Treatment	Hours After Application			
	1	24	48	72
Placebo Gel Combo				
Unrinsed	4.33	0.33	0.33	0.00
Rinsed	1.67	0.00	0.00	0.000
5% Benzoyl Peroxide Gel				
Unrinsed	1.67	0.00	0.00	0.00
Rinsed	0.33	0.00	0.00	0.00
1% Clindamycin Gel				
Unrinsed	4.33	2.00	0.33	0.00
Rinsed	2.33	1.33	0.00	0.00
Clindaben Gel				
Unrinsed	4.67	0.00	0.67	0.00
Rinsed	2.33	0.00	0.00	0.00

b(4)

Conclusions. Gel formulations ———, 1% Clindamycin and Placebo Combo were considered to be mild irritants while 5% Benzoyl Peroxide was non-irritating to the rabbit eye.

2.6.6.7 Special toxicology studies

The following information on the 2 special toxicology studies was duplicated from the review by Dr. S. R. Joshi within the original submission of IND 41,733 in 1993.

b(4)

1. Dermal Sensitization Study in Guinea Pigs with ———

SLS Study No. 3242.29 (*91 GLA P007 S008*)

Study Dates: 3/4/92 to 4/9/92

Materials Tested: Placebo Gel Combination, 5% Benzoyl Peroxide gel, 1% Clindamycin gel, ——— gel.

b(4)

Animals: Hartley-derived albino guinea pigs; 5/sex/group.

Procedure: Modified Buehler methodology.

During the induction phase, the animals (5/sex/test article) were treated once a week for 3 weeks with the appropriate test material for a total of 3 induction applications. Following a 14-day rest period, each test group of guinea pigs was topically challenged with the appropriate test material. A control group of 10 naive animals was also patched with all test articles and vehicle at challenge to serve as a common irritation control group. Challenge responses in each group of induced animals were compared to those of the controls.

Results: For each test article and vehicle, no evidence of contact sensitization was observed following the challenge with the test article. No or minimal dermal reactions (score of 0 to ±) were observed at each test article and vehicle challenge site in both the induced and challenged control animals. Mean dermal scores following challenge were also comparable between the groups.

Conclusions: Based on the results of this study, gel formulations of ——— 1% Clindamycin, 5% Benzoyl Peroxide and Placebo Combination were not considered contact sensitizers in guinea pigs. b(4)

2. Photoirritation Study in Rabbits with ———

SLS study No. 3242.30 (*91 GLA P007 S009*)

Study Dates: 3/16/92 to 3/19/92.

b(4)

Materials Tested: Placebo Gel Combination, 5% Benzoyl Peroxide gel, 1% Clindamycin gel, ——— gel; Oxsoralen Lotion (1% 8-MOP) served as positive controls

Animals: New Zealand albino rabbits; 3/sex/test article; 5 groups.

Procedure: Rabbits received 0.5 ml of each test article or the positive control on two (1 left + 1 right) test sites of intact skin. The treated sites remained under occlusion for 2 hours. The site on the right side of each animal was then uncovered, exposed to UVA light at a dose of 5 Joules/cm for up to 38 minutes and again occluded for the remainder of the 24 hour exposure period. Test sites were scored for dermal irritation for up to 72 hours following initial patch.

Results: Neither the test article nor the vehicle produced a light-mediated dermal irritation. Minimal irritation was produced at the 25 hour scoring for both the UV exposed and non-UV exposed sites for all materials. Oxsoralen lotion was a strong photoirritant.

b(4)

Reviewer comments: Because no positive findings were noted in the clinical photosafety studies with ——— no additional nonclinical photoirritation study is recommended, although this study was conducted only with UVA light.

2.6.7 TOXICOLOGY TABULATED SUMMARY

NA

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Acanya ———Gel (IDP-110 Gel) is a combination product of 1% clindamycin (1.2% clindamycin phosphate) and 2.5% benzoyl peroxide (BPO). Clindamycin is an antibiotic that decreases Propionibacterium acnes (P. acnes) colonization of skin follicles b(4)

and reduces the inflammatory aspect of acne. BPO is an antibacterial agent effective against P. acnes through oxidation. Additionally, BPO reduces non-inflammatory lesions, possibly through induction of keratolysis and desquamation.

