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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 20380 SUPPL-10
Supporting Documents:	SDN #0008
Applicant's letter date:	09/10/2015
CDER stamp date:	09/10/2015
Product:	Differin® (adapalene) Gel, 0.1%
Indication:	For treatment of acne
Applicant:	Galderma Laboratories, L.P.
Review Division:	Division of Nonprescription Drug Products
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1 Executive Summary

1.1 Introduction

This supplemental New Drug Application (sNDA) is an efficacy supplement. It was submitted by Galderma Laboratories, L.P. intended for switch of its dermal product, 0.1% Differin® (adapalene) Gel, from prescription (Rx) to over-the-counter (OTC). The proposed OTC indication is for treatment of acne in patients 12 years of age and older. The proposed OTC dosing regimen is once daily and is the same as the approved Rx product.

Adapalene is the active ingredient in 0.1% Differin® gel. It exhibits biological activities similar to retinoids. If approved, 0.1% Differin® gel would be the first-in-class retinoid OTC drug product in US. It was first approved by the FDA as a prescription treatment for acne vulgaris in May 1996. It is currently available Rx under several pharmaceutical forms including gel, cream, solution and lotion and a higher strength of 0.3% gel. Most recently in July of 2015, FDA approved Epiduo Forte Gel with 0.3% adapalene and 2.5% Benzoyl Peroxide (BZPO) for marketing in the US.

In support of the OTC switch, the applicant conducted five clinical studies as shown below:

Two of the five clinical studies are with subject exposure to study drug.

1. Maximal use pharmacokinetics (PK) trial (MUsT) in adolescent and adult patients with moderate to severe acne to assess application of 0.1% Differin® gel to larger body surface areas (BSAs) and in greater quantities than those assessed in previous PK studies.
2. Pivotal actual use study for 0.1% Differin® gel, an open-label, single-arm, multicenter, 6-week actual use study, to understand how 0.1% Differin® gel would be used in an unsupervised OTC environment.

Three clinical studies are with no subject exposure to study drug.

3. Prescription standard of care (Rx-SOC) study to assess prescribing physician and acne patient behavior regarding retinoids in the prescription environment.
4. Pivotal targeted self-selection study in pregnant and/or breastfeeding women for 0.1% Differin® gel to evaluate the ability of pregnant and/or lactating women with self-assessed acne to read and understand labeling instructions regarding use during pregnancy/lactation.
5. Pivotal label comprehension study in a general population of subjects to test key Drug Facts Label (DFL) instructions and warnings in the general population section.

1.2 Brief Discussion of Nonclinical Findings

Comprehensive nonclinical characterization of the pharmacological and toxicological effects of adapalene was conducted during the development of marketed adapalene products. These studies have been reviewed by the FDA under relevant applications. There are no additional nonclinical studies conducted or submitted in support of the Rx-to-OTC switch. A summary of the available pharmacology and toxicology information on adapalene was submitted in this sNDA.

One major concern regarding the Rx-to-OTC switch of the adapalene product is the teratogenicity associated with the retinoid class of drugs. In previously-conducted embryo-fetal development studies, adapalene has been shown to induce teratogenic effects in animals at sufficiently high systemic doses. In the present nonclinical review, the margin of exposure for adapalene-associated teratogenicity was calculated, particularly based on the results from the newly conducted human maximum use PK study. The margin of exposure is estimated to be at least 70-fold.

There are no drug-related findings in rats at the highest doses tested in either the fertility and reproduction development studies or the prenatal and postnatal development studies. However, adapalene was observed in the breast milk in treated lactating rats.

1.3 Recommendations

1.3.1 Approvability

Based on the agency's previous review of the nonclinical information on the Rx adapalene products, the human use experience of adapalene, and the calculated margin of exposure for adapalene-associated teratogenicity, there is no impediment to approval from a Pharmacology/Toxicology perspective. However, the level of exposure required to cause teratogenicity in humans is unclear and animal studies do not always predict human effects.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

Because of the findings of adapalene-induced teratogenicity in animals and the presence of adapalene in breast milk in treated animals, it is recommended to keep the statement: "If pregnant or breast-feeding, ask a [redacted] (b) (4) before use" on OTC drug facts for the proposed product.

