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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Office Deputy Director Decisional Memo

Date	(electronic stamp)
From	Lesley-Anne Furlong, M.D., Deputy Director, ODE 4
Subject	Office Deputy Director Decisional Memo
NDA/BLA # **Supplement #**	NDA 20380 Supplement 10
Applicant Name	Galderma Laboratories, LP
Date of Submission	10-Sep-2015
PDUFA Goal Date	10-Jul-2016
Proprietary Name / Established (USAN) Name	Differin /adapalene
Dosage Forms / Strength	Gel / 0.1%
Applicant Proposed Indication(s)/Populations	For the treatment of acne
Action:	Approval
Approved Indication(s)/Populations (if applicable)	Rx labeling: For the topical treatment of acne vulgaris

Material Reviewed/Consulted Application, Rx labeling, and OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Reviews	Amy Woitach, DO, and David Kettl, MD, Division of Dermatology and Dental Products Ryan Raffaelli, MD, and Jane Filie, MD, Division of Nonprescription Drug Products
Statistical Review	Scott Komo, DrPH, and Daphne Lin, PhD
Social Scientist Review	Barbara Cohen, MPA
Pharmacology Toxicology Review	Cindy Xinguang Li, PhD, Paul Brown, PhD
OPQ Review	Donald Klein, PhD, Ramesh Raghavachari, PhD Environmental assessment, Raanan Bloom, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Chinmay Shukla, PhD, and Doanh Tran, PhD
OSI	Sharon Gershon
CDTL Review	Jane Filie, MD
OSE/DEPI and DPV II	Lopa Thambi, PharmD, Hongliu Ding, MD, PhD, MPH, Patty Green, Pharm D
OSE/DMEPA	Grace Jones, PharmD, Chi-Ming (Alice) Tu, PharmD
DPMH review 1 DPMH review 2	Mona Khurana, MD, Hari Sachs, MD, through John Alexander, MD Tamara Johnson, MD, Melissa Tassinari, PhD, through Lynne Yao, MD

Material Reviewed/Consulted Application, Rx labeling, and OND Action Package, including:	**Names of discipline reviewers**
DNDP labeling review	Yoon Kong, PharmD, and Steven A. Adah, Ph.D.
DDDP Deputy Director for Safety Summary Review	Tatiana Oussova, MD
DNDP Division Director Summary Review	Theresa Michele, MD

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPMH=Division of Pediatric and Maternal Health
DPV 1 = Division of Pharmacovigilance 1
DNDP = Division of Nonprescription Drug Products

1. Benefit-Risk Assessment

The application proposes a full switch of adapalene gel 0.1% from prescription (Rx) to nonprescription status. The indication is treatment of acne. The drug product will be the first-in-class retinoid for over-the-counter (OTC) use. Retinoids as a drug class are known to be teratogens at sufficiently high systemic exposures[1]; however, topical retinoids have not shown teratogenicity in the Rx setting. Whether adapalene 0.1% gel would be a teratogen under OTC conditions was a key review issue.

Acne is a common, disfiguring skin condition affecting young people of reproductive age. Acne causes emotional distress and may result in permanent skin scarring. It affects more than 85% of teenagers and may persist into adulthood. There are no restrictive measures to prevent prescribing adapalene to pregnant women, and pregnant women have been exposed to adapalene in the Rx setting. Pregnancy exposures can be expected in the OTC setting.

The benefit-risk considerations for this application are the incremental benefits and risks incurred by moving from Rx to OTC marketing. The drug's safety and effectiveness as an Rx product was not at issue: the product was FDA-approved 20 years ago and has had an uneventful postmarketing history in the Rx setting. Acne as an OTC indication was also not at issue: acne is a long-standing OTC indication.

The incremental benefit of the Rx-to-OTC switch of adapalene is easy and timely access to an effective product. Although there are other OTC drug products for acne, only one of them – benzoyl peroxide – is recommended by the American Academy of Dermatology (AAD) as a

[1] Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy N Engl J Med 1985; 313:837-841

first-line treatment for acne.[2] OTC adapalene 1% gel would provide consumers with a second AAD-recommended first-line treatment for acne.

The potential risks are also related to improved access. OTC marketing not only expands the population of potential users, but, by removing the prescriber-gatekeeper, can increase how much drug each consumer can use. The applicant estimates that about 70% of acne sufferers do not seek care from a doctor and therefore do not currently have access to adapalene. The potential population of new users is therefore sizeable.

Adapalene can be a teratogen. Dosing animals orally in sufficiently high doses produces birth defects consistent with retinoid embryopathy. In the Rx setting, however, the clinical trial data, more than twenty years of postmarketing reports, and epidemiologic studies have not produced a signal for teratogenicity in humans. Use of adapalene has been substantial. The applicant estimates that over 40 million patients have used adapalene gel (0.1% and 0.3%) since international market launch of adapalene in 1992. As of July 2014, a total of 5414 subjects were exposed to topical adapalene at concentrations of 0.1% or 0.3% in the applicant's clinical trials. Pregnancies have been reported in women using the product. Despite substantial use, a signal for teratogenicity has not emerged. (See Safety.)

Studies performed to support the application included a label comprehension study, a self-selection study, an actual use study, patient and provider surveys (Rx-SOC Study) to assess prescription practices, and a maximal use PK study. The actual use study, which evaluated consumer behavior, and the maximal use PK study, which allowed for the calculation of a safety margin of exposure for teratogenicity, were of particular relevance to the issue of teratogenicity.

The maximal use PK study assessed systemic levels of adapalene in 24 volunteers with moderate to severe acne who were exposed daily to the product applied to all skin surfaces likely to be affected by acne (face, shoulders, upper back, and upper chest). (See Clinical Pharmacology.) Steady state was reached by day 15 and systemic exposure was detected in all subjects by day 29. The mean ± SD Cmax and AUC_{0-24} on Day 29 were 0.049 ± 0.030 ng/mL and 0.83 ± 0.49 ng.h/mL, respectively. The average medication usage was 1.95 g/day (range 1.21 gm to 2.92 gm).

Data from the subject with the greatest systemic exposure was used to calculate human safety margins. The subject with the greatest systemic exposure was a 16-year-old male subject. His systemic exposure was 3.4 times the mean exposure. His highest systemic exposure was observed at day 29 with a Cmax of 0.171 ng.h/mL and an AUC_{0-24h} of 2.9 ng.h/mL.

The applicant used historical animal data and data from the 16-year-old subject with the greatest systemic exposure to calculate a safety margin of exposure for adapalene-associated teratogenicity. The safety margin was conservatively calculated as the ratio of the systemic exposure (AUC_{0-24h}) at the no observed adverse effect level (NOAEL) for teratogenicity in the most sensitive animal species (the rat) to the highest systemic exposure (AUC_{0-24h}) in the

[2] Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol 2015;74:943-973

maximal use PK study. The safety margin of exposure for teratogenic effects was at least 70-fold. (See Nonclinical Pharmacology/Toxicology.)