One percent clindamycin has been approved for the treatment of acne since September 1981. BPO has been an over-the-counter (OTC) product since the early 1970s. Currently, there are two marketed combination products (1% clindamycin and 5% BPO) as Duac® Topical Gel (Stiefel Laboratories, Inc.) and BenzaClin® Topical Gel (Sanofi-Aventis). The current Sponsor developed a similar combination product containing 1% clindamycin and 5% BPO, described as [redacted] Gel, and submitted an ANDA (65,443) using the already marketed BenzaClin (clindamycin 1% - benzoyl peroxide 5%) Gel as the reference drug. The Sponsor planed to rely on a clinical bridge with BenzaClin and [redacted] and the safety data generated from the [redacted] Gel to support this NDA filing [505(b)(2)] for the Acanya [redacted] Gel (1% clindamycin and 2.5% BPO). However, the formulation for Acanya [redacted] Gel (1/2.5) is different from that for [redacted] Gel, which was tested in all nonclinical studies submitted within this NDA. In addition to the reduced concentration of benzoyl peroxide from 5% to 2.5% and the [redacted] concentration of propylene glycol from [redacted], Acanya [redacted] Gel has Carbomer 980 instead of [redacted] and Carbomer [redacted]

b(4)

Topically applied clindamycin phosphate is absorbed through the skin and hydrolyzed in skin to the more active free base form. Topically applied BPO penetrates the stratum corneum or follicular openings and is converted to benzoic acid in the skin. No significant systemic exposure of clindamycin or benzoic acid was noted after repeated topical application of Clindaben in rats and rabbits. In a 35-day dermal toxicity study, rats were treated topically with up to 2500 mg/kg [redacted] Gel, 1% Clindamycin Gel, or 5% Benzoyl Peroxide Gel twice daily for 35 days. Blood samples were collected at approximately 14 hours after last application. Benzoic acid was not detected in the plasma of any of the treated or placebo group animals (detection limit: 0.2 µg/mL). Clindamycin was not detected in the plasma of the tested or placebo group animals (detection limit: 50 ng/mL).

b(4)

In another 35-day dermal toxicity study, rabbits were treated topically with up to 2500 mg/kg [redacted] Gel, 1% Clindamycin Gel, or 5% Benzoyl Peroxide Gel twice daily for 35 days. Blood samples were collected at 5 hours after the second application of test article on Days 9-10 and 30-31 of the study. Plasma concentrations of endogenous benzoic acid were not affected. Similarly, no clindamycin was detected in plasma (detection limit: 100 ng/mL) of any of the test animals.

b(4)

In both mice and rats, the oral LD_{50}s of [redacted] (1% clindamycin and 5% BPO) were >5000 mg/kg (corresponding to >250 mg/kg BPO and >50 mg/kg clindamycin). The dermal LD_{50} of [redacted] (1% clindamycin and 5% BPO) in rats was >5000 mg/kg.

b(4)

In the 35-day dermal toxicity study in rats, topical treatment with up to 2500 mg/kg [redacted] Gel, 1% Clindamycin Gel, or 5% Benzoyl Peroxide Gel twice daily for 35 days did not produce any signs indicative of systemic toxicity. Local effects at the

occluded application sites consisted of slight to moderate erythema, slight desquamation and edema which occurred in all groups. Histopathologically, minimal to moderate acanthosis, hyperkeratosis and chronic dermatitis were observed; similar findings were occasionally present in untreated skin samples of both control and treated animals.

In the 35-day dermal toxicity study in rabbits, topical treatment with up to 2500 mg/kg ——— Gel, 1% Clindamycin Gel, or 5% Benzoyl Peroxide Gel twice daily for 35 days did not elicit responses indicative of systemic toxicity. Local responses to daily application of all test articles under occlusion were also characterized by slight to moderate erythema, slight desquamation and occasional edema. Microscopy of the application sites revealed minimal to moderate acanthosis and hyperkeratosis and occasional chronic dermatitis. Mild chronic dermatitis was also occasionally found in untreated skin samples of both treated and control animals. b(4)

In the 90-day oral toxicity study, four groups of 12 male and 12 female SD rats received the Placebo Gel at10.0 g/kg/day or the ——— Gel at 1.25, 5.0, or 10.0 g/kg/day orally by gavage for 93 or 94 consecutive days. There were no treatment-related effects on mortality, clinical signs, body weights, food consumption, clinical pathology, ophthalmology, necropsy, or organ weights. Minimal to mild periportal hepatocyte vacuolation was only seen in 5 of 12 males in the 10.0 g/kg/day ——— Gel group. b(4)

Clindamycin phosphate was negative for the induction of structural and numerical chromosome aberrations in the in vitro mammalian chromosome aberration test using human peripheral blood lymphocytes. Although the sponsor submitted a review article on the genotoxicity of clindamycin (Snyder RD and Green JW, A review of the genotoxicity of marketed pharmaceuticals, Mutation Research, 488:151-169, 2001), the information refers to marketed pharmaceuticals. The sponsor further stated that no other literature reports on clindamycin phosphate effects in an Ames test and in vivo micronucleus assay were available. Therefore, the statement, "Clindamycin phosphate was not genotoxic in Salmonella typhimurium or in a rat micronucleus test", should not be included in the label of this drug product. Literature data did support the following statement, "Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in Salmonella typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells," as shown in the labeling of some approved drug products containing benzoyl peroxide.

