CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	**207-917**
Supporting document/s:	SDN-1
Applicant's letter date:	09-17-2014
CDER stamp date:	09-17-2014
Product:	**Epiduo Forte** (adapalene and benzoyl peroxide) **Gel**, 0.3%/2.5%
Indication:	Topical treatment of acne vulgaris (b) (4)
Applicant:	Galderma R&D LLC., Cranbury, NJ
Review Division:	Dermatology and Dental Drug Products
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1 Executive Summary

1.1 INTRODUCTION

Adapalene (Differin^R) with retinoid like mechanistic activity has been globally marketed approximately for three decades in several 0.1% formulations (solution, cream, lotion, and solution) for the treatment of acne vulgaris. There is also a Differin gel, 0.3% formulation that is marketed for the treatment of acne vulgaris. Adaplene's anti-acne action is based on its comedolytic and anti-inflammatory activities.

Non-prescription benzoyl peroxide (BZPO) preparations (2.5 to 10%) have also been long marketed for the treatment of acne vulgaris. BZPO's anti-acne activity involves reduction of population of *Proppionibacterium acnes*.

As in case of approved Epiduo gel (adapalene 0.1%/BZPO 2.5%), the sponsor anticipated that the combination product Epiduo Forte gel (adapalene 0.3%/BZPO 2.5%) may be more effective to treat acne. Thus, the new gel formulation is essentially an extension of the old formulation with triple the concentration of adapalene.

The sponsor owns the nonclinical data to support the safety of adapalene and primarily references the nonclinical data in NDA 22320 for Epiduo gel and NDA 21753 for Differin gel, 0.3%. The sponsor is relying on published literature to provide some of the nonclinical data to support the safety of benzoyl peroxide. Therefore, this NDA is a 505(b)(2) NDA from a Pharmacology/Toxicology perspective because the sponsor is relying in part on published literature to provide pivotal nonclinical data to support Epiduo Forte gel.

1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS

The non-clinical safety profile of fixed-combination Epiduo Forte Gel has been developed from a large number of studies conducted with adapalene up to 0.75% concentration level, a number of published benzoyl peroxide (BZPO) studies, and a few bridging non-clinical and clinical studies conducted with the proposed clinical formulation.

The maximum recommended daily human dose (2 grams) of gel will deliver (assuming 100% absorption) 3.7 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).

BZPO a very fast free-radical generator has never been detected in the tissues or plasma of any species including humans. For obvious reasons, the safety profile of the fixed-combination gel is essentially a safety profile of 0.3% adapalene.

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

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not exhibit any bone-related toxicity; and the epidermal hyperplasia and superficial inflammation developed on the application sites were mild and transient in nature.

In 13-week minipig dermal study with Epiduo Forte Gel (0.25mL/kg/day; equivalent to 0.75mg adapalene/kg/day), skin reactions on the application sites included slight to severe erythema and desquamation. Observed lesions were correlated with the histological findings. There were no treatment-related systemic effects, and only 3/8 animals had quantifiable plasma concentration of adapalene with a maximal concentration reaching 1.34ng/mL.

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

No tumors developed in mice at the highest topical dose of 12mg adapalene/m^2/day; and in rats at oral dose of 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.

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 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 at 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.

Epiduo Forte gel tested as a moderate dermal 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.

In bovine corneal opacity and permeability test, Epiduo Forte gel did not express any ocular irritancy or opacity.

1.3 RECOMMENDATIONS

1.3.1 Approvability

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Approvable provided the sponsor accepts the recommended changes in the labeling.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the EPIDUO FORTE gel label reproduced below. Modifications recommended for the nonclinical portions of the label are consistent with the wording contained in the EPIDUO gel label except that the multiples of human exposure for adapalene are modified since the concentration of adapalene is three times higher in EPIDUO FORTE gel.

----------INDICATIONS AND USAGE----------

EPIDUO FORTE [redacted] (b) (4) is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris [redacted] (b) (4)

8.1 Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with EPIDUO FORTE gel. Animal reproduction studies have not been conducted with the combination gel. Furthermore, such studies are not always predictive of human response; therefore, EPIDUO FORTE gel should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day up to 8 times (mg/m^2/day) the maximum recommended human dose (MRHD) of 2 grams EPIDUO FORTE gel. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥ 25 mg adapalene/kg/day representing 41 and [redacted] (b) (4) times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day ([redacted] (b) (4) -19.5 times MRHD) exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, photocarcinogenicity, genotoxicity, or fertility studies were conducted with EPIDUO FORTE gel.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, 12 mg/m^2/day) and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m^2/day). In terms of body surface area, the highest dose

levels are (b) (4) (mice) and (b) (4) (rats) the MRHD of 2 grams of EPIDUO FORTE gel. In rat study, an increased incidence of benign and malignant ph(b) (4)eochromocytomas reported in the adrenal medulla of male rats was observed.