While the maximal use PK study measured use when the product was applied by investigators, the actual use study (the Juno Trial) provided insights into consumer use in a naturalistic consumer setting. The Juno Trial was a six-week, open label, single arm study conducted in 31 geographically dispersed pharmacy sites in the United States. Subjects were allowed to purchase a maximum of three cartons, each containing a 45 gm tube of adapalene 0.1% gel, which is the same size tube currently available by prescription. Subjects could purchase no more than two cartons per visit. A total of 947 subjects purchased and used the drug.

On average, subjects used about 0.6 gm per day, substantially less than the average use in the maximal use PK study (1.95 gm/day). About 94% of subjects used one tube or less. Subjects remained in the trial on average 41.4 days (almost the entire 42 treatment days of the trial). Mean quantity used was similar for age, gender, and literacy subgroups. Four subjects purchased the maximum of three tubes. By setting a cap on purchase at three tubes, the Juno capped the amount of use; however, no subject used three complete tubes in six weeks of use. Range of use was therefore reasonably well captured by the study. The maximum use was 129.5 grams (out of a possible 135 gm), or about 3 gm per day, which is similar to the maximum use reported for the maximal use PK trial (2.92 gm/day).

Overuse does not improve effectiveness and increases the risk of adverse skin symptoms. Skin symptoms may therefore be a useful deterrent to overuse of adapalene in the OTC setting – skin symptoms are readily recognized by the consumer, non-serious, and reversible with discontinuation of the product. Furthermore, overuse is not reinforced by better results because there is no added benefit from overuse. Prescription labeling notes that erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients, and that overuse will not lead to better results but may lead to 'marked redness, peeling, or discomfort.' (See *Safety information from prescription labeling*.)

Adapalene 0.1% topical gel has markedly different overall risk profile compared with retinoids that are taken orally. The safety labeling for adapalene 0.1% gel distinguishes it decisively from the orally administered retinoid, isotretinoin. For topical adapalene, the main adverse effects are reversible skin symptoms. The only contraindication is hypersensitivity to the product or any of its components. No recommendations for laboratory monitoring appear on its labeling. It is labeled Pregnancy Category C, and 'should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.'

In contrast, isotretinoin capsules are: 1) dispensed under a restricted distribution system because human exposures have resulted in major congenital malformations consistent with retinoid embryopathy; 2) contraindicated ("Category X") in pregnancy and if hypersensitive to the product or its components: 3) associated with psychiatric disorders, pseudotumor cerebri, serious and life-threatening skin reactions, acute pancreatitis, severe lipid abnormalities (marked hypertriglyceridemia in 25% of patients), hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities, and ocular abnormalities. Furthermore, laboratory monitoring, including pregnancy testing, lipid profiles, and liver

function testing, is recommended for patients taking isotretinoin capsules. Among the serious adverse effects in the label for isotretinoin capsules, the only one shared with topical adapalene shares is hypersensitivity to the product or any of its components.

While the differences in safety labeling between topical adapalene and the oral isotretinoin may simply be the result of differences in systemic exposure, there may be other factors at play. Adapalene has a lower affinity for two of five intracellular retinoid binding proteins compared with other retinoids. Compared with tretinoin and tazarotene, adapalene requires a higher oral dose (by 1 to 2 orders of magnitude) to elicit teratogenic effects in animals. (See Nonclinical Pharmacology/Toxicology.) While there is evidence that man is a sensitive species for isotretinoin-induced teratogenicity,[3] adapalene is not isotretinoin.

On April 15, 2016, FDA convened an Advisory Committee AC meeting to consider the acceptability of an Rx-to-OTC switch for adapalene 0.1% gel with a focus on teratogenicity. The committee included standing members of the Nonprescription Drug Advisory Committee, as well as dermatology and reproductive toxicology experts. After hearing presentations of the data from both FDA and the applicant, the AC voted unanimously (16 'yes' and 0 'no') that the safety of adapalene gel 0.1% for OTC had been adequately demonstrated and that the data supported OTC use of adapalene gel 0.1% for acne.

Dr. Raffaelli and Dr. Filie recommended in their reviews that approval be contingent on the maximum tube size being 45 gm to decrease the likelihood of overuse. I have considered their position and agree that the data support safety for a tube size up to 45 gm. The actual use study evaluated consumer behavior with 45 gm tubes, and the Rx product is marketed in the United States in 45 gm tubes. Research has shown that increased package sizing of products leads to increased usage among consumers.[4,5] Conversely, limiting package sizes has been shown to reduce overconsumption by limiting the immediate availability of drugs to the consumer.[6,7] As noted by Dr. Michele in her review, limiting the package size will not limit consumer access in the OTC setting because consumers may purchase more than one package at a time. The applicant proposes a 2 gm sample size, and 15 gm and 45 gm tubes for OTC marketing. These sizes are acceptable. If a larger tube is proposed for OTC marketing in the future, the applicant should justify that larger tube sizes will not adversely impact the safety profile for OTC adapalene.

I concur with the summary reviews, and recommend approval of adapalene gel 0.1% for OTC marketing. Final negotiated labeling is acceptable.

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[3] Nau H. Teratogenicity of isotretinoin revisited: species variation and the role of all-trans-retinoic acid. J Am Acad Dermatol 2001;45:S183-7

[4] Wansink B, 1996, Can Package Size Accelerate Usage Volume? *J Mark*, 60(3): 1-14.

[5] Chandon P, B Wansink, 2002, When are Stockpiled Products Consumed Faster? A Convenience-salience Framework of Postpurchase Consumption Incidence and Quantity, *J Mark Re*s, 39(3): 321-335.

[6] Hawton K, H Bergen, S Simkin, S Dodd, P Pocock, W Bernal, et. al., 2013, Long Term Effect of Reduced Pack Sizes of Paracetamol on Poisoning Deaths and Liver Transplant Activity in England and Wales: Interrupted Time Series Analyses, *BMJ*, 346: f403 (doi: 10.1136/bmj f403).

[7] Weiss S, 2009, Compliance Packaging for Over-the-counter Drug Products, J Public Health, 17(2): 155-164.

2. Further discussion to support regulatory action

Background

FDA approved adapalene gel (0.1%) as a new molecular entity in 1996 for the topical treatment of acne vulgaris in subjects 12 years of age and older. It is currently available as a single entity 0.1% solution, gel, and lotion, as well as 0.3% gel (U.S. approval in 2007). It is also marketed in combination with benzoyl peroxide in both 0.1% and 0.3% strengths. It is available as a nonprescription drug in Russia and was turned down by Germany as a nonprescription drug in 2016. (See Other Relevant Regulatory Issues.)

