CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-320

PHARMACOLOGY REVIEW(S)

Pharmacology/Toxicology Supervisory Memorandum

NDA number: 22-320
Sequence number/date/type of submission: 000 / February 8, 2007 / original submission
Sponsor and/or agent: Galderma Laboratories
Supervisor name: Barbara Hill
Division name: Division of Dermatology and Dental Products
Date: December 5, 2008
Drug: Epiduo (adapalene 0.1%, benzoyl peroxide 2.5%) gel
Drug class: Adaplene: Synthetic retinoid; Benzoyl peroxide: Keratolytic agent
Indication: Acne vulgaris

Introduction and discussion:

This application was submitted under section 505(b)(2) of the FD&C Act. The nonclinical toxicology data provided to support approval of this application is based on nonclinical toxicology studies conducted by the sponsor, submitted acceptable literature references (which do not refer to a marketed drug product) and a right of reference to nonclinical toxicology studies not conducted by the sponsor. No clinical bridge was generated in this application. Therefore, we did not rely on the Agency's findings of safety for any approved drug product to provide nonclinical toxicology data for approval of Epiduo gel.

Epiduo gel is a fixed dose combination drug product for which the sponsor is seeking approval for the topical treatment of acne vulgaris in patients 12 years and older. The sponsor markets Differin gel, 0.1% and Differin cream, 0.1%, which contain adapalene at the same concentration as Epiduo gel, and Differin gel, 0.3%, which contains adapalene at a greater concentration than Epiduo gel. The sponsor is relying on nonclinical toxicology data from studies the sponsor conducted to support the safety of Differin gel/cream to support the safety of the adapalene moiety in Epiduo gel. A review of these studies was conducted by Dr. Kumar Mainigi. Please refer to his full review for additional details, if needed. Therefore, the sponsor owns all of the nonclinical toxicology data that was used to support the safety of the adapalene moiety in Epiduo gel.

The sponsor also conducted six nonclinical toxicology studies with the combination gel product to provide additional data to support the safety of Epiduo gel. These studies were conducted to serve as a nonclinical bridge to both the adapalene and benzoyl peroxide moieties. The toxicity noted in the nonclinical toxicology studies conducted with the combination gel was not greater that the toxicity associated with either adapalene or benzoyl peroxide alone. Therefore, the conduct of these studies provides an adequate nonclinical bridge. These studies have been reviewed by Dr. Kumar Mainigi and are listed below.

1) Rabbit primary irritation study
2) Guinea pig sensitization study
3) Guinea pig phototoxicity/photoallergenicity study
4) 4 week dermal rat toxicology study

5) 4 week dermal dog toxicology study
6) 13 week dermal minipig toxicology study

The nonclinical toxicology data to support the safety of benzoyl peroxide was derived from literature references and studies that the sponsor has obtained a right of reference for. This information was reviewed by Dr. Kumar Mainigi. The data for the genotoxicity associated with benzoyl peroxide was obtained from literature references and a summary of this information was included in the Epiduo gel label.

The data for the dermal carcinogenicity and photoco-carcinogenicity associated with benzoyl peroxide was based on studies conducted by the Consumer Health Products Association (CHPA). The sponsor included a right of reference letter from CHPA for the data from a dermal carcinogenicity study and a photoco-carcinogenicity study conducted with an aqueous benzoyl peroxide carbomer gel formulation in the NDA submission. These studies were reviewed by Dr. Kumar Mainigi. A summary of the results from these studies are included in the Epiduo gel label. In addition, information from literature references concerning the tumor promotion potential of benzoyl peroxide is included in the Epiduo gel label.

The sponsor submitted literature data that describes reproductive toxicology studies conducted with benzoyl peroxide that were basically negative. However, the validity of these studies is questionable due to the rapid breakdown of benzoyl peroxide to benzoic acid. It is not clear if the fetus would ever be exposed to benzoyl peroxide in a reproductive toxicology study due to the short half life of benzoyl peroxide. Therefore, reproductive toxicology information for benzoyl peroxide alone is not included in the Epiduo gel label. However, adequate reproductive toxicology studies have been conducted with adapalene and this information is incorporated in the label for Epiduo gel. The reproductive toxicology information for adapalene in the label is the determining factor for the pregnancy category designation for Epiduo gel (i.e., Pregnancy Category C) due to the teratogenic effects noted at high adapalene doses. Therefore, there is ultimately no need for including reproductive toxicology information for benzoyl peroxide in the Epiduo label.

Conclusion:

The nonclinical toxicology information included in this NDA submission, which included nonclinical toxicology studies conducted by the sponsor, submitted acceptable literature references (which do not refer to a marketed drug product) and a right of reference to nonclinical toxicology studies not conducted by the sponsor are adequate to support the safety of Epiduo gel, from a pharmacology and toxicology perspective. This NDA submission is a 505(b)(2) submission because the sponsor relied on literature data to provide the necessary genotoxicity data for benzoyl peroxide. No clinical bridge was needed for Epiduo gel to provide nonclinical toxicology data for approval of this drug product. Therefore, we did not rely on the Agency's findings of safety for any drug product to provide nonclinical toxicology data for approval of Epiduo gel.

The nonclinical portions of the label for Epiduo gel incorporate the information from the nonclinical toxicology studies conducted by the sponsor for adapalene and/or the combination gel product, the data from literature references (i.e., genotoxicity information for benzoyl peroxide and tumor promotion potential associated with benzoyl peroxide) and data that the sponsor has obtained a right of reference for (i.e., dermal carcinogenicity and photoco-carcinogenicity studies conducted with an aqueous benzoyl peroxide carbomer gel) as outlined in the review by Dr. Kumar Mainigi.

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/s/

Barbara Hill
12/5/2008 05:16:10 PM
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: 22-320

SERIAL NUMBER: N000

DATE RECEIVED BY CENTER: 02/08/08

PRODUCT: **EPIDUO™** (adapalene 0.1% and benzoyl peroxide 2.5%) **Gel**

INTENDED CLINICAL POPULATION: Subjects above 12 years of age

SPONSOR: Galderma Laboratories, L.P.14501 N. Freeway, Fort Worth, TX 76177

REVIEW DIVISION: Division of Dental and Dermal Drug Products (HFD-540)

PHARM/TOX REVIEWER: Kumar D.Mainigi

PHARM/TOX SUPERVISOR: Barbara Hill

DIVISION DIRECTOR: Susan Walker

PROJECT MANAGER: Maria Walsh

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations:

A. Recommendation on approvability: Approvable
B. Recommendation for nonclinical studies: None
C. Recommendations on labeling: The draft submitted by the sponsor is acceptable with some modification.

II. Summary of non-clinical findings:

A. Brief overview of nonclinical findings:

The non-clinical safety profile of fixed-combination EPIDUO Gel (0.1% adapalene and 2.5% BZPO) has been developed from a large number of studies conducted with adapalene, a number of published benzoyl peroxide (BZPO) studies, and a few bridging studies conducted with the proposed clinical formulation.