——————————————————— b(4)

——————————————————— . This study has not been published and it does not appear that the current sponsor has the right to refer to this study. Therefore the statement, "Clindamycin phosphate sulfoxide, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test", which was shown in the labeling of BenzaClin Topical Gel, should not be included in the label of this NDA, since a sufficient clinical bridge has not been established to BenzaClin Topical Gel.

In the two-year 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 ——— 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. There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, and gross pathology examinations. Only females treated with ——— (1/5) Gel or Benzoyl Peroxide 5% Gel showed slight increases in kidney weight. Focal hyperplasia of the pituitary was noted in males in all groups. The incidence of epithelial hyperplasia and hyperkeratosis at the treatment site was markedly increased in all groups treated with ——— Gel or the Benzoyl peroxide 5% Gel. The severity of the epithelial hyperplasia increased progressively with the dose of Benzoyl peroxide. The incidence of epithelial hyperplasia at the treatment site was also increased in the animals receiving 15 mL/kg/day of the Clindamycin Phosphate 1% Gel. 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. The design of this study was not optimal since the volume of administration was increased for the different dose groups. However, the clinical clindamycin concentration and greater benzoyl peroxide concentration of the drug product were evaluated in this study, so the Exec CAC determined that the study was acceptable.

b(4)

b(4)

In the 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 ——— Gel, 0.9 or 3.0 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. There were no toxicologically significant differences in survival, food consumption, hematology, clinical chemistry, necropsy findings, organ weights, non-neoplastic microscopic findings. Rales and hunched posture were seen more frequently in test article-treated animals than in placebo-treated animals. Differences in body weights approached toxicological significance (i.e., decrease of approximately 10%) in males treated with 3.0 mL/kg/day ——— Gel or Clindamycin Phosphate 1% Gel. A trend toward decreased mean body weights (between 5% to 10%) was also noted in females treated with 0.9 or 3.0 mL/kg/day ——— Gel, 0.9 or 3.0 mL/kg/day Benzoyl Peroxide 5% Gel, or 0.9 or 3.0 mL/kg/day Clindamycin Phosphate 1% Gel during the latter part of the study compared to one Placebo Gel group (Group 1). Some commonly observed neoplasms included fibroadenomas, adenomas and adenocarcinomas in the mammary glands of females, and islet cell adenomas of the pancreas and adenomas of the pituitary in males and females. Although there were some statistically significant differences in tumor incidence when the two 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. Therefore, there was no evidence to suggest that oral

b(4)

b(4)

administration of ' ——— Gel, Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel for up to 97 weeks caused an increased incidence of tumors in rats. The design of this study was not optimal since the volume of administration was increased for the different dose groups. However, the clinical clindamycin concentration and greater benzoyl peroxide concentration of the drug product were evaluated in this study, so the Exec CAC determined that the study was acceptable. b(4)

In the 52 week dermal photo-carcinogenicity study (40 weeks of treatment followed by 12 weeks of observation), five groups of 36 male and 36 female hairless mice were treated topically 5 days per week with 0.2 mL Placebo Gel, 0.1 or 0.2 mL ——— Gel, 0.2 mL Benzoyl Peroxide 5% Gel, or Clindamycin Phosphate 1% Gel and irradiated with 120 RBU of solar simulated light (600 RBU/week). Two additional groups were only irradiated with 600 or 1200 RBU/week of solar simulated light as controls. There were no test article-related effects on body weights and clinical observations except the skin reactions. Greater incidences of erythema, flaking, and thickening of the skin were observed in a dose-dependent fashion in mice treated with ——— Gel compared to the Placebo Gel-treated animals receiving 600 RBU/week. Edema was seen in the test article-treated animals, not in the untreated groups receiving 600 RBU/week. Treatment with ' ——— . Gel caused significant decreases in animal survival compared to the Placebo Gel-treated or untreated animals receiving 600 RBU/week. Most of the deaths were because of early sacrifice due to tumor burden. Topical application of ' ——— Gel was associated with apparent enhancement of photocarcinogenesis. The mice in the high UVR group developed skin tumors significantly earlier than the mice in the low UVR groups. The Placebo Gel appeared to cause a slight, not statistically significant enhancement of UV induced skin tumors. The tumor prevalence in mice treated with ——— Gel was increased for all tumor size categories, as compared with mice treated with the Placebo Gel or untreated mice receiving 600 RBU/week of UV irradiation. The time to tumor onset in ' ——— Gel-treated groups was shorter than that in the Placebo Gel group or the untreated group receiving 600 RBU/week. Males tended to be significantly more affected than females. This study was acceptable, because the clinical clindamycin concentration and greater benzoyl peroxide concentration of the drug product were evaluated. A statement warning patients to avoid sun exposure following drug application should be included in the label of this NDA. b(4) b(4) b(4)

The following wording in the labeling of some approved drug products containing benzoyl peroxide, "Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies" and "Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced (squamous cell) skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment", was based on literature data review. These statements should be included in the label of this NDA.