To support the switch OTC switch application, the applicant performed two clinical studies and three additional studies:

1. Maximal use pharmacokinetics trial
2. Actual use study to observe how 0.1% adapalene gel use in an OTC setting
3. Prescription standard of care (Rx-SOC study) to assess prescribing physician and patient behavior in the Rx environment.
4. Self-selection study in pregnancy and/or breastfeeding women
5. Label comprehension study

Comment: The social science reviewer noted methodological deficiencies with the Rx-SOC study and the study was not used to support the regulatory decision. Nonetheless, it was interesting to me that the reports of pregnancy testing among 151 physicians surveyed for the study (physicians who had written a prescription of adapalene in the past six months) were low. Only 21% of physicians reported requiring a pregnancy test for women of child-bearing potential before prescribing a topical retinoid and only 9% reported routinely performing pregnancy tests at follow-up visits. The survey numbers seem likely to be overestimates as they measure what physicians recall, and not what they actually did.

Product Quality

The CMC team recommended approval. The drug substance and drug product are the same as the approved prescription product. Environmental assessment data adequately supported a request for categorical exclusion.

The applicant plans to market a 2-gm sample, 15 gm, and 45 gm tubes for OTC sale. Distribution data in the 2015 annual report and the current Rx labeling indicates that only a 45 gm size was being distributed for the Rx product.

Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology (P/T) review team concluded that there was no impediment to approval of the application from a P/T perspective. The reviewers noted, however, that animal studies do not always predict human effects.

The applicant summarized previously-submitted P/T data for adapalene, and calculated a safety margin of exposure for adapalene-associated teratogenicity based on the results of the maximal use PK study in the submission. The AUC_{0-24} from the human subject with the greatest systemic exposure was used to calculate safety margins. The safety margin of exposure for teratogenic effects was 70-fold based on data in rats and 357-fold based on data in rabbits.

Adapalene did not exhibit any genotoxic or clastogenic effects in vitro (Ames test, Chinese hamster ovary cells assay, and mouse lymphoma TK assay) or in vivo (mouse micronucleus).

When administered orally to rats and dogs at high exposures, bones were the main target organs for toxicity, a finding that is consistent with other retinoids. The LOAELS (lowest observed adverse effect level) for adapalene bone effects were 5 mg/kg/day in 13 week oral rat studies and 1 mg/kg/day in 26 week oral dog studies. The P/T reviewer calculated a margin of safety for bone effects as greater than 260-fold based on data from rats, and 1130-fold based on data from dogs.

A mouse dermal carcinogenicity study did not detect drug-related neoplasia. In a rat oral carcinogenicity study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medullas was observed in high dose male rats at 1.5 mg/kg/day, a finding that has been seen with other retinoid compounds in rodents. However, because of differences in rat and human adrenal glands and a relatively greater susceptibility to pheochromocytomas in rats, the findings are not considered to represent a risk in humans.

When administered orally at doses $\geq$25 mg/kg, adapalene was teratogenic in rats and rabbits. Findings included 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 mg/kg/day.

When administered topically in rats and rabbits at doses up to 6 mg/kg/day, there was no evidence of teratogenicity.

Adapalene was observed the breast milk of treated lactating rats and concentration in the milk followed similar kinetics to concentration in the maternal plasma, with a lag time of about 3 hours.

The table below taken from the P/T review shows a comparison of adapalene teratogenicity compared with two other retinoids. Among the three retinoids, adapalene requires the highest doses to induce teratogenic effects in rats and rabbits.

		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

Source: p. 13, P/T review

For this application, the applicant calculated the safety margin of exposure for adapalene-induced teratogenicity using the highest human AUC_{1-24} in the submitted PK study as 70-fold for rats and 357-fold for rabbits. Historical data from other PK studies of 0.1% gels and lotions gave similar results: the safety margin ranged from 41-fold for adapalene lotion 0.1% to 140-fold for adapalene gel 0.1%. See the following table copied from the P/T review.

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% monad 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.

Source: p. 14, P/T review

Comments: Given orally in sufficiently high doses, adapalene can cause retinoid-like embryopathy in rats and rabbits. Using a conservative estimate of human exposure, the margin of safety for teratogenicity is 70-fold. While reassuring, the margin of safety calculated from animal studies does not always predict effects in humans. Human sensitivity to the teratogenic effects of adapalene is unknown.

Adapalene appears in breast milk in treated rats.

Clinical Pharmacology

The clinical pharmacology team recommended approval from a clinical pharmacology perspective.

The applicant submitted a maximal use pharmacokinetic trial (Study RD.06.SRE.18254) to assess systemic exposure to adapalene under maximal use conditions.

Study RD.06.SRE.18254 was an open-label, multicenter PK study in 24 subjects, including 18 adolescents ages 12-17 years and 6 subjects who were 18 years and older. There were 11 females and 13 males. Subjects had moderate to severe acne vulgaris. Men were required to shave their faces the night before the PK visits and then according to their own routine. Moisturizers and sunscreens were permitted, but not within 2 hours of study drug administration. Adult subjects remained in the clinical unit on Day 1 and until the 24-hour PK blood sample on Day 2; adolescents were not required to spend the night in the clinic on the first day of treatment (Day 1). Otherwise, subjects were outpatients. Other than sunscreen and moisturizers, topical treatments on the treatment area, enzyme inducers/inhibitors, and antibiotics were not permitted.

Drug was applied once daily on the entire face, shoulders, upper chest, and upper back for 29 days. Multiple PK samplings were done on days 1, 15, and 29 and trough samplings were done on Days 2, 10, and 16 in adults and days 2 and 16 in adolescents. Subjects were seen at the study site daily and study personnel applied the study drug.

Steady state was reached by day 15 and systemic exposure was detected in all subjects by day 29. The mean ± SD Cmax and AUC_{0-24} on Day 29 were 0.049 ± 0.030 ng/mL and 0.83 ± 0.49 ng.h/mL, respectively. No significant gender or age differences were detected. The average medication usage was 1.95 g/day (range 1.21 gm to 2.92 gm). No correlation between heavier use and systemic exposure was detected. The mean body surface area (BSA) treated was 1864.7 cm^2 (about 17 inches by 17 inches), with a range from 1387.4 to 2893.9 cm^2. There were no serious adverse events. The most common treatment emergent adverse events were related to skin (16.7%): skin irritation (n=3), pruritus (n=2), erosion (n=1).

Data from the subject (#8139-006) with the greatest systemic exposure was used to calculate safety margins for the pharmacology/toxicology assessment. Subject #8139-006 was a 16 year old male. His systemic exposure was approximately 3.4 times the mean exposure, although his drug use in grams was close to the mean drug use. He received a mean of 1.89 gm of study medication on 1899 cm^2 BSA daily. He had quantifiable adapalene levels starting with the first application. The highest systemic exposure was observed at day 29 with a Cmax reaching a value of 0.171 ng/mL and an AUC_{0-24h} of 2.897 ng.h/mL.