2 Drug Information

2.1 Drug

CAS Registry Numbers:
106685-40-9

Generic Names:
Adapalene

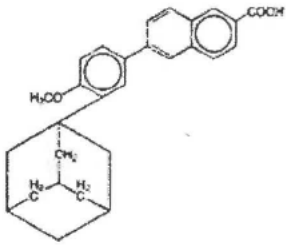
Trade Name:
Differin®

Code Names:
Not Available

Chemical Names:
6-(4-methoxy-3-tricyclo[3.3.1.1 3,7]dec-1-ylphenyl)naphthalene-2-carboxylic acid

Molecular Formulae / Molecular Weights:
$C_{28}H_{28}O_3$ / 412.5

Structure:



Pharmacologic Class:
Naphthenic acid class of anti-acne agent

2.2 Relevant INDs, NDAs, DMFs and other documents

IND 31997 (Lotion), (b) (4) Fort Worth, TX
IND 33540 (Gel), (b) (4) Fort Worth, TX
IND 38508 (Cream), Owen/Galderma Laboratories, Inc., Fort Worth, TX
IND 67801 (Gel), Galderma Laboratories, Fort Worth, TX
IND 116864 (Gel), Galderma Laboratories, Fort Worth, TX

NDA 20338 DIFFERIN® (adapalene solution) Solution 1%, 05/31/1996 (discontinued)
NDA 20380 DIFFERIN® (adapalene gel) Gel 0.1%, 05/31/1996
NDA 20748 DIFFERIN® (adapalene) Cream 0.1%, 05/26/2000

NDA 21753 DIFFERIN® XP (adapalene gel, 0.3%), 06/19/2007
NDA 22320 EPIDUO (adapalene 0.1%+BZPO 2.5%) Gel, 12/8/2008
NDA 20502 DIFFERIN® XP (adapalene lotion, 0.1%), 03/17/2010
NDA 207917 Epiduo Forte (Adapalene 0.3% + BZPO 2.5%) Gel, 07/15/2015

2.3 Drug Formulation

The formulation for the proposed 0.1% Differin® gel OTC product is the same as the Rx product. The compositions are shown in the following table.

Table 1 Quantitative and Qualitative Composition

	Formulation ID No: (b) (4)	
	% (w/w)	mg/g
Drug Substance		
Adapalene	0.1	1
Excipients		
Carbomer 940, NF	(b) (4)	
Propylene Glycol, USP		
Poloxamer 182		
Edetate Disodium, USP		
Methylparaben, NF		
Sodium Hydroxide, NF and/or Hydrochloric Acid, NF		
Purified Water, USP		

2.4 Comments on Novel Excipients

There are no novel excipients in the product. There are no changes to the OTC product formulation comparing to the approved 0.1% Differin® gel Rx product.

The nonclinical review team for the Rx adapalene product under NDA 20380 have assessed the formulation and confirmed that there were no nonclinical issues with the excipients.

2.5 Comments on Impurities/Degradants of Concern

There are no concerns on impurities/ degradants from a nonclinical perspective. As no changes to the product are proposed in this sNDA, details on impurities were not submitted.

The impurities and degradation products have been reviewed by the nonclinical review team for the Rx product under NDA 20380. It was confirmed that the impurities and

degradation products were qualified based on adequate exposure and margins of exposure.

2.6 Proposed Clinical Population and Dosing Regimen

The Rx indication for 0.1% Differin® gel is for "treatment of acne vulgaris". The OTC indication "for treatment of acne and clears up acne pimples and acne blemishes" was proposed by the applicant and "for treatment of acne" is being recommended by the review team.

As described in the labeling of the Rx product, 0.1% Differin® gel should be "applied once a day to affected areas after washing in the evening before retiring. A thin film of the gel should be applied, avoiding eyes, lips, and mucous membranes. During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment".

For the OTC product, the direction of use is proposed as follows: "Use once daily; Clean the skin thoroughly before applying the product; Cover the entire affected area with a thin layer".