The maximum recommended daily human dose (2 grams) of gel will deliver (assuming 100% absorption) 1.22 and 30.71 mg/m^2 of adapalene and BZPO, respectively. The systemic safety of adapalene has been established at $36mg/m^2$ (0.3% gel), and the safety of BZPO has been repeatedly proved at $123.21mg/m^2$ (10% solution). Studies with EPIDUO gel have soundly confirmed the fact that adapalene and BZPO did not synergize, potentiate, or antagonize the local or systemic effects of each other.

BZPO a very fast free-radical generator has never been detected in the tissues or plasma of any species including humans. Because of its extremely short half-life (fraction of a second), as soon as the molecule comes in contact with the skin, it undergoes oxidation to benzoic acid, which is nontoxic (up to 40ppm). Benzoic acid is fast eliminated as conjugate of glycine (hippuric acid). For obvious reasons, the safety profile of the fixed-combination gel is essentially a profile of 0.1% adapalene.

Irrespective of the nature of the formulation and or the drug concentration, the average topical absorption of adapalene in most species including humans did not exceed 5 percent. No significant drug accumulation was observed in the dermal studies of any duration. Adapalene is extensively biodegraded in animals and humans, and the parent drug and metabolites are mainly found in organs (liver, GI-tract) involved in the excretory metabolism.

The topical applications of $36mg$ adapalene$/m^2$/day for 4-26 weeks did not cause any systemic toxicity in rats. The dose-related scab formation and acanthosis disappeared during 8 weeks of recovery period. Dogs treated topically at the same dose level for 26 weeks did not exhibit any bone-related toxicity; and the epidermal hyperplasia and superficial inflammation developed on the application sites were mild and transient in nature.

Both, adapalene and BZPO are non-mutagenic. The former has also been established as non-clastogenic.

No tumors developed in mice at topical doses of 1.2, 3.9, and 12mg adapalene/m^2/day; and in rats at oral doses of 0.15, 0.5, and 1.5mg/kg/day. In rats, a slight increase in benign pheochromocytoma of the adrenal gland was restricted to high-dose males ($p<0.05$). This species-specific incidence was most probably due to disturbed calcium homeostasis. There is no evidence that in man perturbation of calcium homeostasis in any way is linked to adrenal medullary lesions. Second, there are many morphological and biochemical differences between the adrenal glands of rat and man. Third, the incidence of pheochromocytoma in man is very low (0.005 to 0.09%).

In rodent dermal carcinogenicity studies, BZPO at dose levels of 25 and 45mg/animal/day (mouse and rat, respectively) did not cause any significant increase in tumor formation. Also, no increase in UV-induced tumor formation was observed in hairless mice treated with 5% BZPO gel.

In the oral studies (1.5-20mg/kg/day), adapalene did not alter the reproductive performance, fertility, litter size, growth, development, weaning, and subsequent reproductive performance of offspring.

In the dermal teratology studies (6mg adapalene/kg/day) in rats and rabbits, no teratologic changes were observed. However, in oral studies in rats and rabbits (5, 25, and 60mg/kg/day), adapalene caused significant teratologic changes (skeletal and visceral malformations) at 25mg/kg/day.

In the prenatal and postnatal development studies (0.15, 1.5, and 15mg/kg/day), the highest dose of adapalene had no effect on the litter parameters (development after weaning, mating and fertility) of F_0 and F_1 generations, and on F_2 fetuses. Since adapalene was excreted in the milk, it is inferred that the pups were exposed both *in utero* and during lactation.

In an oral reproductive and developmental toxicity study in rats, the following NOELs for BZPO were established: teratogenicity 500, male fertility 500, and female fertility 1,000mg/kg.

In dermal studies with the combination gel, absolutely no systemic toxicity was observed in 4-week rat and dog studies and 13-week mini pig study. All the skin lesions were mild and transient in nature.

No carcinogenicity and reproductive developmental toxicity studies were conducted with the combination gel. Waivers from these studies were granted based on the following facts: 1) The safety profiles of adapalene and BZPO are based on studies conducted at much higher concentrations than present in the combination gel, 2) it was apparent that BZPO did not alter the

pharmacokinetics and pharmacodynamics of adapalene, and 3) new studies would have only duplicated the existing safety data of 0.1% adpalene formulations (gel, solution, and cream).

The combination gel tested as a mild irritant in rabbits, and a strong sensitizer in guinea pigs. These BZPO linked reactions resulted from the maximized conditions (maximum feasible dose under occlusion) used in assays. Accordingly, a high incidence of sensitization is not expected to occur under the recommended (night time application without occlusion) conditions for human use.

B. Pharmacologic activity:

Adapalene in addition to displaying typical retinoid effects (e.g. normalization of the maturation of follicular epithelium) also exhibits some anti-inflammatory properties. However, some pharmacodynamic differences separate adapalene from tretinoin. First, although adapalene binds to specific retinoic acid nuclear receptors (RARα, RARß, and RARγ), the affinity of adapalene for RARα is much lower than tretinoin. 9-*cis*-retinoic acid has been established as a physiologic ligand of tretinoin, not adapalene. Second, unlike tretinoin, adapalene does not bind to cellular retinoid binding protein II (CRAB II). Possibly, due to these differences, the dermal lesions caused by retinoid like biological activity of adapalene are always much less severe and transient in nature.

Animal studies have indicated that adapalene is a potent modulator of cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris. Thus, topical adapalene normalized the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. It also inhibited the lipoxidation of arachidonic acid to inflammatory mediators.

BZPO has been shown to be effective against *Propionibacterium acnes*, the organism involved in the pathogenesis of acne vulgaris and found in sebaceous follicles and comedones. The antibacterial action of BZPO is linked to its potent oxidizing properties; its oxidation to benzoic acid in the skin generates free radicals, reducing the population of *P acnes*. Additionally, BZPO may also act as a keratolytic as well as a keratogenic agent. Its antiacne activity is also believed to derive from its irritant properties. It induces proliferation of epithelial cells, leading to sloughing and repair.

In conclusion, from the non-clinical safety view point, EPIDUO Gel was well tolerated.

B. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY:

Adapalene formulations for the treatment of *acne vulgaris* are sold in several European, African, Latin and North American countries and Australia. Two products, DIFFERIN™ (adapalene solution) Solution 0.1% (NDA 20-338) and DIFFERIN™ (adapalene gel) Gel 0.1% (NDA 20-380) have been marketed in the United States since August 1996. DIFFERIN™ (adapalene) Cream 0.1% (NDA 20-748) and DIFFERIN® XP™ Gel (adapalene 0.3%) (NDA 21-753) were approved in May 2000 and June 2007, respectively.

Non-prescription consumer products (bar, lotion, cream, gel, mask, and cleanser) containing 2.5 to 10% BZPO have long been marketed globally for the treatment of *acne vulgaris;* and for the same indication peroxide at various concentrations has also been used in combination with other drugs (e.g. clindamycin phosphate and erythromycin). It is assumed that adapalene and BZPO used together will be more effective in the treatment of *acne vulgaris,* the adpalene due to its comedolytic activity and BZPO for reducing the population of *Propionibacterium acnes.*

The safety of adapalene and BZPO has been individually evaluated in a large number of non-clinical studies at concentrations greater than present in the proposed formulation. To meet the criteria for a 505 (b) (2) submission, a number of bridging non-clinical studies were also conducted with to be marketed formulation.