Comments: By enrolling subjects with moderate and severe acne, applying to all the body surfaces typically affected by acne every day, requiring facial shaving in men, allowing the use

of moisturizers and sunscreens as needed, and conducting the study under largely out-patient (i.e., varying) conditions, the study was reasonably well-designed to assess maximum exposure. It is clear that systemic exposure is variable. Data gaps include:

- *Occlusion. PK was not assessed under occluded conditions; however, it seems unlikely that a person would apply an acne drug, particularly one that dries and irritates the skin, under bandaged skin. Also, bandaged skin is likely to be damaged skin and DFL labeling cautions against applying to damaged skin (cuts, abrasions, eczema, sunburn). The DFL message to not use on damaged skin performed well in the label comprehension study (97.5% understanding, see Social Scientist review.)*
- *Concomitant use of certain non-topical drugs. However, Rx labeling does not indicate any drug-drug interactions that could increase exposure.*
- *Concomitant use of other topical drugs. It is possible that other topical drugs could affect absorption, although allowing the use of topical moisturizers and sunscreens was a reasonable 'real-life' accommodation in the study.*

There is no reason to think that occlusion and concomitant use of other medications are issues unique to the OTC setting.

Clinical/Statistical – Efficacy

Effectiveness was not re-evaluated in the application. According to the American Society of Dermatology topical retinoids and/or benzoyl peroxide, alone or in combination with each other or with antibiotics, are first-line treatments for acne.[8]

Safety

The clinical trial data, postmarketing data, and epidemiologic studies for adapalene 0.1% gel have not detected a signal for retinoid teratogenicity in humans. The applicant estimates that over 40 million patients have used adapalene gel (0.1% and 0.3%) since its international market launch in 1992. As of July 2014, 10,933 subjects had been studied in the applicant's clinical development program, and a total of 5414 subjects had been exposed to adapalene at concentrations of 0.1% or 0.3%. Most of the clinical trials for adapalene evaluated exposure for 12 weeks, although three studies provided longer term data.

[8] Guidelines of care for the management of acne vulgaris. American Academy of Dermatology Inc., 2016

Safety information from prescription labeling

Safety language in prescription labeling for adapalene 0.1% gel focuses on non-serious local skin effects. The main points relevant to safety are:

- Adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients. Pruritus or burning immediately after application also occurs in approximately 20% of patients.
- If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur.
- Hypersensitivity is the only contraindication.
- The only warning is that patients with sunburn should be advised not to use the product until fully recovered.
- Precautions focus avoiding concomitant use with other skin irritants and a recommendation not to apply to broken skin.
- The drug is pregnancy Category C and 'should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.'
- Labeling for nursing mothers states, 'It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when adapalene gel is administered to a nursing woman.'
- Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Comments: Adverse skin symptoms are a useful deterrent to overuse in the OTC setting because skin irritation is readily recognized by the consumer, non-serious, and reversible with discontinuation of the product. Furthermore, overuse will not be reinforced by better treatment results because there is no added benefit from overuse.

As noted by Dr. Raffaelli, there are other Pregnancy Category C drugs (and D drugs) approved for OTC use.

The safety labeling for adapalene 0.1% gel distinguishes it clearly and decisively from the orally administered retinoid, isotretinoin. In contrast to adapalene 0.1% gel, isotretinoin capsules are: 1) dispensed under a restricted distribution system because human exposures have resulted in major congenital malformations consistent with retinoid embryopathy; 2) contraindicated ("Category X") in pregnancy: 3) associated with psychiatric disorders, pseudotumor cerebri, serious and life-threatening skin reactions, acute pancreatitis, severe lipid abnormalities (marked hypertriglyceridemia in 25% of patients), hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities, and ocular abnormalities. Furthermore, laboratory monitoring, including pregnancy testing, lipid profiles, and liver function testing, is recommended for patients taking isotretinoin capsules.

Safety Data from self-selection study

The primary objective of the targeted self-selection study was to assess whether pregnant or breastfeeding women would ask a health care professional prior to use, as per the directions on the drug facts label (DFL). The study enrolled 293 women who self-reported being pregnant and/or breastfeeding and who had acne: 242 subjects were enrolled in Cohort 1, the general population cohort, and 112 subjects were enrolled in Cohort 2, the low literacy cohort. (Sixty-one low literacy subjects were in both cohorts). Only 37% of subjects were pregnant. Women were asked 'is it ok for you to use this medication today or not?' followed by 'why did you say that?' Success was defined as 90% of women correctly responding. Incorrect responses included subjects who were correct on the first question but incorrect on the follow-up or incorrect on both questions. Overall, among 242 women (25% low literate), only 74.4% (95% CI 68.4%-79.8%) of subjects correctly stated that they would ask a healthcare provider before using the product. The study failed to meet its pre-specified endpoint.

Comment: The self-selection study support that a substantial number of pregnant or breastfeeding women with acne thought it was okay to use the product that day (that is, without consulting a healthcare provider.)

Safety data related to pregnancy from the clinical trial database

A total of 18 pregnancies were reported in the applicant's clinical trial database. Four pregnancies were reported in the Actual Use Study 100931, and 14 pregnancies were reported in Japan Study 27006, a one-year, safety trial. No major malformations were reported.

Outcomes included:

- 9 normal births
- 2 premature births
- 1 miscarriage at 13 weeks
- 1 stillbirth following placental abruption
- 2 elective abortions
- 3 lost to follow-up

Safety Data from the actual use study

The applicant performed an actual use study, the Juno Trial (Protocol 13049) to support the application. The trial provided evidence that consumer are unlikely to overuse the product and likely to apply it to acne areas of the skin. The Juno Trial also showed that some pregnant women will use the product.

The Juno Trial was a six-week, open label, single arm study conducted in 31 geographically dispersed sites in the United States. Recruitment targeted consumers with acne; therefore the trial did not address the potential for off-label use. Subjects were allowed to purchase a maximum of two cartons, each containing a 45 gram tube, at each visit. Subjects could not purchase more than three cartons in six weeks. A total of 947 subjects purchased the drug and

applied at least one dose. The mean age was 29.9 years, 21.4% were teens, and 68% were female. The trial met its pre-specified endpoints. The primary endpoints were once daily use at the same acne location (89.1% of subjects) and use on sites of acne only (99.3% of subjects). A total 97.5% reported using the product on undamaged skin and avoiding eyes or mucus membranes. According to the DNDP clinical review, among subjects who used the product more than once a day, reasons included reapplying after showering (35 of 103), trying to get faster or greater benefit (25 of 103), trying to treat more severe acne (19/103), or misunderstanding (9 of 103). Reasons for misuse did not identify any safety concerns.

There were no deaths or serious adverse events. Eight subjects discontinued due to adverse events, including skin irritation, skin dryness, or worsening acne. Headache, dry skin, and erythema were the most commonly reported adverse events.

Five of nine pregnant subjects wished to purchase the product but were excluded from the use phase of the trial. Four subjects became pregnant during the trial and continued using the product. One subject did not know she was pregnant until the end of the trial. There was one healthy newborn, two pregnancies were lost to follow-up, and one subject chose to terminate her pregnancy for personal reasons.