2.7 Regulatory Background

The 0.1% Differin® (Adapalene) gel was first approved by the FDA as a prescription treatment for acne vulgaris in May 1996. It is currently marketed as a prescription drug in US, Canada, Japan, European Union and Australia, along with many other Latin American and Asian countries under several pharmaceutical forms (gel, cream, solution and lotion) for the cutaneous treatment of acne vulgaris. The 0.1% Differin® gel has also been marketed OTC in Russia since 2001.

A higher strength of Rx Differin® gel containing 0.3% adapalene has been marketed in the US since 2007. A fixed-dose combination of Adapalene 0.1%/BZPO 2.5% is marketed under the name Epiduo® in about 56 countries. A higher strength of Epiduo containing Adapalene 0.3%/BZPO 2.5% was approved by the FDA in July 2015 under the trade name of Epiduo Forte®.

The NDAs submitted by Galderma over the years for various adapalene products are provided in the following table.

Table 1 New Drug Applications filed for adapalene alone or in combination with benzoyl peroxide

Drug	NDA number	Approval Date
Differin (adapalene) gel, 0.1%	20-380	May 1996
Differin (adapalene) cream, 0.1%	20-748	May 2000
Differin (adapalene) lotion, 0.1%	22-502	March 2010
Differin (adapalene) solution, 0.1% [a]	20-338	May 1996
Differin (adapalene) gel, 0.3%	21-753	June 2007
Epiduo gel (adapalene 0.1%/benzoyl peroxide 2.5%)	22-320	December 2008
Epiduo Forte gel (adapalene 0.3%/benzoyl peroxide 2.5%)	207-917	July 2015

[a] Differin (adapalene) solution, 0.1% was withdrawn from the market for marketing reasons not related to safety or efficacy.

The following is a timeline of major events in the Rx-to-OTC development program of 0.1% Differin® gel:

On March 12, 2013, Galderma met with the Agency to review the proposed Rx-to-OTC switch of 0.1% Differin® Gel (NDA 20380). In this meeting, the Agency stated that four new clinical studies would be required to support the Rx-to-OTC switch of this product: label comprehension, self-selection, actual use, and a maximal use PK study.

On January 6, 2014, the Agency sent written comments to Galderma (Type C Meeting; Written Response Only) regarding questions related to the actual use and maximal use PK studies submitted on October 24, 2013.

On June 30, 2014, the Agency sent comments to Galderma on the draft maximal use PK study protocol submitted on April 1, 2014.

On July 10, 2014, Galderma submitted IND 116864 which included the revised clinical protocol for human MUsT Study titled "A Pharmacokinetic Study to Determine the Systemic Exposure in Differin® 0.1% Topical Gel During Dermal Application Under Maximal Use Conditions for 4 weeks in Adolescent and Adult Subjects with Acne Vulgaris".

On October 22, 2014, the Agency sent comments to Galderma on the draft actual use study protocol submitted on June 13, 2014.

On November 18, 2014, Galderma submitted the new clinical protocol titled "Actual Use Study for Adapalene Gel, 0.1%" to IND 116864.

On January 12, 2015, Galderma submitted a Request for Proprietary Name Review to IND 116864.

On June 10, 2015, Pre-NDA (Type B) Meeting was held.

On April 15, 2016, an Advisory Committee meeting was held where a nonclinical summary was presented. The committee discussed data submitted by the applicant to support OTC marketing of 0.1% Differin® Gel. There were 16 voting members and all of them voted in favor (Yes) that the safety of 0.1% Differin® gel for OTC use for the treatment of acne has been adequately demonstrated and the totality of the data support the use of this product OTC.

3 Studies Submitted

3.1 Studies Reviewed

The applicant referred to the nonclinical information from the previously approved adapalene product under NDA 22320 [EPIDUO (adapalene 0.1%+BZPO 2.5%) Gel, 12/8/2008]. A summary of the available pharmacology and toxicology information on adapalene was submitted in the present sNDA. No additional nonclinical studies were conducted or submitted in support of the present OTC switch.

3.2 Studies Not Reviewed

There are no nonclinical studies conducted or submitted under this sNDA.

3.3 Previous Reviews Referenced

Reference is made to the nonclinical pharmacology and toxicology reviews for the approved Rx adapalene products under NDA 20338, NDA 20380, NDA 20748, NDA 21753, NDA 20502 and NDA 207917.