NDA number: 22-320
Review number: 01
Sequence number/date/type of submission: N000/02/08/2008/original

Information to sponsor: No
Sponsor and/or agent: Galderma Laboratories, L.P., Fort Worth, TX
Manufacturer for drug substance: Laboratories Galderma SA
Alby-Sur-Cheran, France

Reviewer name: Kumar D. Mainigi

Division name: Dermal and Dental Drug Products
HFD #: 540

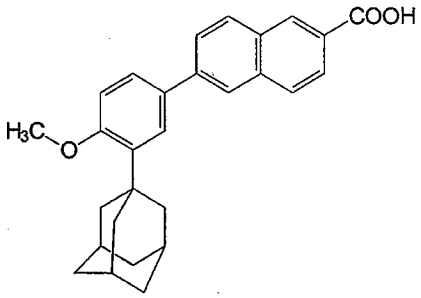
Drug:
Trade name: **EPIDUO** (adapalene 0.1% and benzoyl peroxide 2.5%) **Gel**
Generic name: None
Code names: CD271 (Adapalene) Benzoyl peroxide (BZPO)

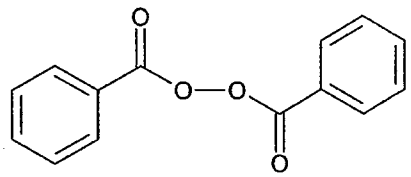
Chemical names:
Adapalene:
1) 2-Naphthalenecarboxylic acid, 6-(4-methoxy-3- tricyclo[3.3.1.1^{3,7}]dec-1-ylphenyl-;
2) 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

Benzoyl peroxide: Dibenzoyl peroxide

CAS registry number: Adapalene: 106685-40-9
Benzoyl peroxide: 94-36-0

Molecular formula/molecular weight: Adapalene: $C_{28}H_{28}O_3$/412.52
Benzoyl peroxide: $C_{14}H_{10}O_4$/242.23





Relevant INDs/NDAs/DMFs:
INDs..
33, 540 (Gel), Dermatological Products of Texas, Inc., Fort Worth, TX b(4)
67, 801 (Gel), Galderma Laboratories, Fort Worth, TX

NDAs 20-338 DIFFERIN^R (adapalene solution) Solution 1% approved 05/31/1996
20-380 DIFFERIN^R (adapalene gel) Gel 0.1%, 05/31/1996
20-748 DIFFERIN^R (adapalene) Cream 0.1%, 05/26/2000
21-753 DIFFERIN^R XPTM (adapalene gel, 0.3%), 06/19/2007
50-741 Clindoxyl Gel (clindamycin phosphate +BZPO) August 26, 2002
50-756 —— Topical Gel (clindamycin phposphate+BZPO), 12/21/02 b(4)

Drug class: Adapalene: Napthoic acid class of anti-acne agent
Benzoyl peroxide: Keratolytic agent

Intended clinical population: Subjects above 12 years of age

Clinical formulation:

Ingredient	Percent (w/w)
Adapalene	0.10
Benzoyl peroxide, USP	2.50
Simulgel 600	—
Docusate sodium, USP	—
Edetate disodium, USP	—
Glycerin,USP	—
Poloxamer 124, NF	—
Propylene glycol, USP	—
Purified water, USP	—

b(4)

Route of administration: Topical

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

[For (b)(2) applications: Applicable

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of [NDA 22-320] are owned by [Galderma Laboratories] or are data for which [Galderma Laboratories] has obtained a written right of reference. Any information or data necessary for approval of [NDA 22-320] that [Galderma Laboratories] does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that [Galderma Laboratories] does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of [NDA number 22-320].

Studies reviewed within this submission: None

Studies not reviewed within this submission:

Most of the studies cross referred in this submission were conducted by the current sponsor under various INDs and NDAs, and related supplements. In addition, for this 505 (b) (2) NDA, the applicant has also relied on the published literature (especially for BZPO) to support the non-clinical safety of the proposed combination drug product.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: Adapalene a synthetic analog of retinoic acid selectively binds to RARβ and –γ nuclear receptors of retinoic acid, however, it does not bind to CRABPII (cellular retinol-binding protein II). In addition to displaying typical retinoid effects (e.g. normalization of the maturation of follicular epithelium), adapalene also exhibits anti-inflammatory properties. Like retinoic acid, adapalene also activates nuclear receptors and inhibits transglutaminase I, an enzyme involved in the terminal differentiation of keratinocytes. The drug also expressed comedolytic activity in Rhino mouse containing a high density of spontaneous comedones.

BZPO has also been shown to be effective against *P acnes*, the organism involved in the pathogenesis of acne vulgaris and found in sebaceous follicles and comedones. The antibacterial action of BZPO is linked to its potent oxidizing properties; its oxidation to benzoic acid in the skin generates free radicals, reducing the population of *P acnes*. Additionally, BZPO may also act as a keratolytic as well as a keratogenic agent. Its antiacne activity is also believed to derive from its irritant properties. It induces proliferation of epithelial cells, leading to sloughing and repair.

2.6.2.2 Primary pharmacodynamics: The biochemical and pharmacological profiles of the napthoic acid class of agents are similar to retinoids and some other anti-inflammatory drugs. Animal studies have indicated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris. Thus, topical adapalene normalized the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. In human keratinocytes, adapalene inhibited the activity of transglutaminase I, a membrane associated enzyme involved in the terminal differentiation of keratinocytes (i.e. formation of stratum corneum). The data of both *in vivo* and *in vitro* studies had revealed that adapalene inhibited the chemotactic (directional) and chemokinetic (random) responses of human polymorphonuclear leukocytes. It also inhibited the lipoxidation of arachidonic acid to inflammatory mediators.

The primary action of BZPO is linked to its oxidizing properties; its oxidation to benzoic acid in the skin generates free radicals. These radicals cause oxidative damage to proteins including bacterial proteins in the sebaceous follicles, thus reducing the population of *P acnes*.

2.6.2.3 Secondary pharmacodynamics: Adapalene in 0.1% gel form was efficient in repairing the signs of UVB-induced photodamage (acanthosis, inflammation, elastosis etc.) on the skin of hairless mice.

At higher concentrations (e g. 20% lotion), the rapid wound healing properties of BZPO has been demonstrated.

2.6.2.4 Safety pharmacology: The gavage doses (10, 30, 100mg/kg) of adapalene did not affect the behavior, physical health, spontaneous locomotor activity, hexobarbital sleeping time, pain response, basal tone of ileum, and gastrointestinal motility in CD-1mice. However, between post-dose hours 2-5 at the mid- and high dose levels, drug caused a moderate transient decrease in body temperature. On the other hand, the same oral doses did not alter the functioning of the cardiovascular, respiratory, and central nervous systems in Beagle dogs, and urine volume and electrolyte excretion in Wistar rats.

Most safety pharmacology studies with BZPO were either conducted in the isolated tissue/organ systems, or using non-dermal routes of administration. In rabbits, 0.1% BZPO exhibited slight effects on atria, thoracic aorta, and slightly suppressed the spontaneous movement of duodenum. In mice, oral BZPO (102mg/kg) caused a slight prolongation of thiopental-sleeping time, induced a slight suppression of motor activity, and a slight reduction in strychinine-induced tonic convulsion. In dogs, at intravenous doses of 1-3mg/kg, BZPO decreased the respiration, heart rate, and blood pressure.