On average, subjects used about 0.6 gm per day based on weights of returned tubes at the end of the trial. Approximately 94% of subjects used one tube. Subjects remained in the trial an average of 41.4 days (almost the entire 42 days of the trial). Mean quantity used was similar for age, gender, and literacy subgroups. A total of 61 subjects purchased more than one tube (N=61); 50 of 61 purchased two tubes at the first visit; four subjects purchased the maximum of three tubes. The maximum use was 129.5 grams, or about 3 gm per day, which is similar to the maximum use reported for the MUsT trial (2.92 gm/day).

Comments: The actual use study confirmed that pregnant women are likely to be exposed to the drug in the OTC environment. This is to be expected as acne is a skin condition of people in their reproductive years, and many pregnancies are unplanned and/or undiagnosed until well into the first trimester or beyond. Pregnancy exposures have also occurred in the Rx environment, which is also to be expected for the same reasons and because there is no standard of care recommending physicians perform pregnancy testing for topical adapalene in the Rx environment.

Regarding use, it was reassuring to see that the average use in a naturalistic OTC setting was well below the average use in the maximal use PK study (0.6 gm/day compared with 1.92 gm/day), and that the greatest use was similar to the greatest use in the maximal use PK study (3 gm/day vs. 2.92 gm/day).

By setting a cap on purchase to 3 tubes, the actual use study did not allow for extremes of overuse. However, the subject who used the most drug used 129.5 gm, which is less than the contents of three tubes (135 gm), suggesting that the likely range of use in the OTC setting was reasonably well-captured by the study.

Postmarketing safety data

FDA's Office of Surveillance and Epidemiology (OSE) provided a review of abnormal pregnancy outcomes focused on congenital anomalies associated with adapalene and other topical retinoids in the FDA Adverse Events Reporting System (FAERS) and the medical literature. In addition, OSE reviewed all serious adverse events reported in adapalene users and provided drug utilization data for adapalene products.

As noted in the OSE review, most proven human teratogens result in a spectrum – or syndrome – of adverse events and not one isolated birth defect. Therefore the review included an assessment for a known or unique clustering of birth defects. Individual cases were assessed for the clinical features of retinoid embryopathy[1]: craniofacial anomalies (microtia or anotia, accessory parietal sutures, narrow sloping forehead, micrognathia, flat nasal bridge, cleft lip and palate, and ocular hypertelorism), cardiac defects (primarily conotruncal malformations), abnormalities in thymic development, and alterations in central nervous system development.

Five cases of congenital anomalies were identified, none of which had features of retinoid embryopathy. Three of the five reported an isolated anomaly, (limb malformation, club feet, and Dandy Walker malformation). One was VACTERL[9] syndrome and one was a chromosomal deletion. DPV did not find reasonable evidence to support a causal association between adapalene and these events.

Drug utilization patterns showed that about 974,000 single ingredient adapalene prescriptions were dispensed to 563,000 unique patients in the 12-month period ending in Nov 2015. The largest demographic group was women aged 12-45 years, and the most common diagnosis was acne.

Literature review showed that findings from epidemiologic studies of topical retinoids in general do not suggest an increased risk of birth defects among women exposed in early pregnancy. However, none of the reviewed studies assessed adapalene-specific risks. Small sample sizes and other methodological limitations were noted by the OSE review team. Between 2004 and 2012, OSE performed seven other postmarketing safety reviews for adapalene topical products. Other than a recommendation to add hypersensitivity to the Epiduo labeling, no substantive labeling changes were recommended.

The OSE conclusion was "Based on a lack of a clear pattern of congenital anomalies consistent with retinoid embryopathy, and a lack of compelling medical literature in FAERS cases and epidemiological data, there does not appear to be a signal for adapalene-associated congenital anomalies at this time."

The applicant's postmarketing surveillance

[9] VACTERL stands for vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. For more information, see https://ghr nlm nih.gov/condition/vacterl-association#genes

The applicant submitted a review of postmarketing safety database with a cutoff date September 30, 2014. A total of 332 pregnancies were exposed to adapalene (including Epiduo products that combine adapalene with benzoyl peroxide). Fifty-six pregnancies were reported during clinical trials and 276 were reported in postmarketing surveillance. Ninety percent were prospectively collected. Outcomes were known for 169 pregnancies: 109 health infants, 18 elective abortions, 23 miscarriages, and 19 abnormal outcomes.

The 19 abnormal outcomes were reviewed by Elizabeth Gnasia, MD, PhD, an external expert in medical genetics and teratology. Dr. Gnasia's conclusions were that 'the role of adapalene was considered dubious or was excluded; in some cases, other explanations were identified, in others the type of anomaly observed was not compatible with the time of exposure during pregnancy, and sometimes the information was too scare to lead to any conclusion (consumer case).' The cases are summarized in the following table.

Nineteen Abnormal Pregnancy Outcomes in the Applicant's Postmarketing Database

Outcome	Case ID	PMS	Clinical trials	Prospective/ retrospective	Total
Malformations					
Hydrops fetalis	BR14003185	1		Prospective	1
Talipes	NL14001284	1		Retrospective	1
Polymalformative syndrome (fetal malformation, brain malformation, corpus callosum agenesis, congenital foot malformation, malformation venous)	FR13003020	1		Retrospective	1
Neurofibromatosis type I	US-GDP-12415335	1		Retrospective	1
Fallot tetralogy	BR-GDP-11410861 FR-GDP-11412410	2		1 Prospective 1 Retrospective	2
Dandy Walker syndrome	AT-GDP-10409257	1		Retrospective	1
Congenital Hand malformation	CH-GDP-09406029	1		Retrospective	1
Chromosomal deletion (2Q37)	US-GDP-09406176	1		Retrospective	1
Vacterl syndrome	FR-GDP-08403799	1		Retrospective	1
Scimitar syndrome (cardiovascular defect)	CH-GDP-0511972	1		Retrospective	1
Multiple fetal abnormalities (cleft lip, cleft palate, congenital central nervous system anomaly, congenital gastric anomaly, congenital cardiovascular anomaly, congenital intestinal malformation)	US-GD-0310567	1		Retrospective	1
Multiple congenital abnormalities: congenital optic nerve anomaly, congenital eye disorder, congenital central nervous system anomaly)	FR19960020	1		Retrospective	1
Aarskog syndrome	FR19970008	1		Retrospective	1
Kidney malformation, single umbilical artery	FR199636045	1		Retrospective	1
Functional anomalies					
Respiratory distress, renal failure, hydronephrosis, anasarca	USCTMX0101		1	Retrospective	1
Others					
Placenta abruptio, fetal death	JP-GDP-0411379		1	Prospective	1
Premature baby	CH-GDP-11412563	1		Retrospective	1
Convulsion, areflexia	FI20000002	1		Retrospective	1
Total		17	2		19

† From Applicant's submitted review, Module 5.3.6., Elisabeth Gnasia, MD, PhD. Review of exposures to topical adapalene gel, cream, lotion during pregnancy. February 2015. Table 3, page 4.

There is no specific pattern among the cases. Case US-GD-0310567 had a cleft lip, which is described in retinoid embryopathy (and is a relatively common birth defect in the absence of retinoid exposure), but the case is otherwise inadequately documented to ascribe the defects to

retinoid exposure. Based on Dr. Gnasia's discussion, the case of optic nerve abnormality appears to be the case of anophthalmia and growth restriction that is discussed in the literature review, below.

