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^2, respectively) did not cause any increase in tumors. b(4) 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 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^2, respectively) for up to 97 weeks did not cause any increase in tumors. b(4) 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.

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^2) revealed no effects on fertility or mating ability. b(4)

Suggested labeling: The following wording was proposed by the Sponsor:

8.1 Pregnancy

b(4)

b(4)

b(4)

b(4)

b(4)

b(4)

Signatures (optional):

Reviewer: Jiaqin Yao NDA No. 50-819

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

cc list:
HFD-540/CSO/WhiteTA
HFD-540/Pharm. Sup./HillB
OPS/ONDQA/DPA II/CMC/AgarwalR
HFD-540/MO/VaughanB
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HFD-540/DDD/KukichS
HFD-540/DD/WalkerSU

APPENDIX/ATTACHMENTS

Executive CAC
Date of Meeting: July 22, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Barbara Hill, Ph.D., DDDP, Team Leader
Jiaqin Yao, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jiaqin Yao, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA: 50-819
Drug Name: Acanya ——— Gel (IDP-110 Gel) b(4)
Sponsor: Dow Pharmaceuticals

Background:

The original IND (41,733) was submitted by Glaxo Dermatology and then was transferred to the current Sponsor. The Sponsor submitted an ANDA [65,443, ——— (1/5)] using the already marketed BenzaClin (clindamycin 1% - benzoyl peroxide 5%) Gel as the reference drug. The formulation for Acanya ——— Gel (1/2.5) is different b(4)
from that for ——— (1/5), which was tested in the two carcinogenicity studies. In addition to the reduced concentration of benzoyl peroxide from 5% to 2.5% and the ——— concentration of propylene glycol from ———; Acanya ——— Gel has Carbomer 980 instead of ———, and Carbomer ———. The sponsor plans to rely on a clinical bridge with BenzaClin and ——— (1/5) and the safety data generated from the ——— (1/5) Gel to support this NDA filing [505(b)(2)] for the Acanya ——— Gel (1/2.5).

Rat Oral Carcinogenicity Study:

Seven groups of 62 male and 62 female ——— CD(SD)IGS BR rats were treated via gavage with 0.3, 0.9, or 3.0 mL/kg/day Admixture Active Gel ———, 0.9 or 3.0 b(4)
mL/kg/day Benzoyl Peroxide 5% Gel, or 0.9 or 3.0 mL/kg/day Clindamycin Phosphate 1% Gel for up to 97 weeks. Two additional control groups were treated with the Placebo Gel at 3.0 mL/kg/day as the test articles. The study was terminated at Week 97 due to mortality. No range finding data were available for this study and the adequacy of the study was discussed based on the toxicity. A maximum tolerated dose appeared to have been achieved based on differences in body weights (i.e., decrease of approximately 10%) in males and females in groups treated with the high dose of Admixture Active Gel or Clindamycin Phosphate 1% Gel. Although there were some statistically significant

differences in tumor incidence when control groups 1 and 2 were compared to the various treated groups, it appears that these differences were not biologically significant, due to either no trend with increasing dose or no difference from one of the placebo controls.

Mouse Dermal Carcinogenicity Study:

Seven groups of 60 male and 60 female CD-1 mice were treated topically with 0.9, 2.7, or 15 mL/kg/day Admixture Active Gel (————), 2.7 or 15 mL/kg/day Benzoyl Peroxide 5% Gel, or 2.7 or 15 mL/kg/day Clindamycin Phosphate 1% Gel for 2 years. Two additional control groups were treated with the Placebo Gel at 15 mL/kg/day as the test articles. No range finding data were available for this study and the adequacy of the study was based on dermal effects. A maximum tolerated dose appeared to have been achieved since animals in the high dose groups exhibited hyperkeratosis and epithelial hyperplasia at the treated site. Although there were some statistically significant differences in tumor incidence when control groups were compared to the various treated groups, it appears that these differences were not biologically significant, due to either no trend with increasing dose or no difference from one of the placebo controls.

b(4)

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was acceptable, although not optimal.
- The Committee concurred that there were no drug-related neoplasms in this study.

Mouse:

- The Committee agreed that the study was acceptable, although not optimal.
- The Committee concurred that there were no drug-related neoplasms in this study
- The Committee noted that another formulation by another sponsor, using the same active ingredients, caused drug-related skin neoplasms in a 2-year rat dermal carcinogenicity study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DDDP
Barbara Hill/HillB/Team leader, DDDP
Jiaqin Yao/YaoJ/Reviewer, DDDP
Tamika White/WhiteTA/CSO/PM, DDDP
Adele Seifried/ASeifried, OND IO

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

/s/

Jiaqin Yao
9/25/2008 10:38:19 AM
PHARMACOLOGIST

Barbara Hill
9/25/2008 10:46:29 AM
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