The combination gel (0.125, 0.250, and 0.750mg adapalene/animal) did not alter any cardiovascular functions in the 13-week minipig dermal study.

Abuse liability: Not known

Other: N/A

2.6.2.5 Pharmacodynamic drug interactions: No studies were conducted

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: Irrespective of the nature of the formulation and the drug concentration, the average topical absorption of adapalene in most species including humans did not exceed 5 percent. The systemic absorption in rabbits was greater. The drug and its metabolites were mainly found in tissues and organs (liver, GI-tract) involved in the excretory metabolism. Adapalene did not exhibit any affinity for lipid-rich or melanin-containing tissues or organs (skin, hair, and eyes). In single-dose studies, the drug related radioactivity in amounts of 20-30ppm (of the applied dose) was retained in the adrenal glands (mainly in the cortex) and spleen of rats and

male rabbits, and thymus and ovaries of rats. However, no such accumulation was observed after repeated applications. Adapalene is extensively metabolized in animals and humans; however, its metabolic pathways and metabolites have not been fully characterized.

In rats, the placenta formed a partial barrier to adapalene and its metabolites during organogenesis and thereafter. Adapalene is secreted in the milk.

The topical applications of BZPO result in its rapid conversion to benzoic acid in the skin, and irrespective of the amount of BZPO applied, only benzoic acid is found in the plasma.

2.6.4.2 Methods of Analysis
[see under individual study reviews]

2.6.4.3 Absorption: Following a single topical dose of 0.6mg/kg [^{14}C]-adapalene, the detectable amounts of the parent drug were found in the plasma of mouse, rat, rabbit, and dog (level of detection=0.15ng/mL). The single dose topical mass balance studies with 0.6mg/kg [^{14}C]-adapalene (from 0.1% solution) under occlusion indicated absorption of 2.5 to 8% in hairless nu-ICO rats. However, the repeated daily applications at the same dose level increased the absorption up to 12 percent. Among the species tested (mice, rats, rabbits, and dogs), only in rabbits absorption (up to 14%) was greater than 5 percent. The bioavailability via the dermal route was also greater (4%) in rabbits than rats (2%).

In a 26-week gavage (0.5% aqueous CMC) study in rats, with a T_{max} of 2-3 hours, approximate bioavailabilities at dose levels of 0.15, 1.5, and 15mg/kg/day, were 75%, 17%, and 3%, respectively. In the rat teratology study with 0.1% aqueous topical gel (0.6, 2.0, and 6.0mg adapalene/kg), the bioavailability on day 10 was about 10%. In a single dose oral study in beagle dogs, the systemic bioavailability of 4-5% was achieved.

In 13-week minipig dermal study with the combination gel (125, 250, and 750mg gel/3-19 Cm^2), after the first application, plasma adapalene in all groups was below the detection limit. In week 13, no drug was detected in the low-dose group, it was present in 2/4 mid-dose females and 1/4 males and 2/4 females at the high-dose level. In females, a dose-related increase in the plasma drug level was recorded. The value for AUC in the high-dose females was 2.6-fold greater than at the mid-dose. In females, Tmax increased several fold with an increase in the dose level. Lack of systemic toxicity was attributed to low drug exposure.

Following the oral radioactive doses (0.1 and 1.0mg/kg) of adapalene to pregnant rats, the peak drug levels in the mother and fetus were achieved at 3 and 4 hours, respectively. The amount of radioactivity in the plasma of fetus at 1 hour accounted for 4% of the maternal plasma radioactivity. The

$T_{1/2}$ in the mother was about 14 hours at both dose levels, while in fetus, the values were 29 and 40 hours for the low and high doses, respectively.

No drug was detected in the plasma of women treated topically with 2g of 0.1% adapalene gel per day for 3 months. The absorption studies with human skin preparations or keratinocyte cultures revealed a slightly higher absorption (never exceeding 10%) than in the intact animals of most species.

In excised human skin, ^{14}C-BZPO penetrated through the stratum corneum and follicular openings, and was recovered as benzoic acid on the dermal side (Nacht et al. 1981). It is suggested that BZPO penetrated into the skin layers to be metabolized to benzoic acid, which then enters the systemic circulation.

After about a month of daily topical applications of 10% BZPO in various gels and lotion forms, no drug was detected in the plasma of rabbits; the plasma levels of benzoic acid ranged between 838 to 1656ng/mL at 30 minutes post-application (Sahut et al. 1985).

2.6.4.4 Distribution: In single and multiple-dose plasma kinetic studies in rats, irrespective of the dose (0.12-0.5mg/kg), vehicle (PEG-400/CMC/gel) or route of administration (intravenous, oral, topical) always more drug related radioactivity was found in the plasma of females. In a 21-day rat topical study, a steady-state plasma drug level was achieved in males (0.92ng/mL) and females (1.21ng/mL) at days 8 and 13, respectively.

Following a single topical application of 0.3% adapalene solution in the male rats, at 24 hours post-dose, approximately 7% of the applied dose was present in the skin. Out of it, 3% was present in the *stratum corneum*. It was indicated that radioactivity diffused from the *stratum corneum* to dermis and hypodermis and also to a very little extent (<0.1% of the dose applied) to the subcutaneous tissue. After 7 days, the amount in the skin was reduced to 0.1%. The apparent elimination $T_{1/2}$ ranged between 3 to 4 days. In a similar study in rabbits, the corresponding amounts on days 1 and 7 were 3.5 and 1%, respectively. The maximum amount of radioactivity was found in the *stratum corneum*, which acts as a reservoir for drug release.

In a 28-day topical rat study (0.1mg/animal) with 0.1% adapalene solution, after the last application, approximately 2% of the applied dose was present in the skin. The amount of radioactivity found in the tissues accounted for 0.06-0.08% of the administered dose. The elimination half-lives in the adrenals, ovaries, spleen, and uterus were much longer than plasma.

Seven days after the intravenous dose (male rats, rabbits and dogs), adrenals, liver, bile and spleen contained more radioactivity than the plasma. Each species exhibited a characteristic pattern of distribution, whereas in rat the highest amount of radioactivity was found in the adrenals, in dogs, liver and fat contained the highest amounts. The amount of radioactivity decreased rapidly in all tissues and organs, except for adrenal glands, thymus, and

ovaries of rats and rabbits. A small amount (20-30ppm) of radioactivity was retained in the adrenal cortex for up to 72 hours.

In the whole body autoradiography study in rats, a major accumulation of drug related radioactivity was observed in organs and tissues involved in the excretory metabolism.

In rats, the placenta formed a partial barrier for drug and metabolite related radioactivity after single and repeated dosing during organogenesis and upon single dosing during late pregnancy.

In a human study, 26% of the ^{3}H-adapalene was bound to erythrocytes and the total binding in the blood was more than 99%, mostly to lipoproteins and albumin.