4 Integrated Summary and Safety Evaluation

Adapalene is a synthetic napthoic acid derivative structurally different from retinoic acid by the presence of a phenoxy-adamantyl group. Its structure results in low percutaneous flux and thereby limits systemic exposure. The effectiveness of dermal adapalene in the treatment of acne is thought to be due to affecting the abnormal processes of epidermal keratinization and differentiation of follicular epithelial cells, reducing comedogenesis, expelling mature comedones, and exerting anti-inflammatory properties, all of which are important features in the pathogenesis of acne.

Adapalene is a compound that exhibits biological activities similar to retinoids. Typical retinoid compounds exert their pharmacological activities by binding to specific retinoic acid nuclear receptors (RARα, ß, γ) and cellular retinoid binding proteins I and II (CRAB I and II). Compared to typical retinoids, adapalene has much lower binding capacity to RARα and does not bind to CRAB II. One major concern regarding the OTC switch of adapalene products is the teratogenicity associated with the retinoid class of drugs. Adapalene may differ from other retinoids in regard to its teratogenicity profile because of its different binding at RARα and CRAB II.

Currently there are five active ingredients available OTC for the topical treatment of acne. These ingredients include benzoyl peroxide, resorcinol, resorcinol monoacetate, salicylic acid, and sulfur. Teratogenic effects have been observed with salicylic acid at 65 mg/kg/day in rats and 86 mg/kg in rabbits, but have not been observed with the other ingredients.

In support of the OTC switch, the applicant submitted a human maximal use PK trial in the sNDA:

- It was a multicenter, open label PK study in 24 subjects 12 years and older with moderate to severe acne vulgaris following once daily application of the drug for 29 days.
- Drug was applied on the entire area of the face, shoulders, upper chest and upper back. Mean daily medication usage was 1.95 g/day (range 1.21 g to 2.92 g).
- All 24 subjects completed the trial and this included 18 adolescent subjects (aged 12 to 17 years) and 6 adult subjects (aged 18 years and older).
- PK assessment via serial blood sampling was done on Days 1, 15 and 29 and additional trough concentrations were assessed on Days 2, 10, 16 and 22 in Adults and Days 2 and 16 in adolescent subjects.
- By Day 29, systemic concentrations of adapalene were quantifiable in all 24 subjects and steady state was reached by Day 15. The mean C_{max} and AUC_{0-24} on Day 29 were 0.049 ± 0.030 ng/mL and 0.83 ± 0.49 ng.h/mL, respectively. Due to lack of sufficient quantifiable systemic concentrations, $T_{1/2}$ could not be reliably estimated in all subjects and hence was not reported.
- **The highest systemic exposure was observed in one adolescent at day 29 with a C_{max} reaching a value of 0.17 ng/mL and an AUC_{0-24h} of 2.9 ng.h/mL.**

There are no new nonclinical studies conducted or submitted in support of the OTC switch. Comprehensive nonclinical characterization of the pharmacological and toxicological effects of adapalene was conducted during the development of currently marketed adapalene products. These studies have been reviewed by FDA under relevant applications.

The table below shows a summary of the toxicology program with adapalene conducted by Galderma in support of Rx product approvals.

Table 1 Toxicology Program Conducted with Adapalene and Topical Formulations of Adapalene