No significant increase in tumor formation was observed in rodents topically treated with 15-25% benzoyl peroxide carbopol gel (6-10 times the concentration of benzoyl peroxide in EPIDUO FORTE gel) for two years. Rats received maximum daily applications of 138 (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area these levels are 27-40 time the MRHD. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for rest of the 2 year study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. The significance of this finding in humans is unknown.

In a photocarcinogenicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV-induced tumor formation was observed in hairless mice topically treated for 40 weeks.

No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects *in vitro* (Ames test, Chinese hamster ovary cell assay, or mouse lymphoma TK assay) or *in vivo* (mouse micronucleus test).

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results; mutagenic potential was observed in a few but not in a majority of investigations. It has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, caused DNA-protein cross-links in the human cells, and also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells.

In rat oral studies, 20 mg adapalene/kg/day did not affect the reproductive performance and fertility of F_0 males and females, or the growth, development and reproductive function of F_1 offspring.

No fertility studies were conducted with benzoyl peroxide.

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2 Drug Information

2.1 DRUG

CAS Registry Number (Optional): Adapalene: 106685-40-9
Benzoyl peroxide: 94-36-0

Generic Name: None

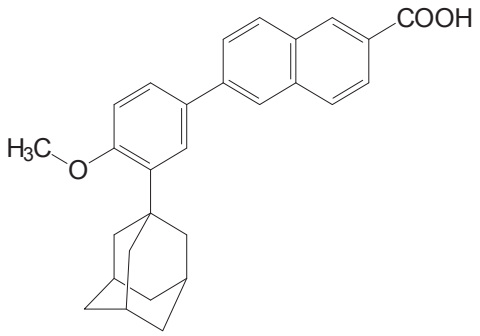
Code Name: CD271 (adapalene) BZPO (Benzoyl peroxide)

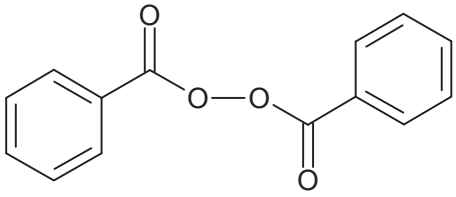
Chemical Name:1) 2-Naphthalenecarboxylic acid, 6-(4-methoxy-3- tricyclo[3.3.1.1^{3,7}]dec-1-ylphenyl-;
2) 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid

Benzoyl peroxide: Dibenzoyl peroxide

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

Structure or Biochemical Description





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

2.2 RELEVANT INDS, NDAS, BLAS AND DMFS

INDs (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%, approved 05/31/1996
20-748 DIFFERIN^R (adapalene) Cream 0.1%, approved 05/26/2000
21-753 DIFFERIN^R XPTM (adapalene gel, 0.3%), approved 06/19/2007
50-741 Clindoxyl Gel (clindamycin phosphate +BZPO), approved August 26, 2002

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50-756 Clinoxin Topical Gel (clindamycin phosphate+BZPO), approved 12/21/02
22-320 Epiduo[R] Gel (adapalene+BZPO), approved 12/8/2008

2.3 DRUG FORMULATION

The quantitative composition for EPIDUO FORTE gel is provided in the following table.

Ingredients	(%w/w)	Function
Adapalene	0.3	Active agent
Benzoyl peroxide	2.50	Active agent
(b) (4)	(b) (4)	
Docusate disodium		
Editate disodium		
Glycerin		
Poloxamer 124		
Propylene glycol		
Purified water		

2.4 COMMENTS ON NOVEL EXCIPIENTS

None

2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN

None

2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN

(b) (4) and older

2.7 REGULATORY BACKGROUND

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[R] XP™ Gel (adapalene 0.3%) (NDA 21-753) were approved in May 2000 and June 2007, respectively. EPIDUO GEL was approved in June 2008.

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).

3 Studies Submitted

3.1 STUDIES REVIEWED

In vitro absorption through dermatomed human skin

Reference ID: 3753870

13-week dermal toxicity study in minipigs

Primary cutaneous irritation test in rabbit

Bovine corneal opacity and permeability test

Buehler test for sensitization

3.2 STUDIES NOT REVIEWED

Not applicable

3.3 PREVIOUS REVIEWS REFERENCED

All primary IND and NDA reviews for adapalene and BZPO combinations, especially review of Epiduo Gel.