Following topical application of ^{14}C-BZPO (from 10% gel) on the skin of hairless rats, biodisposition was examined at 3, 8, and 24 hours. Most of the applied dose was retained in the horny layer where metabolic conversion to benzoic acid was low. The reservoir effect of the stratum corneum produced slow, sustained diffusion of radioactivity toward the living layers of skin down to the deeper dermis indicating the localized action of BZPO. In the dermis, conversion to benzoic acid increased sharply and the metabolite was taken up by the systemic circulation (Wepierre et al. 1986).

2.6.4.5 **Metabolism:** In humans, adapalene is extensively metabolized in hepatocytes. Similar metabolic profiles were observed in dogs and humans. The data from multiple studies indicated that metabolic conversion probably involved only the methoxybenzene moiety. However, out of 7 fecal metabolites, only one was identified. Adapalene did not interact with cytochrome P450, nor did it exhibit any potential for enzyme induction.

BZPO undergoes a copper-dependent metabolism in the skin to radical and non-radical metabolites. The initial cleavage of the peroxide bond yields short-lived benzoyloxyl free radicals, which can fragment to form phenyl radicals plus CO_2, or can attract hydrogen atoms to form benzoic acid (Swauger et al. 1991).

Percutaneous penetration and metabolism of BZPO were assessed *in vitro* using human skin and in 5 patients with leg ulcers. In the excised skin, BZPO was metabolized to benzoic acid primarily in the dermis. The portion that penetrated the intact skin was benzoic acid only (Morsches and Holzmann, 1982).

2.6.4.6 **Excretion:** After the intravenous administration of [^{14}C]-adapalene, glucuronides, a sulfo-conjugate, and the parent drug represented 63, 17, and 19% of the metabolic pool in the bile of rats. In rat enterohepatic circulation study, 3-6 hours after the intravenous dose of radioactive drug into the duodenum, 75% of the metabolic pool was in free form, and 24% had undergone glucuronidation, but sulfonation was almost negligible. After

reabsorption, the compounds were once again eliminated via the fecal route, indicating the existence of a substantial enterohepatic circulation of adapalene and its metabolites. In rabbit urine, about 5% of the radioactivity following the intravenous dose was found to consist largely of polar compounds (55%).

In four human volunteers, the total amount of ^{14}C-radioactivity found in the feces following a topical application of 0.1% adapalene solution amounted to 0.02-0.06% of the applied dose. No significant amount of radioactivity was found in the urine.

In monkeys, following the topical or intramuscular administration of ^{14}C-BZPO, up to 98% of the radioactivity in the urine was associated with benzoic acid. Since no hippuric acid was found in the urine, it was inferred that in monkey, the renal clearance of BZPO was sufficiently rapid so as to preclude its hepatic conjugation with glycine (Nacht et al. 1981).

2.6.4.7 Pharmacokinetic drug interactions: Not investigated

2.6.4.8 Other Pharmacokinetic Studies: N/A

2.6.4.9 Discussion and Conclusions

Irrespective of the route of administration, female rats absorbed more adpalene. The bioavailability was also greater in females; however, it was much less via the dermal route. At the same concentration level, the dermal absorption in rabbits was almost 3 times more than in rats; however, the bioavailability was only 1.7 times greater. No drug was detected in the plasma of women treated with 2grams of 0.1% adapalene gel per day for 3 months.

In animals as well as humans, the amount of drug absorbed via the dermal route caused no systemic toxicity. The local transient lesions related to retinoid like action of adapalene were not severe in nature.

Irrespective of the nature of formulation and the drug concentration, the topically applied BZPO is rapidly metabolized into benzoic acid, and only benzoic acid is found in the plasma.

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: In an acute dermal study in rats, 2grams/kg of 0.3% adapalene gel did not produce any systemic and or local toxicity. In two separate studies where Iffa credo OF1 mice received gavage (110, 300, and 500mg /kg) and intraperitoneal doses (30, 60, and 80mg/kg) of adapalene for two weeks (10 doses), hypervitaminosis A syndrome characterized by loss of hair, body weight, and spontaneous long bone fractures and skeletal resorption were observed.

The topical applications of 36mg adapalene/m^2/day for 4-26 weeks in rats did not cause any systemic toxicity. The dose-related scab formation and acanthosis disappeared during 8 weeks of recovery period. Dogs treated topically at the same dose level for 26 weeks did not exhibit any bone-related toxicity; and the epidermal hyperplasia and superficial inflammation developed on the application sites were mild and transient in nature.

The incidence of skin irritation (erythema, edema) has been associated with the topical use of BZPO (Mills, 1986). A few isolated cases of allergic contact dermatitis have also been reported. However, some scattered reports about the phototoxic and photoallergic potential of BZPO have been contradictory.

In the 4-week rat dermal study, the daily applications of the proposed formulation produced acanthosis, hyperkeratosis, and sebaceous gland hypertrophy on the application sites. These lesions resemble retinoid like side effects. In a similar dog study, the application sites developed moderate to severe erythema and desquamation. The associated microscopic lesions included minimal to moderate hyperplasia and perivascular mononuclear cell infiltration in the dermis.

The lack of systemic toxicity in 13-week minipig dermal (0.125, 0.250, and 0.750mg adapalene/animal) study with the combination gel, was attributed to a minimal drug absorption. An increase (21-28% at $p<0.05\%$) in absolute liver weights in the high-dose males was linked to an adaptive or compensatory hyperplasia. The low intensity dermal lesions (acanthosis, scabs, hyperkeratosis on the application sites) were similar to that observed in the topical rodent studies conducted with (0.1-0.3%) adapalene alone. Apparently, BZPO did not synergize, potentiate or anatognize the local or systemic toxicity of adapalene. Only adapalene was detected in the plasma.

EPIDUO Gel was evaluated as a mild irritant in the rabbit primary irritation assay. In the guinea pig assay, it was established as a strong sensitizer. However, it did not express any potential for phototoxicity or photoallergenicity.

Genetic toxicology: Adapalene was evaluated as non-mutagenic in gene mutation assays (Ames and mouse lymphoma tests with/without S-9 fraction), and non-clastogenic *in vitro* (Chinese hamster ovary cells with/without S-9 fraction) and *in vivo* (mouse micronucleus assay at 6,000mg/kg) tests. The dose selection in all studies was based on the dose range-finding studies, and all tests were simultaneously validated with positive controls.

Multiple bacteria assays (Ames test) confirmed BZPO as non-mutagenic. However, Matula et al. (1987) attributed these negative results to the difficulty of dissolving BZPO in DMSO at an adequate concentration. When dissolved in acetone, BZPO exhibited weak mutagenic activity in Ames assay. In addition, this molecule has also been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, to cause DNA-protein cross-links in the human cells, and neoplastic transformation in mouse epidermal cells (Saladino et al. 1985; Hartley et al. 1985; Gensler and Bowden, 1983; Gindhart et al. 1985). It was also reported that BZPO induced a dose-dependent increase in the incidence of sister chromatid exchanges in Chinese hamster ovary cells (Jarventaus et al.1984). It must be mentioned that none of these studies were ever repeated to confirm the previous findings.

No genotoxicity studies were conducted with the proposed formulation.