As Dr. Abby Jacobs, Associate Director of Pharmacology/Toxicology pointed out that the missing data for clindamycin (i.e., the Ames test and in vivo micronucleus assay) was not an approvability issue for this NDA, because the sponsor has conducted carcinogenicity studies (oral and dermal) which both were negative. Also, information

will be incorporated into the label describing the genotoxicity of benzoyl peroxide. Since one active moiety of the drug product is presumed to be genotoxic, then it is presumed the entire drug product is genotoxic and the missing genotoxicity data for clindamycin is not as critical.

The following statements in the labeling of some approved drug products containing clindamycin, "Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin revealed no effects on fertility or mating ability" and "Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day revealed no evidence of teratogenicity", was based on literature data review. These statements should be included in the label of this NDA. A statement, "Developmental toxicity studies performed in rats and mice using subcutaneous doses of clindamycin up to 200 mg/kg/day revealed no evidence of teratogenicity", which was also based on literature data, should also included in the label of this drug product. Since the rabbit is peculiarly intolerant to any antibiotic which alters the intestinal flora as a result of activity against gram-positive organisms, the teratologic studies in the mouse were used to support this NDA for a regulatory purpose.

In the skin irritation test, only negligible skin response was observed in rabbits exposed to [redacted] Gel, Benzoyl Peroxide 5% Gel, and Clindamycin 1% Gel for 6 hours under occlusion. In the eye irritation test in rabbits, [redacted] Gel, Cindamycin 1% Gel, and Placebo Gel were considered to be mild irritants, while Benzoyl Peroxide 5% Gel was non-irritating to the rabbit eye. The eye irritation resolved prior to 72 hours in the unrinsed groups and prior to 48 hours in the rinsed groups. [redacted] Gel, Clindamycin 1% Gel, and Benzoyl Peroxide 5% Gel were negative in the dermal sensitization test in guinea pigs. In the photoirritation test, topical treatment with [redacted] Gel, Clindamycin 1% Gel, or Benzoyl Peroxide 5% Gel under occlusion to rabbits for a 24-hour period resulted in only a negligible to slight irritant effect in both UVA and non-UVA exposed test sites. Although this study was conducted only with UVA light, no additional nonclinical photoirritation study is recommended, because no positive findings were noted in the clinical photosafety studies with [redacted]

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[redacted] major degradation products of clindamycin phosphate and benzoyl peroxide: [redacted], has been identified and qualified (up to [redacted], respectively) as per ICH guidelines (see CMC review). [redacted] is an approved antibiotic and available data indicate that it would not be a safety concern in this drug product. As the CMC reviewer pointed out that the amount of [redacted] in this drug product was less than that in an earlier FDA approved NDA for topical dosage form (BenzaClin Topical Gel) which had been marketed for the last 8 years, the sponsor provided data on the mean percentage of these degradation products found in IDP-110 Gel and BenzaClin Topical Gel for baseline and up to 3 months of admixture storage at 25 °C/60% RH (see the Table below). In the carcinogenicity studies, the gel formulation containing 1% clindamycin and 5% benzoyl peroxide was stored under ambient conditions and used for up to 3 months before initiating a new supply. It is expected that the degradation products in the formulation tested in the carcinogenicity

b(4)

studies after up to 3 months of storage would be similar or greater than those found in IDP-110 Gel stored for the same amount of time. In addition, the expiration date of this drug product after mixing clindamycin phosphate with benzoyl peroxide is only 2 months, shorter than the expiration date of BenzaClin Topical Gel (3 months). The concentration of benzoyl peroxide in this drug product (2.5%) is lower than that in the BenzaClin Topical Gel (5%). This drug product will be topically used once daily while the BenzaClin Topical gel was recommended twice daily. Therefore, from the Pharmacology/Toxicology perspective, these major degradation products in this drug product would not be a safety concern at this time point.

Table 1.1.2.1 BenzaClin Topical Gel and IDP-110 Degradation Products

Degradation Product/Metabolite	BenzaClin Topical Gel				IDP-110 Gel			
	T= 0	1 mo	2 mos	3 mos	T=0	1 mo	2 mos	3 mos

b(4)

Conclusions: This NDA is approvable from a Pharmacology/Toxicology perspective.

Unresolved toxicology issues (if any): None

Recommendations: 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^2, 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^2, respectively) revealed no evidence of teratogenicity.

b(4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility