphate 1.2%) and benzoyl peroxide 2.5% intended for once a day topical treatment of acne vulgaris in patients twelve years of age and older. Clindamycin is an antibiotic with the activity against the *Propionibacterium acnes (P acnes)*. Bezoyl peroxide is an antibacterial agent that is active against *P. acnes* based on its oxidizing properties. It also has keratolytic and desquamative effects.

Each of the active components in this aqueous gel formulation is also marketed individually; clindamycin as a prescription product and benzoyl peroxide is available at concentrations up to 10% as a prescription or over-the-counter drug product. Topical formulations of 1% clindamycin and a higher concentration of benzoyl peroxide 5% are marketed as Duac and BenzaClin with a recommendation for once a day and twice a day applications, respectively, for the treatment of acne vulgaris. In addition to topical solution, gel, and lotion formulations, clindamycin is also available for oral, IM and IV routes of administration.

Benzoyl peroxide could be used alone or as adjunct to other acne treatments. It acts by increasing epithelial cell turnover resulting in desquamation and as an antibacterial agent by decreasing a number of anaerobic bacteria; it does not have any effect on the production of sebum. Benzoyl peroxide is converted to benzoic acid as soon as is absorbed in the skin. Less than 2% of benzoyl peroxide applied to the skin enters the systemic circulation as benzoic acid and is rapidly excreted by the kidneys. Topical application of benzoyl peroxide is associated with a mild to moderate skin irritation.

b(4)

In the NDA submission the applicant referred to this product as Clindaben1/2.5 ——— or IDP-110 Gel. The proposed tradename, Acanya for this product was found to be acceptable.

2. Background

Acne is a common skin disease affecting the sebaceous follicles and occurs mostly in adolescents, however, can occur in adults also. While the etiology of acne vulgaris is not known, the pathogenesis involves follicular hyperkeratinization, increase in sebum production, colonization with *P. acnes* and inflammation. Acne vulgaris usually appears on the face but can appear on the chest, neck, shoulders, and upper back.

Acne is characterized by open and closed comedones which can be present alone or with pustules, papules and nodules. The severity is generally assessed by type and number of lesions. Mild to moderate acne is commonly treated with topical applications of benzoyl peroxide, topical retinoids or topical antibiotics and severe acne with systemic agents alone or

in combination with topical products. Combining different classes of medications in the treatment of acne is a common practice.

Regulatory issues regarding the development program for this product were discussed at guidance meetings on November 12, 2003, March 7, 2005 and June 27, 2006, an End-of-Phase 2 meeting on September 18, 2006 and a Pre-NDA meeting on November 27, 2007.

At the initial meeting with the sponsor, the development plan under 505(b)(2) pathway for 1% clindamycin/5% benzoyl peroxide was discussed in great detail. Under 505(b)(2) pathway, the sponsor would need to establish a clinical bridge to Duac or BenzaClin as a listed drug to be able to refer to nonclinical findings included in respective labels. The clinical bridge would be a well-controlled clinical study [21 CFR 320.24(b)(4)] that would establish relative bioavailability via clinical endpoints and would include the sponsor's combination product vs. the listed drug vs. the sponsor's vehicle. In addition, the sponsor would need to conduct two adequate and well-controlled four-arm studies to establish the efficacy of 1% clindamycin/2.5% benzoyl peroxide.

At the March 2005 Guidance meeting for 1% clindamycin/2.5% benzoyl peroxide, it was stated that for a 505(b)(2) application, the sponsor should conduct comparisons to the reference listed product(s) to provide clinical information on comparative bioavailability, 21 CFR 320.24 (b)(4). Because this is a fixed combination product as per 21 CFR 300.50 the sponsor should also adequately demonstrate that the combination dyad product is superior to each of the monads and the vehicle alone for each of the primary endpoints via two adequate and well-controlled clinical studies. The sponsor was also asked to conduct dermal safety studies.

At the June 2006 Guidance meeting, it was discussed that if a sufficient clinical bridge is not established the sponsor would need to provide additional nonclinical information to support the 505(b)(2) application. In addition, the sponsor provided a rationale for not conducting an absorption study for 1% clindamycin/2.5% benzoyl peroxide gel under maximal use conditions, however, a waiver was not granted at this meeting.

At the September 2006 End-of-Phase 2 meeting, it was again discussed what would be needed in support of the NDA submission under 505(b)(2).

At the November 2007 Pre-NDA meeting, the sponsor acknowledged in their question to the Agency that nonclinical information could come from literature or from nonclinical studies conducted with [redacted] Gel if a clinical bridge was not established via bioequivalence study with [redacted] and BenzaClin, already approved formulation of 1% clindamycin/5% benzoyl peroxide. **b(4)**

In support of 505(b)(2) application the applicant has submitted the following information:

RLD List

BenzaClin Package Insert	Pharmacodynamics
Literature regarding clindamycin and benzoyl peroxide	Pharmacokinetics, Genotoxicity, Reproductive and Development Toxicity
Study 2104-047-051-053-056 In Vitro Percutaneous Absorption of Clindamycin and Benzoyl Peroxide from BenzaClin®, Clindaben (1/2.5) [redacted] and Duac® Topical Gel Using Intact Human Skin from Two Healthy Donors	Clinical pharmacology
DPS-07-07-2005-001 A Phase 3, Multi-Center, Randomized, Evaluator-Blind, Vehicle Controlled Trial to Evaluate the Bioequivalence of [redacted] Gel to BenzaClin® Gel, and Superiority to [redacted] Gel Vehicle, in the treatment of Acne Vulgaris	Clinical pharmacology

b(4)

The comparative bioavailability 10-week clinical endpoint study, DPS-07-07-2005-001, was multi-center, randomized, vehicle- controlled, three-arm study designed to evaluate bioequivalence of [redacted] to BenzaClin and superiority to [redacted] vehicle. This study was intended to allow the Agency to use our findings of safety for BenzaClin (the listed drug) so the applicant can reference necessary safety information including genotoxicity information in the BenzaClin label for clindamycin. [redacted] contains a higher concentration of benzoyl peroxide and propylene glycol than the formulation intended for marketing. This study is a part of the ANDA under review in the Office of Generic Drugs.

b(4)

It appears that the [redacted] formulation included in the relative bioavailability study (clinical bridge) is similar to the formulation of 1% clindamycin/2.5% benzoyl peroxide proposed for marketing but is not exactly the same. In summary, a clinical bridge did not include to-be-marketed formulation of 1% clindamycin/2.5% benzoyl peroxide.

b(4)

To support safety and efficacy of 1% clindamycin/2.5% benzoyl peroxide the applicant submitted results from two Phase 3 active- and vehicle-controlled trials that compared 1% clindamycin/2.5% benzoyl peroxide to active monads and vehicle and one small phase 2 exploratory study. In addition, the applicant has submitted contact irritation/sensitization study, cumulative irritation, and phototoxicity and photoallergy studies conducted with [redacted] formulation. A waiver was granted for the sponsor not to conduct any additional topical safety studies because it was determined that to-be-marketed formulation was similar enough to [redacted] so no additional topical safety studies were needed.

b(4)

3. CMC/Device

ACANYA Gel in a combination of clindamycin phosphate, a water-soluble ester of lincomycin antibiotic, and benzoyl peroxide, an antibacterial and keratolytic agent. The

formulation is an opaque, white to off-white, smooth, semi-solid gel that is not pourable with pH ranging from [redacted]. This product contains [redacted] propylene glycol, potassium hydroxide, [redacted] water and Carbomer 980, [redacted]. Since the product contains [redacted] water it is classified as an aqueous gel. b(4)

The proposed drug product is prepared by the pharmacist at the time of dispensing using a package that contains two components: [redacted]. Clindamycin is added to the [redacted] and mixed with a [redacted] spatula for at least 1.5 minutes until homogeneous prior to dispensing. The proposed expiry period before dispensing is [redacted] months and after dispensing is 2 months. b(4)

The proposed formulation is different from the [redacted] (clindamycin [redacted], benzoyl peroxide [redacted]) Gel formulation in respect that it contains less propylene glycol and benzoyl peroxide.

Ingredient	TRADENAME Formulation	[redacted]	BenzaClin
Clindamycin phosphate	1.2%	[redacted]	1% clindamycin as clindamycin phosphate
Benzoyl Peroxide	2.5%	[redacted]	5%
Propylene Glycol	[redacted]		[redacted]
Carbomer 980			-
Potassium Hydroxide			-
Purified Water			-

b(4)

In addition to the 50 gram size jar to be marketed, the applicant proposed a physician sample packaged in [redacted] gram jar. The physician sample is already [redacted], and it does not need to be mixed by the patient or pharmacist.

I concur with the conclusions reached by the chemistry reviewer, Dr. Rajiv Agarwal, regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months for each component of the combination and 2 months for the product after mixing by the pharmacist. Regarding physician [redacted] sample, it can be stored for up to [redacted] months at room temperature after dispensing to physician. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies conducted with the [redacted] and data from the published literature were submitted in support of this NDA. Genotoxicity, developmental and reproductive toxicity were not conducted with the proposed formulation of clindamycin/benzoyl peroxide. b(4)

Literature support for the benzoyl peroxide appears adequate. For the clindamycin, in the absence of acceptable clinical bridge the reference to genotoxicity data in the approved

BenzaClin label could not be made. Clindamycin phosphate did not elicit any genotoxic effect in the in vitro mammalian chromosome aberration assay; however, benzoyl peroxide was genotoxic. The applicant has conducted a 2-year dermal carcinogenicity study in mice and 2-year oral carcinogenicity study in rats with 1% clindamycin/5% benzoyl peroxide and both studies did not show any increase in tumors. Therefore, data from the Ames test and in vivo micronucleus assay regarding clindamycin were not necessary for approval of this product.

The applicant has also conducted a 52-week dermal photocarcinogenicity study in hairless mice with 1% clindamycin/5% benzoyl peroxide admixture that showed a shorter median time to tumor formation and increase in number of tumors compared to controls.

There is also information available that there is a dose-dependent increase in keratoacanthoma at the treated skin site demonstrated in a 2-year dermal carcinogenicity study in rats conducted with slightly different formulation of 1% clindamycyn/5% benzoyl peroxide.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that would preclude approval.

5. Clinical Pharmacology

In 2007, the applicant submitted a request for the waiver of the requirement to conduct an in vivo bioavailability study under maximum use conditions with 1% clindamycin/2.5% benzoyl peroxide. This request was based on the in vitro skin absorption study, results from the Phase 2 study, Phase 3 clinical bioequivalence study and the literature data. Because 1% clindamycyn/2.5% benzoyl peroxide contains less propylene glycol and is applied once a day it is expected that expose to clindamycin and benzoyl peroxide would be less than with b(4)

The applicant has submitted a report of the In Vitro Percutaneous Absorption Study of Clindamycin and Benzoyl Peroxide from BenzaClin, Clindaben (1/2.5), , and Duac Topical Gel Using Intact Human Skin from Two Healthy Donors. However, in vitro skin absorption study could not be accepted as a surrogate for in vivo bioavailability study. The permeation properties of the skin are altered by the use of normal and non-viable skin. b(4)

I concur with the conclusions reached by the clinical pharmacology reviewer that the applicant did not provide adequate information regarding in vivo bioavailability of 1% clindamycin/2.5% benzoyl peroxide as per 21 CFR 320.24. In this instance, the maximum use systemic exposure bioavailability study in the targeted patient population to determine the extent of systemic absorption of 1% clindamycin/2.5% benzoyl peroxide can be conducted post-marketing.

6. Clinical Microbiology

Clindamycin is a 7(S)-chroro-7 deoxy derivate of lincomycin and belongs to the lincosamide class of antimicrobials. It is active against Gram-positive cocci including *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae,* most anaerobic bacteria, and