Carcinogenicity: In the topical study, mice received one daily application of 0.03, 0.1, and 0.3% aqueous gel (equivalent to 1.2, 3.9 and 12mg adapalene/m^2/day). Gross pathological examination revealed thickening of the skin. The histopathologic examination indicated acanthosis, hyperkeratosis, scabs, ulcers, diffused subcutaneous inflammation, collagen deposition, atrophy of glandular and follicular structures, and increased superficial follicles in the drug treated skin. Most of these incidences were statistically significant and dose-related. No drug related neoplastic changes were observed.

In the rat dietary study, animals received daily doses of 0.9, 6, or 9 mg adapalene/m^2/day for 104 weeks. Significant drug related non-neoplastic changes observed at 78 week interim sacrifice (chronic toxicity phase) included adrenal medullary hyperplasia in both sexes, and centrilobular hepatocytic vacuolation and extramedullary hemopoiesis in the high-dose females. The high incidences of periacinar hepatocytic fatty vacuolation, chronic inflammation of stomach, tubular mineralization of testes, and transitional cell hyperplasia of urinary bladder were observed in the high-dose males. High dose females also had a higher incidence of uterine dilation.

The absolute and relative adrenal weights were significantly increased. The high-dose males exhibited a significant ($p<0.05$) incidence of benign pheochromocytoma of the adrenals. The combined number of benign and malignant pheochromocytoma, and pancreatic islet tumors in drug-treated males indicated a higher incidence. Reportedly, the high incidence of pheochromocytoma is a characteristic of compounds acting like retinoids.

However, there are many morphological and biochemical differences between the adrenal glands of the rat and man. Second, the incidence of pheochromocytoma in man is very low (0.005 to 0.09%). A high incidence of carcinomas and adenomas of thyroid was observed in the drug treated females.

The status of BZPO as a generator of free radicals is well established. There is also strong evidence to suggest that the free radical generating ability of BZPO is responsible for its tumor promotional effects. These include an increase in dark basal keratinocytes, epidermal hyperplasia, and increased terminal differentiation, and inhibition of intercellular communication in mouse, hamster, and human cells (Slaga et al. 1981; Klein-Szanto and Slaga, 1982; Lawrence et al. 1984; Saladino et al. 1985; Binder and Volpenhein, 1988).

BZPO not only shares most of the tumor-promoting features of well-known tumor promoter TPA (Tetradecanoyl phorbol acetate), but also exhibits several properties of a complete carcinogen not shared by TPA. These include resistance to inhibition by retinoic acid, and induction of a high ratio of carcinomas to papillomas (Klein-Szanto and Slaga, 1982, Slaga et al. 1982, 1983). However, BZPO did not exhibit some critical properties required of a complete carcinogen, such as potential to initiate a growth. A complete carcinogen is an agent capable of initiation, promotion, and progression to cancer (e.g. urethan).

In a 52-week study in mice ($B6C3F_1$ and SENCAR), BZPO was shown to promote tumor formation initiated by dimethylbenzanthracene or methyl-nitro-nitrosoguanidine. At its own, BZPO did not produce tumors in any strain (NTP TR 441, 1996).

In 20-week transgenic (TG. AC) mouse topical assay, BZPO (5 and 10mg in acetone) exhibited tumor promotion activity (Spalding et., 1993).

In the past, most of the topical studies conducted to investigate the carcinogenicity potential of BZPO were conducted with the SENCAR (i.e., sensitive to carcinogens) mice. While promotion was observed in almost all the studies, the potential for carcinogenicity was observed in a select few. However, all of these non-GLP studies were deficient in terms of appropriate period of treatment, proper dose selection, number of animals, data collection, and some even lacked adequate controls.

Finally, on Agency's recommendation, the Consumer Health Products Association (CHPA, formerly the Nonprescription Drug Manufacturers Association/NDMA) conducted topical carcinogenicity studies in rodents with an aqueous carbopol gel formulation of BZPO (FR56 (102):37622, August 7, 1991). No significant increase in tumor formation was observed in rats treated for 104 weeks at BZPO concentrations of 1.67, 5, and 15% (maximum 45mg/rat/day). Similar results were obtained with mice treated at a

concentration of 5%, or with 25% for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide (maximum 25mg/animal/day).

No photocarcinogenicity studies were conducted with adapalene or the combination gel. For the combination gel, a waiver from carcinogenicity and photocarcinogenicity studies was granted. Instead, in the WARNING AND PRECAUTIONS section it is stated that the [b(4)

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The photocarcinogenicity study conducted by CHPA (5% BZPO carbopol gel) failed to detect any increase in UV-induced tumor formation in hairless mice. Irrespective, BZPO enhances the skin's sensitivity to the sun; therefore, some protection from light after its application is always warranted.

After a critical review of animal and human (epidemiologic) data, the International Agency (IARC) on Cancer concluded that BZPO was not classifiable as a human carcinogen.

Reproductive toxicology: In the oral segment 1 study, where F_0 female rats were treated with (1.5, 5, or 20mg adapalene/kg/day) for 15 days prior to pairing and throughout the gestation and lactation periods, no effects on reproductive performance and fertility, F_1 litter size, growth, development to weaning, and subsequent reproductive performance of the offspring, were observed.

In dermal teratology studies with adapalene gel (0.03, 0.1, and 0.3%), the number of ribs in rats and rabbits at the highest dose (6mg/kg/day) level were increased. There were slight increases in the incidence of pre-sacral vertebrae (rabbit), asymmetric pelvis (rat) and small additional fissure in the parietal bone (rat), or more varied anomalies of the interparietal bone (rabbit).

In the rat oral teratogenicity study (5, 25, 60mg/kg/day), based on significant skeletal and visceral malformations both mid and high-doses were established as teratogenic. Only minimal skeletal variations (additional ribs) occurred at the low dose level. This dose was considered to be the NOAEL for teratogenicity.

In segment 3 rat oral study (0.15, 1.5, and 15mg/kg/day), the highest dose of adapalene had no effect on the litter parameters (development after weaning, mating and fertility) of F_0 and F_1 generations, and on F_2 fetuses. Since adapalene was excreted in the milk, it was inferred that the pups were exposed both *in utero* and during lactation.

A single teratology study in white Leghorn chicken eggs indicated that at all dose levels, BZPO increased malformations at a moderate frequency, and except for the lowest dose, there was a dose-related increase in embryonic deaths (Korhonen et al. 1984). In the hamster study, benzoic acid, the major

metabolite of BZPO caused resorptions and malformations. However, no such abnormalities were observed in two rat studies.

In an oral reproductive and developmental toxicity study in rats (0, 250, 500, and 1,000mg BZPO in 5mL corn oil/kg/day), decreased weights of testes and epididymides were associated with microscopic hypotrophy. However, indices such as mating and fertility, number of live births, sex ratio, and birth rat were not affected at any dose level. A single case of spina bifida was recorded at the lowest dose level. In addition, cases of runts (20, 20, 18, and 60) were recorded in all the treatment groups including controls. No other variants were observed. The following NOELs were established: teratogenicity, 500; male fertility 500; and female fertility, 1,000 mg/kg (Song et al. 2003).

No reproductive and developmental toxicity were conducted with the combination gel.