Dr. Gnasia did a subgroup analysis of prospectively identified pregnancies. As she pointed out, prospectively reported cases do not suffer from the bias that normal pregnancies are less likely to be reported than those ending up with an adverse outcome. There were 122 prospectively identified pregnancies, 91 in postmarketing surveillance and 31 in clinical trials. Outcomes for these pregnancies appears in the table below.

Outcomes of prospectively identified pregnancies

Pregnancy Outcome	**PMS**	**Clinical trial**	**Total**	**Rate %**
Total	**91**	**31**	**122**	
Elective abortion	2	1	3	2.5
Miscarriage	4	3	7	5.7
Among births	**85**	**27**	**112**	
Healthy BB	83	26	109	97.3
Malformation	2	0	2	1.8
Other Abnormal outcome (abruption placenta and fetal death)	0	1	1	0.9

Source: Module 5.3.6, submitted Sep 10, 2015, Dr. Gnasia's report.

The two malformations were hydrops fetalis and Tetralogy of Fallot; neither are typical of retinoid embryopathy. The rate of major congenital structural malformations in the general population is usually cited as between 2-4%; in this small sample of adapalene-exposed pregnancies, it was 1.6%.

Literature review

I accessed two databases, Reprotox and TERIS, on May 8, 2016. These databases are references for providers who counsel pregnant women.

Reprotox stated that application of adapalene gel to the skin is not expected to increase the risk of congenital anomalies based on animal studies and the small degree of systemic absorption after topical use. The section on human reports included the case report of the pregnancy in which a fetus was found at 22 weeks gestation to have growth restriction, anophthalmia, and agenesis of the optic chiasm.[10] Reprotox points out that the authors of the report noted that anophthalmia and agenesis of the optic chiasm are not abnormalities typically associated with retinoid exposure. A collaborative study from 11 teratology information services reported no increase in major or minor malformations or spontaneous abortion in 235 pregnancies with exposure to topical retinoids.[11] Twenty-four of 235 exposures were to adapalene. No child showed features of retinoid embryopathy. The authors noted that their study was powered to detect a 2-3 fold increase in malformations. Reprotox notes that the quality and completeness of the outcome information in this study was unknown.

TERIS' summary statement was 'Although the risk of this agent is undetermined, a high risk of congenital anomalies in the children of women treated topically with adapalene during pregnancy is unlikely due to its low systemic bioavailability following dermal application.' The bibliographic search date for TERIS was stated as 04/14.

A recent publication performed a meta-analysis of published data regarding the outcomes of topical retinoid-exposed pregnancies.[12] The meta-analysis included 654 pregnant women who were exposed to topical retinoids and 1375 unexposed control pregnant women. No significance increases were detected in the risk of major malformations. (Odds ratio 1.22, 95% CI 0.65-2.29). The authors concluded that the meta-analysis did not suggestion an association between exposure to topical retinoids in the first trimester and the risk of major congenital malformation, but the relatively small sample size did not justify the use of topical retinoids during pregnancy.

Additional literature is summarized in Dr. Raffaelli' s review, including two publications retrospectively looking at physician behavior when prescribing potential teratogens (defined as Category D or X medications) to reproductive-aged females. Both publications found that contraception or counseling was documented in fewer than half of charts.

Advisory Committee Meeting

An Advisory Committee meeting was held on April 15, 2016. The committee included standing members of the Nonprescription Drug Advisory Committee, as well as dermatology and reproductive toxicology experts. The focus of the AC was on the issue of teratogenicity. The AC voted unanimously (16 'yes' and 0 'no') that the safety of adapalene gel 0.1% for OTC had been adequately demonstrated and that the data supported OTC use of adapalene gel

[10] Autret E, et al. Anophthalmia and agenesis of optic chiasm associated with adapalene gel in early pregnancy (letter). Lancet 1997; 350:339
[11] Panchaud A, et al. Pregnancy outcome following exposure to topical retinoids: a multicenter prospective study. J Clin Pharmacol 2012; 52:1844-1851
[12] Kaplan, et al. Pregnancy Outcomes Following First Trimester Exposure to Topical Retinoids: a systematic review and meta-analysis. Br J Dermatol. 2015; 173(5):1132-41

0.1% for acne. Regarding proposed labeling for pregnancy and lactation, 'if pregnant or breast-feeding, ask a (b) (4) before use,' the committee did not reach consensus. Opinions ranged from removing any labeling from the Drug Facts Label (DFL) about pregnancy and lactation to accepting the proposed language, with intermediate positions including modified language or removal of either the pregnancy or the breast-feeding language.

Comment: The proposed DFL statement about pregnancy and lactation is consistent with labeling for other OTC products, and is a reasonable OTC 'translation' of the current Rx labeling. Current Rx labeling does not contraindicate use in pregnancy or lactation, but says 'caution should be exercised when Differin cream is administered to a nursing woman' and 'adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.'

Pediatrics

DNDP issued two consults to DPMH. In the first, DNDP consulted DPMH for an opinion regarding whether adapalene may be used by OTC adolescent consumers safely and effectively without prescriber oversight. DPMH concluded that there appeared to be no safety concerns in adolescents that are distinct from those in older patients. DPMH suggested that DNDP consider expanding pediatric use down to age 9 years: 1) because acne can occur in this age range, and 2) to be aligned with the labels for the combination products, Epiduo and Epiduo Forte. In this consult, DPMH did not opine about reproductive risks, beyond noting that if DNDP decided there were reproductive risks, the drug should remain Rx.

DNDP also consulted DPMH for an opinion related to pregnancy concerns, including teratogenicity. DMPH reviewed the literature and human safety data provided by the Applicant and concluded that 'there is no robust safety signal to clearly establish an association between adapalene and an increase in incidence for major congenital malformations.'

Comment: DNDP considered expanding the age range to 9 years, but decided against it primarily because there were no consumer data for younger children and the applicant was not seeking a broader age range.

Other Relevant Regulatory Issues

The Office of Scientific Inspections (OSI) inspected the contract research organization with a focus on two pharmacy sites involved in the actual use study (Juno trial). No issues impacting data integrity were noted.

Adapalene is OTC in Russia; however, Germany's Expert Committee for Prescription recommended against adapalene 0.1% for OTC use in Jan 2016. The concern in Germany was the potential risk of teratogenicity. Concerns were expressed about the safety margins not taking into account absorption on broken skin or concomitant use of products that could

enhance absorption, simultaneous use of vitamin A-containing dietary supplements, and man as a sensitive species for retinoids.

Comments: While it is true that there could be enhanced absorption on broken skin and simultaneous use with Vitamin A-containing supplements, this can happen in the Rx setting as well as the OTC setting. The long marketing history and the failure to identify retinoid embryopathy (or, for that matter, any of the other serious systemic effects described for retinoids) is reassuring. While there is evidence that man is a sensitive species for isotretinoin,[13] adapalene is not isotretinoin. In animals, adapalene requires a substantially greater dose to elicit teratogenicity compared with tretinoin and tazarotene. See Nonclinical Pharmacology/Toxicology.