Study Type and Duration	Route of Administration	Species
Single-Dose Toxicity	Dermal Oral	Rats, Dogs Mice, Rats, Dogs
Repeat-Dose Toxicity		
4 weeks	Dermal	Rats, Dogs, Minipigs
	Oral	Rats, Dogs
13 weeks	Dermal	Mice, Rabbits, Minipigs
13 weeks	Oral (diet)	Rats
26 weeks	Dermal	Rats, Rabbits, Dogs
	Oral	Rats, Dogs
78 weeks	Oral (diet)	Rats
Genotoxicity		
Reverse mutation test	*In vitro*	*S. typhimurium* and *E. coli*
Mouse lymphoma TK locus assay	*In vitro*	Mouse lymphoma L5178Y cells
Chromosome aberration assay	*In vitro*	CHO cells K1-BH4
Micronucleus test	Oral	Mice
Photo-genotoxicity		
Reverse mutation test	*In vitro*	*S. typhimurium*
Chromosome aberration assay	*In vitro*	CHO cells K1-BH4
Carcinogenicity		
104 weeks	Dermal	Mice
104 weeks	Oral (diet)	Rats
Reproductive and Developmental Toxicity		
Reproductive function and fertility	Oral	Rats
Embryo-foetal development	Dermal	Rats, Rabbits
Prenatal and postnatal development	Oral	Rats, Rabbits
	Oral	Rats
Local Tolerance		
Primary skin irritation	Dermal	Rabbits
Cumulative skin irritation	Dermal	Rabbits
Primary eye irritation	Ocular	Rabbits
Skin sensitization		
Sensitization:	Dermal/Intradermal	Guinea pigs
Challenge:	Dermal	
Skin phototoxicity/photosensitization		
Sensitization:	Dermal	Guinea pigs
Challenge:	Dermal	
Other Toxicity Studies		
Antigenicity		
Sensitization:	Oral and IP	Mice
Challenge:	Intravenous	Rats (PCA test)
Sensitization:	Oral & SC	Guinea pigs
Challenge:	Intravenous	Guinea pigs (ASA and PCA tests)

IP: intra perfoneal; SC: sub-cutaneous; PCA: passive cutaneous anaphylaxis, ASA: active systemic anaphylaxis

Relevant findings of adapalene that are associated with the current Rx-to-OTC switch are summarized below.

(1) **Genetic toxicity:** Adapalene did not exhibit any genotoxic or clastogenic effects in both in vitro (Ames test, Chinese hamster ovary cell assay, and mouse lymphoma TK assay) and in vivo (mouse micronucleus test) studies.

(2) **General toxicology:**

a. When administered orally to rats and dogs at sufficiently high systemic exposures, bones were the main target organs, with brittleness and/or thinning; excessive osteoblastic and osteoclastic activities. This finding is consistent with the effects of other retinoids known to affect both long and flat bones by activating the remodeling process. The LOAELs (Low-Observed-Adverse-Effect-Level) for adapalene associated bone effects are 5 mg/kg/day in 13 week oral rat studies and 1 mg/kg/day in 26 week oral dog studies. Liver and kidney weights were increased in the 26-week dog study at the highest dose of 20 mg/kg/day and in the 78-week rat study at 0.5 and 1.5 mg/kg/day. In the absence of related histopathological findings, this was probably due to adaptative changes to high circulating levels of adapalene or an indirect effect secondary to an imbalance of calcium homoeostasis induced by the effect of adapalene on bone remodelling.

b. Hematological and biochemical effects have been observed with oral and dermal adapalene treatment, particularly at high doses. These effects are reversible and have also been reported with other retinoids. Adapalene decreased red blood cell counts in oral and dermal studies (sometimes associated with extramedullary hematopoiesis in oral studies, only). Changes in clinical chemistry parameters were mostly decreases in protein and albumin concentrations, increases in triglyceride concentration (rats only) and alkaline phosphatase activity, increases in glucose and corticosterone (rats only), decrease in cholesterol (rat only) and changes in calcium levels (dogs only). These changes were observed in rats and dogs when adapalene was given orally and in rats only when adapalene was given dermally. There was no microscopic change in the liver and it is believed the elevation of alkaline phosphatase activity was most probably due to the adapalene effects on bone.

c. The margin comparing the exposures of animals at the LOAEL for bone effects to human maximum use exposure was calculated to estimate the risks for adapalene-induced bone toxicities. The AUC_{0-24} from repeat dose oral rat or dog studies was not available. The plasma concentrations of a single oral dose of adapalene is 44.7 ng·h/mL in rats and 193 ng·h/mL in dogs at their corresponding LOAELs for bone toxicities. Based on the newly-conducted human maximal use trial with 0.1% adapalene gel, the highest human C_{max} values was 0.171 ng·h/mL. The following table shows the margin calculations and the margin is estimated to be greater than 260-fold.