Excipient Simulgel 600 PHA (SEPPIC, France): Among the excipients, some concern has been expressed about the safety of Simulgel 600 (SEPPIC, France). This complex high molecular weight ingredient contains acrylamide/sodium acryloyldimethyltaureate copolymer, the isohexadecane vehicle, and surfactants polysorbate 80 and sorbitan oleate. Simulgel 600 and its individual components are used in cosmetics, often in combination with isohexadecane as a dispersion agent. The vehicle itself has been used in facial cleansers, eye make-up (e.g. mascara), and sun protection creams. The two surfactants have long been used in diversified products for dermal and systemic use. Simulgel 600 has also been used in some dietary supplements (e.g. vitamin E) as a thickener.

Because of very high linear molecular weight (~10 million daltons), Simulgel 600 molecule as a whole is not expected to absorb topically. In addition, acrylamide polymers are known to be chemically inert to the enzyme systems. In Japan, the use of Simulgel 600 in cosmetics is permitted at 5% level (equivalent to 2% acrylamide polymer).

The oral LD_{50} for Simulgel 600 in rats was greater than 2g/kg. In the proposed clinical use, a subject will receive a maximum (assuming 100% absorption) of 1.3mg/kg/day of Simulgel 600.

In the skin irritation assay in rabbits, Simulgel 600 tested as a nonirritant. In four-week dermal studies, both 0.1% adapalene gel and 0.1% adapalene 2.5% BZPO gel produced similar lesions on the application sites of rats (acanthosis, hyperkeratosis, and sebaceous gland hypertrophy) and dogs (minimal to moderate hyperplasia and perivascular monocellular infiltration in the dermis).

In Ames and *in vitro* mouse lymphoma assays, the Simulgel 600 tested non-mutagenic. *In vitro* application of 5% Simulgel to chorioallantoic membrane of

eggs did not cause any vasodilatation or an increase in the number of capillaries, hemorrhage or coagulation.

The main concern for the safety of Simulgel 600 centers on the suspected presence of residual acrylamide monomers in the excipient. The approximate daily intake (ADI) for acrylamide (AA) in direct food contact materials (based on 90-day oral rat study) is 200ng/kg/day (CFSAN 2003). Recently, CFSAN has listed the AA content in some common foods (Reference: The updated exposure assessment for acrylamide, April 13, 2004).

Food	AA conc. (μg/kg)	AA (μg/portion)
Breakfast cereals	131.0	7.3
French fries	333.7	48.8
Potato chips	545.9	16.4
Prune juice	174.0	24.4

The acrylamide is a byproduct of high-temperature cooking processes. Based on the high-dose animal studies, it was evaluated as a potential human carcinogen and genotoxicant. It is also a known human neurotoxin in the industrial environment. The NOEL for neurotoxicity in a 2-year oral rat carcinogenicity study was 0.5mg acrylamide/kg/day, and the lowest effective dose for tumor formation ranged between 1-2mg kg/day. The oral LD_{50} in rats, guinea pigs, and rabbits was 150-203mg/kg, and dermal LD_{50} in rats was 400mg/kg/day.

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OVERALL CONCLUSIONS AND RECOMMENDATIONS

Abstract: A comfortable safety profile for the fixed–combination EPIDUO™ (adapalene 0.1% and benzoyl peroxide 2.5%) Gel has emerged from the merger of individual safety profiles of adapalene and BZPO, and a few bridging studies conducted with the combination gel. Adapalene in 0.3% gel formulation did not cause any systemic toxicity; and 1-10% BZPO as a single moiety or in combination with other consumer chemicals including drugs was found to be safe. In addition, the evaluation of combination gel undoubtedly established that the two active ingredients acted independently without potentiating, synergizing, or antagonizing the local or systemic effect(s) of each other.

Individual safety profiles of adapalene and BZPO: The 100mg/kg of oral adapalene did not alter the behavior, physical health, and spontaneous locomotor activity, hexobarbital sleeping time, pain response, basal tone ileum, and gastrointestinal motility in mice. At the same dose level, functioning of the cardiovascular, respiratory, and central nervous systems in dogs, and urine volume and electrolyte excretion in rats were not altered.

Most safety pharmacology studies with BZPO were either conducted in the isolated tissue/organ systems, or using non-dermal routes of administration. In rabbits, 0.1% BZPO exhibited slight effects on atria, thoracic aorta, and slightly suppressed the spontaneous movement of duodenum. In mice, oral BZPO (102mg/kg) caused a slight prolongation of thiopental-sleeping time, induced a slight suppression of motor activity, and a slight reduction in

strychinine-induced tonic convulsion. In dogs, at intravenous doses of 1-3mg/kg, BZPO decreased the respiration, heart rate, and blood pressure.

The combination gel (0.125, 0.250, and 0.750mg adapalene/animal) did not alter any cardiovascular functions in the 13-week minipig dermal study.

Irrespective of the nature of the formulation and or the drug concentration, the average topical absorption of adapalene in most species including humans did not exceed 5 percent. No significant drug accumulation was observed in the dermal studies of any duration. Adapalene is extensively biodegraded in animals and humans, and the parent drug and metabolites are mainly found in organs (liver, GI-tract) involved in the excretory metabolism. Adapalene did not exhibit any affinity for lipid-rich or melanin containing tissues or organs (skin, hair, and eyes).

The topical applications of 0.3% adapalene gel in rats at the maximum feasible dose of 2mL/kg (36mg adapalene/m^2/day) for 4-26 weeks did not cause any systemic toxicity. The dose-related scab formation and acanthosis disappeared during 8 weeks of recovery period. Dogs treated topically (120mg/m^2/day) for 26 weeks did not exhibit any bone-related systemic toxicity; and the epidermal hyperplasia and superficial inflammation developed on the application sites were transient and mild in nature.

BZPO a very fast free-radical generator has never been detected in the tissues or plasma of any species including humans. In a real sense, such molecules "react but do not interact". Because of its extremely short half-life (fraction of a second), as soon as the molecule comes in contact with the skin, it undergoes oxidation to benzoic acid, which is nontoxic (up to 40ppm). Benzoic acid is fast eliminated as conjugate of glycine (hippuric acid).

No systemic toxicity has ever been reported in subjects treated with BZPO; however, dermal reactions (local irritation, contact allergy) have occurred in 10% of the patients. The percutaneous penetration and metabolism of BZPO was assessed in 5 patients with leg ulcers. The only portion that penetrated through the skin was benzoic acid.

Both, adapalene and BZPO are non-mutagenic. The former has also been established as non-clastogenic. According to one report, BZPO has produced single-strand DNA breaks in human bronchial epithelial cells in culture.

No adapalene related tumors developed in mice at topical doses of 1.3, 3.9, and 12mg/m^2, and in rats at oral doses of 0.15, 0.5, and 1.5mg/kg/day. In rats, a slight increase in the benign pheochromocytoma of the adrenal gland was restricted to the high-dose males. This species-specific incidence was most probably due to disturbed calcium homeostasis. There is no evidence that in human perturbation of calcium homeostasis in any way is linked to adrenal medullary lesions.

In rodent dermal carcinogenicity studies, mice and rats were treated at maximum daily doses of 25 and 45 milligrams, respectively. No tumors developed in either of the species. In another study, BZPO did not exhibit any potential for photo-co-carcinogenicity. It must be mentioned that the sponsor has the right of reference for these publically available study reports. CHPA provided the final reports on 2-year carcinogenicity studies with topically applied benzoyl peroxide gels to Docket No. 81N-0114, "Acne products for OTC Human Use". This is now part of the public record. Accordingly, this information can also be used in the label.

At an oral dose level of 20mg/kg/day, adapalene did not alter the reproductive performance or fertility of F_0 male and female rats. Also, there were no detectable effects on the growth, development, and subsequent reproductive function of F_1 offspring. In rats, adapalene was non-teratogenic at an oral dose level of 5mg/kg/day. No fetotoxicity was observed in rats and rabbits at a topical dose level of 6mg/kg/day.

In an oral reproductive and developmental study in rats (0, 250, 500, and 1,000mg/kg/day), the following NOELs were established: teratogenicity, 500; male fertility, 500; and female fertility, 1,000mg/kg (Song et al. 2003). From the regulatory view point, reproductive and developmental toxicity studies should involve 20-25 animals/dose level. Therefore, this study with only10 rats/sex/dose group is not included in the label.

Safety of combination gel: Six non-clinical studies were conducted with the proposed drug product. In 4-week dermal studies in rats and dogs (adapalene 2mg/kg/day+BZPO 50mg/kg/day), no systemic toxicity was observed, and the observed transient skin lesions were mild to moderate in nature. In rabbits, the product tested as a mild irritant; but it did not exhibit any potential for phototoxicity or photoallergenicity in guinea pigs.

In another guinea pig assay, the drug product tested as a strong sensitizer. In a similar study in healthy human volunteers, the rate of sensitization (~63%) was similar in subjects treated with the combination gel or 2.5% BZPO gel, thus linking the incidence to BZPO. However, it must be mentioned that the maximized conditions used in both assays (maximum feasible dose under occlusion) produced excessive irritation, which in turn lead to increased sensitization. Accordingly, such high incidence is not expected to occur under the intended conditions (night time application without occlusion) of human use.

Absolutely, no systemic toxicity was observed in the 13-week mini pig study at a maximum topical dose level of 2.03mg/m^2/day (58µg/kg/day), indicating minimal drug absorption. The maximum recommended adapalene dose in humans is 1.221 mg/m^2/day (33µg/kg/day). The low intensity dermal lesions

(acanthosis, scabs, hyperkeratosis on the application sites) observed in the minipig study were similar to that recorded in the topical rodent studies conducted with adapalene alone (0.1 and 0.3% gels). Apparently, BZPO did not synergize, potentiate or antagonize the local or systemic toxicity of adpalene.

Waiver from the dermal carcinogenicity and reproductive and developmental toxicity studies were granted. Reasons: 1) A large number of studies have already been conducted at adapalene dose levels ranging from 0.1 to 0.3%, 2) BZPO did not interact to alter the pharmacokinetics or pharmacodynamics of adapalene, and 3) at no dose level, BZPO has ever been detected in the plasma or tissues, or have caused any systemic toxicity in animals or humans, therefore, such studies would have only duplicated the existing safety data for 0.1% adapalene formulations (gel, solution, cream).

Margin of safety: The maximum recommended therapeutic dose of 2 grams gel/day will provide 1.221 and 30.710mg/m^2/day of adapalene and BZPO, respectively. In the13-week minipig dermal study, absolutely no systemic toxicity was observed at adapalene dose level of 2.03mg/m^2/day.

In a 10-day dermal study with 0.3% adpalene gel (6mg/kg/day), $AUC_{(0\text{-}24hr.)}$ values of 204 and 1036 ng.h/mL were achieved in rats and rabbits, respectively. In the 4-week human dermal study with the combination gel, the highest individual AUC value on day 21 was 1.9945ng.h/mL; the highest individual value with 0.1% adapalene gel was 2.648 ng. h/mL. The data also indicated that the topical absorption of adapalene from the combination gel is reduced. Irrespective, the margin of safety for adapalene in the fixed-combination is at least 102 times (204/1.9945).

Any safety calculation for BZPO is purely theoretical, because the molecule is not absorbed intact via any route. Irrespective, assuming 100% oxidation of BZPO, 0.83mg/kg of benzoic acid from the clinical dose will be 48 times lower than its established nontoxic dose of 40ppm.

Adapalene like other retinoids could induce teratogenicity at sufficiently high systemic doses (oral doses from 25mg/kg/day). A dermal NOAEL of 36 and 72mg/m^2/day was established in rat and rabbit embryo-toxicity studies, respectively. This dose is 29-59 times greater than the maximum recommended dose. Furthermore, during a decade of extensive global use of 0.1% adapalene preparations, not a single case of teratogenicity in humans has been reported.

Adapalene was established as non-genotoxic in a battery of *in vitro* and *in vivo* assays. The drug also tested non-carcinogenic in mice dermal study. The mechanism involved in the formation of benign pheochromocytomas of adrenal glands in the rat oral carcinogenicity study is species specific, and is not operational in humans.

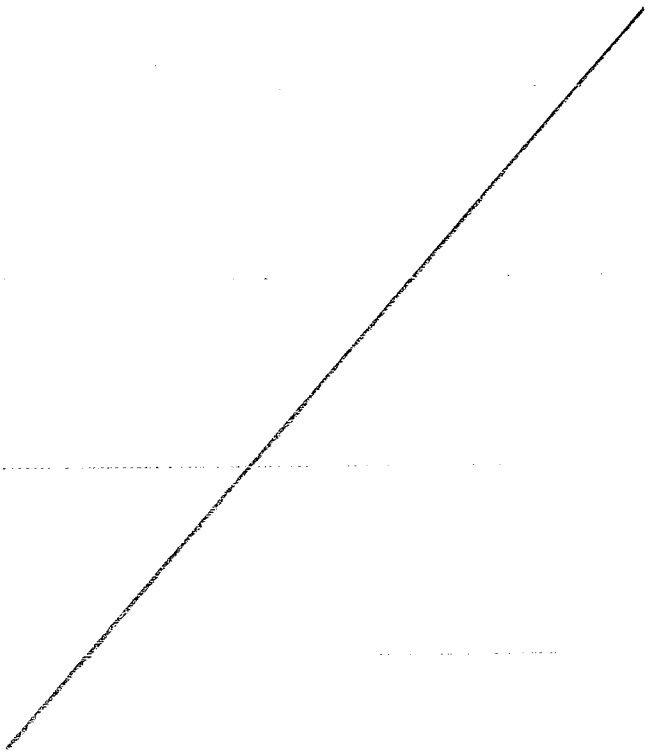
The specification for acrylamide (AA) in Simulgel 600 is ——. A therapeutic dose will provide 400ng AA/subject, or 6.7ng/kg/day. Assuming 100% systemic absorption, this dose is 30 times lower than the ADI for AA, and 74627 times lower than the NOEL for neurotoxicity, and almost negligible to produce any tumors. b(4)

The dermal lesions (dry skin, contact dermatitis, application site burning and irritation etc.) reported in the clinical trials (n=1036) were not of severe or life-threatening nature.

Unresolved toxicology issues (if any): None

Recommendations: The non-clinical safety of the combination gel is well established, therefore, I have no objection to the approval of this New Drug Application.

Suggested labeling:



b(4)

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

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