4 Pharmacology

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.

4.1 PRIMARY PHARMACOLOGY

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

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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*.

4.2 SECONDARY PHARMACOLOGY

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.

4.3 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.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

***In vitro* interaction study between CD0271 (adapalene) and CD1579 (benzoyl peroxide) during percutaneous absorption in human skin** (RDS.03.SPR.31119; 07-25-2013)

Facility: (b) (4)

<u>Materials and Methods</u>

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Test system: Human skin samples obtained during abdominal surgery from four donors. Residual fat was removed from the skin prior to mounting on the diffusion cells

Receptor fluid: PBS buffer 0.01M pH 7+0.25% Tween 80

The test sample (10mg/cm^2) was applied on the skin, and each formulation was tested in triplicate from 4 different donors. The receptor fluid was collected as a 0-24 hour single fraction under static conditions. Concentrations of adapalene and BZPO were determined from the skin surface washing, epidermis (including the stratum corneum), dermis, as well as rinse of receptor compartments. Adapalene was determined using HPLC method with fluorescence detector (1ng/mL), and BZPO was determined as benzoic acid using HPLC method with UV detection (25ng/mL).

Results and conclusions: Irrespective of the formulation, adapalene was mainly distributed in the epidermis/stratum corneum. The amount found in the dermis was relatively small, and the concentration in the receptor fluid was below the limit of quantification (table1)

For BZPO, a high variability (CV 33 to 94%) for skin penetration was observed between the donors. The peroxide was mainly distributed in the epidermis/stratum corneum, and a small amount was found in the receptor fluid (table2).

Table1. Percent (of applied amount) distribution (*ex vivo*) of adapalene in skin compartments

	Adapalene 0.3% +BZPO2.5%Gel	Adapalene 0.3% Gel	Adapalene 0.3% BZPO 0%Gel
Epidermis (including *stratum corneum*)	6.72	9.04	3.43
Dermis	0.45	2.38	0.43
Receptor fluid	0.03	0.01	BLQ
Total absorbed	7.20	11.42	3.86

Table2. Percent (of applied amount) distribution (*ex vivo*) of BZPO in skin compartments

	Adapalene 0.3% +BZPO 2.5%Gel	Cutacnyl Gel* 2.5%	Adapalene 0% BZPO 2.5% Gel
Epidermis (including *stratum corneum*)	3.98	5.93	1.02
Dermis	0.26	0.51	0.22
Receptor fluid	2.16	2.16	3.20
Total absorbed	6.39	8.60	4.44

BLQ: Below the limit of quantification
*BZPO gel from Galderma

5.2 TOXICOKINETICS

(If not included in toxicity studies)

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6 General Toxicology

6.1 SINGLE-DOSE TOXICITY

Not required

6.2 REPEAT-DOSE TOXICITY

Study title: Sub chronic GLP compliant (CD0271.3%-CD1579 2.5% Gel): 13-week dermal toxicity study in the Gottingen minipig

Study no.:	RDS.03.SPR.8775
Study report location:	SDN-1
Conducting laboratory and location:	Galderma Research & Development Les Templiers, Biot France
Date of study initiation:	05-21-2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Adapalene purity 101%

Key Study Findings

In 13-week minipig dermal study with Epiduo Forte Gel (0.25mL/kg/day, equivalent to 0.75mg adapalene /kg/ day), skin reactions on the application sites included slight to severe erythema and desquamation. Observed lesions were correlated with the histological findings. There were no treatment-related systemic effects, and only 3/8 animals had quantifiable plasma concentration of adapalene with a maximal concentration reaching 1.34ng/mL.

Methods

Doses:	Adapaene 0.3% and BZPO 2.5% gel
Frequency of dosing:	Daily
Route of administration:	Topical
Dose volume:	0.25mL/kg/day
Formulation/Vehicle:	Placebo gel, clinical formulation
Species/Strain:	Minipig/Gottingen
Number/Sex/Group:	4
Age:	4-5 months
Weight:	6.8-8.9kg
Satellite groups:	None
Unique study design:	Nothing significant
Deviation from study protocol:	Nothing significant

Each test formulation was equally applied over two sites on each flank in order to achieve a treated area of approximately 10% of the total body surface. Treated sites were semi occluded during 6 hours of exposure (or 24 hours on non-working days).