	LOAEL (mg/kg)	Plasma Level (ng/mL)	Margin
Rat, Oral 13 wk	5	44.7	44.7 / 0.171 = 261
Dog, Oral, 26wk	1	193	193 / 0.171 = 1129
Human	Dermal	0.171*	-

*highest value in the human maximal use trial with 0.1% adapalene gel

(3) **Carcinogenicity of adapalene was evaluated in rats and mice:**

a. In a rat oral carcinogenicity study, increased incidence of benign and malignant pheochromocytomas in the adrenal medullas was observed in high dose male rats at 1.5 mg/kg/day. Pheochromocytoma is a finding that has been associated with other retinoid compounds in rodents. There are many morphological and biochemical differences between the adrenal glands of the rat and man. Rats are relatively more susceptible to pheochromocytoma and the incidence of pheochromocytoma is very low in humans. The findings are not considered to represent a risk in humans.

b. In a mouse dermal carcinogenicity study, no drug-related neoplastic lesions were observed at topical doses of 1.3, 3.9, and 12 mg/m^2/day.

(4) **Reproductive and developmental toxicity studies:**

a. When administered orally at doses ≥ 25 mg/kg, adapalene has been shown to be teratogenic in rats and rabbits. Findings include cleft palate, microphthalmia, encephalocele and skeletal abnormalities in the rat and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in the rabbit. No teratogenic effect was seen in rats and rabbits at an oral dose of 5.0 mg/kg/day of adapalene.

b. When administered topically in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, adapalene showed no evidence of teratogenicity, but there were variations in fetuses: increases in supernumerary ribs in both species and delayed ossification in rabbits. A dermal NOAEL of 6 mg/kg/day (i.e. 36 or 72 mg/m^2/day for rat or rabbit, respectively) was established in embryo-fetal development toxicity studies for both rats and rabbits.

c. There are no drug-related findings in the fertility and reproduction development studies in rats at up to 20 mg/kg/day.

d. There are no drug-related findings in the prenatal and postnatal development studies in rats at up to 15 mg/kg/day.

e. In rats, the placenta acted as a partial barrier to drug and its metabolites during organogenesis and thereafter. Placental/fetal transfer was studied in pregnant female rats after single oral and repeated oral dose and after

single intravenous administrations. A single oral dose of 0.1 or 1 mg/kg adapalene administered on gestation Day 13 gave exposures to the fetuses corresponding to 47% (0.1 mg/kg dose) and 28% (1 mg/kg dose) of the maternal plasma values in terms of AUC_{0-72}. After repeated oral administration at 0.1 or 1 mg/kg between gestation Days 6 and 13, fetal AUC values were less than 60% of the maternal plasma values. After a single intravenous dose of 0.5 mg/kg 14C-adapalene on gestation Day 11 and 18, exposures of the fetuses corresponded to 12% and 30% of maternal plasma levels, respectively.

f. Adapalene is also observed in the breast milk in treated lactating rats. When ^{14}C-adapalene was dosed either orally or intravenously to lactating rats, radioactivity was excreted in the milk and followed similar kinetics to the radioactivity in plasma, although with a lag time of approximately 3 hours.

Overall, it has been observed that adapalene can induce teratogenic effects in animals at sufficiently high systemic doses. A comparison of the teratogenicity findings in animals with adapalene and other retinoid or retinoid-like Rx acne drug products has been made. Compared tp tazarotene or tretinoin, adapalene requires the highest doses to induce teratogenic effects. The table below shows the summary of the comparisons.

		Adapalene	Tretinoin	Tazarotene
First Approved in		1996	1971	1997
Route		Dermal	Dermal	Dermal
Indication		ACNE Vulgaris	ACNE Vulgaris	ACNE Vulgaris
Formulation		0.1% Gel	0.01-0.025% Gel	0.05-0.1% Gel
Pregnancy Contraindication		No	No	Yes
		Lowest Teratogenic Dose in mg/kg		
Oral	Rat	25	0.4	0.25
	Rabbit	25	2	0.2
Dermal	Rat	> 6	> 1	0.25
	Rabbit	> 6	> 0.2	0.25

Although the teratogenic effects were not observed through the dermal route in the embryo-fetal development studies in tested animal species, the exact risk of teratogenicity in humans due to dermal exposure of adapalene is unknown because the precise sensitivity of humans to the possible teratogenic effect is unknown. In order to estimate the risks for adapalene-induced teratogenicity from a nonclinical perspective, a margin of exposure comparing the exposures of animals at the NOAEL for teratogenicity to the human maximum use exposure was calculated:

- Dermal: The NOAEL for teratogenicity of 6 mg/kg/day was established in dermal embryo-fetal development toxicity studies for both rats and rabbits. In a separate

10-day animal dermal PK study with 6 mg/kg/day adapalene gel, the mean AUC_{0-24h} values of 204 and 1036 ng·h/mL were achieved in rats and rabbits, respectively. Based on the newly-conducted human maximal use trial with 0.1% adapalene gel, the mean and the highest human AUC_{0-24h} values were 0.83 and 2.9 ng·h/mL, respectively. The margin of exposure for adapalene-induced teratogenicity is estimated to be approximately 246-fold using the average human AUC_{0-24h} or 70-fold using the highest human AUC_{0-24h} for rats; and 1248-fold using the average human AUC_{0-24h} or 357-fold using the highest human AUC_{0-24h} for rabbits. The following table is adapted from the submission showing the summary of the margin of exposure based on different clinical PK studies including the MUsT study.

Safety margins for teratogenicity based on the dermal rat teratogenicity study and human PK data obtained with 0.1% adapalene formulations

Formulation	Clinical PK Study No.	Number of subjects and age	Highest AUC_{0-24h} reported (ng.h/mL)	Safety margin
Adapalene gel 0.1% (Differin 0.1%)	18115	25 (Adults)	3.47	59
	18254	6 (Adults)	1.46	140
	18254	18 (Adolescents 12 – 17 years)	2.90	70
Adapalene in Epiduo gel 0.1%*	18097	12 (Adults)	2.65	77
Epiduo Gel fixed combination		12 (Adults)	1.99	102
Adapalene lotion 0.1 %	18108	14 (Adults)	2.00	101
	18190	13 (Adolescents 12 – 17 years)	4.93	41

* Adapalene 0.1% mixed in the Epiduo gel formulation, different for Differin gel.

** Safety margins calculated by dividing the AUC_{0-24h} of 204 ng.h/mL corresponding to the dose of 6 mg/kg/day applied dermally to rats identified as the NOAEL for teratogenicity by the human exposure obtained in acne patients in the different studies performed with different 0.1% adapalene formulations.

Note: the term "Margin of Safety" here is equivalent to "Margin of Exposure" in the review.

- Oral: There were no data on the AUC_{0-24} values from oral repeat dose rat or rabbit studies. The AUC_{0-24} value for a single oral dose of 0.5 mg/kg/day adapalene was 104 ng·h/mL in rats. The margin of exposure based on this result is estimated to be 125-fold [104/0.83 (average human AUC_{0-24h})] or 36-fold [104/2.9 (highest human AUC_{0-24h})]. The dose level of 0.5 mg/kg/day is 10-fold lower than the NOAEL of 5 mg/kg/day identified in the oral rat embryo-fetal development toxicity study. Therefore the corresponding margin with 5 mg/kg/day through the oral route is expected to be much higher than 36-fold.

Based on the calculated margin of exposures and adapalene's different pharmacological activity, there are less concerns for adapalene-induced retinoid related teratogenicity from a nonclinical perspective. One caveat is that, animal studies do not always predict effects in humans and the human sensitivity to adapalene is unknown. With certain retinoid compounds, the human appears to be a sensitive species for drug-related teratogenicity. To date, there are no adequate and well-controlled studies in pregnant woman, or reports of teratogenic outcomes in human fetuses exposed to adapalene in utero. The level of human fetal exposure is unknown and the actual levels required to cause teratogenicity in humans is unclear.

In summary, adapalene can induce teratogenicity in animals at sufficiently high systemic doses (oral doses from 25mg/kg/day). The margin of exposure for adapalene-induced teratogenic effects is estimated to be over 70-fold. However, animal studies do not always predict human effects and the level of exposure required to cause teratogenicity in humans is unclear. Based on the agency's previous review of the nonclinical information on the Rx adapalene products, the human use experience of adapalene, and the calculated margin of exposure for adapalene-associated teratogenicity, there is no impediment to approval from a Pharmacology/Toxicology perspective.

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/s/

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06/03/2016

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