Labeling

The label comprehension study assessed the statements 'use once daily' and 'do not use on damaged skin' as primary objectives. A total of 586 subjects ages 12 years and older were enrolled. Overall, performance was satisfactory. In subgroup analyses, the social science review noted that low literates and 12-14 year olds tested lower than normal literates and older participants, respectively. The social science review recommended reinforcing the 'use once daily' message and raised an issue about 'once' meaning 'eleven' in Spanish. The team recommended the text 'use only one time a day' in the Directions section of the DFL.

The team discussed the pregnancy/breastfeeding language at some length and ultimately opted to agree with the applicant about the statement to ask a healthcare provider. As noted in the social science review, to delete the pregnancy statement could imply to consumers that this product is inherently safer than many products on which the statement currently appears. This statement is used on other DFL's for drugs where passage into breast milk is unknown. It would be difficult to say with 100% certainty that any medication is completely safe in pregnancy or lactation, and for that reason reviewing a pregnant/lactating patient's medications (OTC and Rx) is good practice. Discussing with the patient the very low likelihood of risk to the baby against the seriousness of her acne is reasonable.

DMEPA found the name, Differin Gel, acceptable, and the proposed container and carton labeling acceptable from a medication error perspective.

Risk Evaluation and Mitigation Strategies

None.

Postmarketing Requirements and Commitments

Routine pharmacovigilance is recommended.

[13] Nau H. Teratogenicity of isotretinoin revisited: species variation and the role of all-trans-retinoic acid. J Am Acad Dermatol 2001;45:S183-7

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/s/

LESLEYANNE FURLONG
07/07/2016

Deputy Director for Safety Summary Memo

Date	June 21, 2016
From	Tatiana Oussova, M.D., M.P.H.
Subject	Deputy Director for Safety Summary Memo
NDA/BLA # **Supplement #**	NDA 020380/S-010
Applicant Name	Galderma Laboratories, L.P.
Date of Submission	September 10, 2015
PDUFA Goal Date	July 8, 2016
Proprietary Name / **Established (USAN) Name**	Differin (adapalene)
Dosage Forms / Strength	Gel, 0.1%
Proposed Indication(s)	Topical treatment of acne in patients 12 years of age and older. Proposed Rx to OTC switch
Recommended Action	*Approval*

Material Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Amy Woitach, M.D.
Clinical Pharmacology Review	Chinmay Shukla, Ph.D.
Pharmacology/Toxicology Review	Cindy Xinguang Li, Ph.D.

Social Scientist Review	Barbara Cohen, MPA
OND / DPMH / Pediatric Team OND / DPMH / Maternal Health Team	Mona Khurana, MD / John Alexander, MD, MPH Tamara Johnson, MD, MS / Melissa Tassinari, PhD
Post-marketing Review	Lopa Thambi, PharmD, Division of Pharmacovigilance (DPV II) Hongliu Ding, MD, PhD, MPH Division of Epidemiology (DEPI I)

Deputy Director for Safety Summary Memo

1. Introduction

This is a supplemental application to NDA 020380 for Differin (adapalene gel) Gel, 0.1% indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.
This supplement was submitted to DNDP and proposes to switch prescription Differin Gel, 0.1% to over-the-counter (OTC) use. Prescription product currently resides with the Division of Dermatology and Dental Products (DDDP).
All primary reviews have been completed for this application. DDDP clinical reviewer does not recommend approving OTC switch due to potential concerns of teratogenic risk to the fetus. This Memo will briefly summarize the results of relevant primary reviews, clinical team conclusion, my disagreement with clinical reviewer non-approval recommendation and discuss my recommendation for approval. For more detailed reviews of data submitted with this supplement, the reader is referred to primary reviews.

2. .Background

Acne vulgaris is a skin disease that occurs when hair follicles become clogged with dead skin cells and oil from the skin. Acne is characterized by areas of blackheads, whiteheads, pimples, and greasy skin, and may result in scarring. The resulting appearance can lead to anxiety, reduced self-esteem and, in extreme cases, depression or suicidal ideation. Many treatment options are available. Retinoids are considered the first-line therapy and are available in both topical and oral formulations. Oral isotretinoin is usually reserved for severe acne due to potential serious side effects.
The first-generation, non-aromatic retinoids used to treat acne were associated with a relatively high incidence of adverse events, which led to a search for more optimal compounds. Synthetic analogues of the first-generation retinoids were developed as the second-generation, mono-aromatic retinoids. Further modifications resulted in the third-generation, polyaromatic retinoids. Adapalene is a third-generation retinoid derived from naphthoic acid. It is believed to modulate the cellular differentiation, keratinization, and inflammatory processes involved in the pathogenesis of acne vulgaris. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.
Adapalene was first approved as Differin® (adapalene) Solution, 0.1% in France on July 3, 1992 and later in the US on May 31, 1996. Adapalene is currently available in several dosage forms and two strengths:

- 0.1% solution (NDA 20-338), approved 5/31/1996, now discontinued
- 0.1% gel (NDA 20-380), approved 5/31/1996
- 0.1% cream (NDA 20-748) approved 5/26/2000

- 0.3% gel (NDA 21-753), approved 6/19/2007
- 0.1% lotion (NDA 22-502) approved 3/7/2010

There are two combination products containing adapalene as 0.1% (Epiduo) and 0.3% (Epiduo Forte) strength, both available by prescription and indicated for the topical treatment of acne.
There are no topical retinoids available OTC on the US market. Per the applicant, OTC adapalene available only in Russia. Germany was considering approving adapalene for OTC use but the application was not approved due to concerns about the teratogenic risk. Differin if approved would be the first OTC topical retinoid in the US. This would give consumers an important option for an effective topical treatment of acne.
One of the major safety concerns with retinoids is their teratogenic effect on developing fetus. This became the main focus of reviews under this sNDA. Retinoid acid embryopathy is well defined and includes characteristic pattern of malformation involving craniofacial, cardiac, thymic, and central nervous system structures. With oral retinoids, there is a common assumption that there is no dose of a retinoid or a window of exposure during pregnancy that can be considered safe for a human fetus. There are no adequate and well-controlled studies in pregnant women and the data comes mostly from animal studies and from post-marketing surveillance. Less data are available about the risk of topical adapalene to the human fetus.

Prescription Differin is a pregnancy category C drug as are most acne products available OTC. Its prescription label has a warning that it can be used in pregnancy only if potential benefit outweighs the potential risk to the fetus. There are no other warnings in the label related to pregnancy exposure.