Observations and Results

Mortality

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Animals were examined daily for toxicity, tolerance, morbidity and mortality.

No deaths occurred during the treatment period.

Clinical Signs

Drug treatment caused slight to severe desquamation on the application sites. Other lesions such as abnormal yellow color, scratches, or crusts/scrubs were found in treated and placbo groups were attributed to the vehicle.

Body Weights

Body weights were determined pre-dose and weekly thereafter.
There were no treatment-related changes in body weights or gain in body weight.

Feed Consumption

Food consumption was visually determined each day.

There was no inter-group difference in food consumption.

Ophthalmoscopy

Ophthalmic examinations were conducted pre-dose and on day 84.

Testing did not reveal any changes in visual functions. Bilateral ocular lesion such as blepharitis (slight eyelids inflammation) on day 84 in control female and one treated male was considered to be within the normal ocular occurrence in Gottingen minipigs.

EKG

EKGs were recorded pre-dose and day 86 using standard leads I, II, and III. Following cardiovascular parameters were determined: heart rhythm, heart rate, PR and QT, and ST intervals and QRS-complex duration.

There were no significant drug effects on heart rate, waves, amplitude, PR and ST segments, QT/QTc intervals or on QRS-complex duration.

Hematology/coagulation/Clinical Chemistry

Blood samples for clinical pathology were drawn from all animals after the first and last application at 1, 3, 6, and 24 hours.

The spectrum of evaluated parameters did not reveal any drug–related changes.

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Urinalysis

Urine samples were collected at the end of treatment period.

None of the six urinary parameters revealed any consistent drug-related change.

Gross Pathology

Terminal necropsy involved macro- and microscopic examinations of approximately 57 tissues/organs.

Only remarkable treatment-related effects restricted to application sites included very slight to severe erythema, and slight to severe desquamation. Very slight erythema was also observed on application sites treated with the vehicle.

Organ Weights

Fifteen major organs were weighed to determine the absolute and relative organ weights.

Drug treatment did not induce any change in organ weights.

Histopathology

Adequate Battery
Yes
Peer Review
Yes

Histological Findings: Microscopic findings associated with the topical lesions on the application sites included acanthosis, parakeratosis, and/or hyperkeratosis, exocytosis/spongiosis and minimal dermal inflammatory infiltrates.

Special Evaluation

None

Toxicokinetics

Blood samples collected on days 1 and 91 were analyzed for adapalene plasma concentration using a validated HPLC validated method with 0.25ng/mL as limit of quantification.

Only two females and one male (3/8 animals) had a quantifiable amount of adapalene with maximal concentration reaching 1.34ng/mL. With very slow systemic absorption, Cmax was achieved between 3 and 24 hours post-application.

Dosing Solution Analysis

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Target concentration for dosage form was achieved, and it remained stable during the dosing period.

7 Genetic Toxicology

No genotoxicity studies were conducted with Epiduo Forte Gel

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.

8 Carcinogenicity

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.

9 Reproductive and Developmental Toxicology

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.

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10 Special Toxicology Studies

CD0271 0.3%/CD1579 2.5% gel-Primary cutaneous irritation test in the rabbit

Study #: RDS.03.SRE.12941
Facility: [redacted] (b) (4)
Study initiation date: 06-10-2013

Materials and Methods

Animals: Male NZW rabbits (n=3); age 3 months; weight 3-3.1kg

Epiduo Forte (right flank) and its placebo gel (left flank) were applied to the application sites under semi-occluded conditions for approximately 24 hours. Skin was examined at 24, 48, and 72 hours post-application for dermal reactions. An index of Primary Cutaneous Irritation (PCI) was calculated for 24 and 72 hour scoring for erythema and edema.

Results and conclusions: Clearly visible erythema and slight edema were observed in all rabbits up to 72 hours. These lesions persisted until day 4. PCI was 2.33, and the test substance was established as a moderate dermal irritant.

CD0271 0.3%/CD1579 2.5% gel and its placebo: Evaluation of the ocular irritancy potential using the isolated bovine corneal opacity and permeability test (BCOP Test)

Study #: RDS.03. SRE. 12942
Study initiation date: 06-18-2013
Facility: [redacted] (b) (4)

Materials and Methods

Test substances: Epiduo Forte and placebo gels
Test system: Corneas isolated from fresh bovine eyes obtained from the slaughterhouse
Negative control: Physiological saline
Positive control: 10% (w/w) Benzalkonium chloride in saline
Medium of incubation: Eagle's Minimum Essential Medium

Test gels were applied on the epithelium of cornea for 10 minutes. After exposure, thoroughly rinsed cornea was incubated in the fresh medium, followed by opacity measurement; permeability of corneas was determined after 90 minutes incubation with sodium fluorescein.

The opacitonometer determined the difference in light transmission between each control and treated cornea in an air filled chamber.

The mean opacity and the mean permeability values (OD_{490}) were used to calculate the in v*itro* irritancy score.

Results and conclusions: The mean *in vitro* irritancy score for the positive control was 136. The corresponding values for Epiduo Forte and placebo gels were -0.9 and 0.1, respectively. It was inferred that none of the test gels were severe irritants and or corrosive.

CD0271 0.3%/CD1579 2.5% gel: Evaluation of the sensitizing potential in the guinea pig (modified Buehler test-9 induction applications).

Facility: (b) (4)
Study: RDS.03.SPR.12943
Study initiation date: 06-17-2013

Materials and Methods

Test substances: Epiduo Forte and placebo gels
Negative control: Water for injection
Positive control: Dinitrochlorobenzene (DNCB) in propylene glycol
Test system: Young adult Hartley guinea pigs (Crl:HA); males 349-376g, females 338-468g
Animals/sex/group: Water for injection 5; rest of the groups 10

Study design

Group	Induction phase	Challenge phase	
	Anterior left/right flank	Posterior right flank	Posterior left flank
1	water for injection	Epiduo Forte gel	water for injection
2	Gel placebo	Gel placebo	water for injection
3	Epiduo Forte gel	Epiduo Forte gel	water for injection
4	DNCB	DNCB	Propylene glycol

The study was conducted in three phases:

-Induction phase (days 0-18): Animals received nine occlusive topical applications (0.5mL) of the group test material.
-Rest phase (days 1927): no applications
-Challenge phase (day 28): a single application of 0.5mL of the group test material

Cutaneous reactions were scored at 24, 48, and 72 hours after the challenge application.

Results and conclusions: In group 3 at 24 hour, slight erythema observed in 3/10 females increased to 6/10 males and 5/10 females at 48 hour, and at 72 hours to 8/10 males and 7/females, with time severity of lesion was increased. No erythema was observed on the contralateral control flank, and placebo groups. It was concluded that Epiduo Forte gel exhibited strong sensitizing potential.

11 Integrated Summary and Safety Evaluation

The non-clinical safety profile of Epiduo Forte Gel is based on a large number of non-clinical studies conducted under various INDs with up to 0.75% concentration level of adapalene, a

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number of published benzoyl peroxide (BZPO) studies, and 5 bridging non-clinical and 18 bridging clinical studies of 24 hours to 12 months duration (n=5322) conducted with the proposed clinical formulation.

The maximum recommended daily human dose (2 grams) of gel will deliver (assuming 100% absorption) 3.7 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).

BZPO a very fast free-radical generator has never been detected in the tissues or plasma of any species including humans. For obvious reasons, the safety profile of the fixed-combination gel is essentially a safety profile of 0.3% adapalene.

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.

In 13-week minipig dermal study with Epiduo Forte Gel (0.25mL/kg/day; equivalent to 0.75mg adapalene/kg/day), skin reactions on the application sites included slight to severe erythema and desquamation. Observed lesions were correlated with the histological findings. There were no treatment-related systemic effects, and only 3/8 animals had quantifiable plasma concentration of adapalene with a maximal concentration reaching 1.34ng/mL.

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

No tumors developed in mice at the highest topical dose of 12mg adapalene/m^2/day; and in rats at oral dose of 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.

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 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 at 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.

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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.

Epiduo Forte gel tested as a moderate dermal 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.

In bovine corneal opacity and permeability test, Epiduo Forte gel did not express any ocular irritancy or opacity.

12 Appendix/Attachments

Reference ID: 3753870

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/s/

DAIVENDER K MAINIGI
05/13/2015

BARBARA A HILL
05/13/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207917 **Applicant: Galderma** **Stamp Date: 09-17-2014**

Drug Name: Adapalene/BZPO Gel,0.3%/2.5% **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for filing:

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

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?		N/A	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes_____

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

N/A

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

None

Kumar D. Mainigi, MSc, Ph.D., M.P.H., DABT
Reviewing Pharmacologist — October 28, 2014
Date

Barbara Hill, Ph.D — see sign off date
Team Leader/Supervisor — Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

DAIVENDER K MAINIGI
11/03/2014

BARBARA A HILL
11/03/2014