To support the OTC switch, the applicant conducted two clinical studies and three additional studies:

1. Maximal use pharmacokinetics trial
2. Actual use study
3. Prescription standard of care study to assess prescribing physician and patient behavior in the Rx environment.
4. Self-selection study in pregnancy and/or breastfeeding women
5. Label comprehension study

Systemic exposure was measured in the maximal use study conducted by the applicant in subjects with psoriasis. Based on this exposure, we were able to calculate the safety margin of adapalene exposure with regards to its teratogenic effect as decribed in sections below.
For more detailed reviews of studies submitted with this application, please, consult their respective discipline reviews.
Adapalene efficacy has been established under the NDA and is not being discussed in this application.

3. CMC/Device

No new CMC data were submitted with this application.

4. Nonclinical Pharmacology/Toxicology

Nonclinical data on the pharmacological and toxicological effects of adapalene was reviewed under relevant NDAs.
No additional nonclinical studies were conducted in support of the Rx-to-OTC switch. The applicant provided a summary of the available pharmacology and toxicology in this sNDA.
In embryo-fetal development studies, adapalene has been shown to induce teratogenic effects in animals at sufficiently high systemic doses.
In a 10-day animal dermal toxicology 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. The human maximal use study with adapalene gel, 0.1% showed that the highest individual human exposure was 2.9 ng·h/mL expressed as AUC_{0-24h} value by one subject at Day 24. These values were used to calculate the safety margin as a conservative measure, instead of utilizing the mean AUC_{0-24h}. The margin of safety for adapalene was calculated to be approximately 70 times (204/2.9) for rats and 357 times (1036/2.9) for rabbits.
Even though animal studies do not always predict human effects, the wide range of safety margins provide sufficient reassurance that the teratogenic risk in pregnancies exposed to Differin Gel, 01% is very small.

5. Clinical Pharmacology/Biopharmaceutics

In support of OTC switch, the applicant conducted a multiple-dose pharmacokinetic study under maximal use conditions to evaluate absorption through the skin in an adolescent and adult population with acne. Systemic absorption was measured at different time points. This study results were used to calculate safety margin of exposure and provided important reassurance about the low risk of teratogenic effect to human fetus.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

Adapalene efficacy has been established under the NDA and is not being discussed in this application.

8. Safety

There are extensive human data accumulated from clinical development program and from millions of uses during 20+ years of product marketing worldwide.

Per applicant submission, a total of 18 pregnancies were reported in clinical development program. No major malformations were reported.
In addition, four subjects became pregnant during a newly conducted Juno Trial (six-week, open label, single arm study) and continued to use the product. One subject did not know she was pregnant until the end of the trial. There was one healthy newborn, two pregnancies were lost to follow-up, and one subject chose to terminate her pregnancy for personal reasons.
In the postmarketing safety database submitted by the applicant there were a total of 332 pregnancies exposed to adapalene products. Fifty-six pregnancies were reported during clinical trials and 276 were reported in postmarketing surveillance. There were 19 abnormal outcomes among 169 known. Those outcomes were reviews by external experts hired by the applicant. None of the outcomes were considered to be retinod embryopathy related to adapalene exposure.

Reviews of AERS postmarketing reported cases conducted by OSE in 2004 and 2006 identified eight cases of adapalene-exposed pregnancies and their outcomes. Current review of FAERS identified five additional cases. Review of those cases of congenital anomaly reported in adapalene-exposed pregnancies appear to be isolated malformations. DPV did not find reasonable evidence to support a causal association between adapalene and these events. They concluded that "Based on a lack of a clear pattern of congenital anomalies consistent with retinoid embryopathy, and a lack of compelling medical literature in FAERS cases and epidemiological data, there does not appear to be a signal for adapalene-associated congenital anomalies at this time".

9. Advisory Committee Meeting

On April 15, 2016 the Nonprescription Drugs Advisory Committee (NDAC) was convened to provide advice on the regulatory decision making process related to the approval of Differin (adapalene gel) Gel, 0.1% for over-the-counter marketing in the US. The Committee universally recommended approval of OTC switch. They agreed that the safety of Differin (adapalene gel) Gel, 0.1% for the treatment of acne has been adequately demonstrated and the totality of the data support the use of this product OTC.
Committee members acknowledged that there is a risk of teratogenicity associated with the product however that risk is minimal and benefits outweigh the risk.
Members of the NDAC could not agree on the labeling for pregnancy. Some members recommended not including a pregnancy warming on the label and some recommended strengthening the warning around pregnancy. Committee suggestions were considered during labeling discussion.
I agree with the inclusion of pregnancy and breastfeeding-related recommendations on the label.

10. Pediatrics

Differin (adapalene) Gel, 0.1% is indicated for use in patients age 12 and above. OTC product would also be indicated for patients aged 12 and older.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues

12. Labeling

The Drug Facts Label for Differin (adapalene) Gel, 0.1%, sufficiently conveys the most important safety and dosing information. The labeling will advise pregnant and breastfeeding women to speak with their doctors before using the drug and to stop use and speak with their doctor if they become pregnant, or plan to become pregnant, while using the drug. It will include the statement "Stop use and ask a doctor if you become pregnant, or are planning to become pregnant, while using the product". The prescription label for Differin Gel 0.1% states that the drug should be used during pregnancy if the potential benefit justifies the potential risks. The label also states that it is unknown if the drug is excreted in breast milk. Even though we believe that the risk to a fetus in exposed pregnancies is minimal, it is important for women who are pregnant or breastfeeding to discuss with their doctors whether the benefit of using Differin Gel 0.1% outweighs any potential risk. The leaflet will provide some information differentiating adapalene from retinoid drugs known to cause birth defects in humans.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action – I recommend this application to be approved.

- Risk Benefit Assessment

The major concern with Differin (adapalene) gel, 0.1% OTC switch is its potential risk of teratogenicity. Differin belongs to a class of retinoids where oral drugs are known for their teratogenic adverse effects on developing fetus. More, there is no dose or exposure window with the use of oral retinoids that is deemed safe. No studies in pregnant woman exist and conducting such studies would be unethical therefore we need to rely on limited data from controlled clinical trials, animal and pharmacologic data and postmarketing safety data if available.

Data available for Differin (adapalene) Gel, 0.1% suggest that the risk of teratogenicity associated with the use of topical adapalene is very low. I considered the following factors while making an assumption that the risk of teratogenicity is minimal.

As it was shown in MuST study, the adsorption through the skin is very low. There are factors that could increase adsorption and those are use on damaged skin, concomitant use of substances or dressings that increase absorption, heavy or frequent application of a product, and application to a larger body surface area.
Even though the absorption might increase due to the above factors, the wide safety margins calculated based on data from MuST study and previously conducted animal studies provide reassurance that the risk continue to remain very low.
Those margins are estimated to be approximately 70 times for rats (considered to be the most sensitive species) and 357 times for rabbits.
Post-marketing safety data from 20 years of prescription use identified a few cases of abnormal pregnancy outcomes in exposed pregnancies with no clear-cut cases of teratogenic effects due to adapalene. Prescription product does not require mandatory pregnancy testing, nor does it require contraception during adapalene use. Therefore, it can be speculated that there were multiple cases of exposed pregnancy among millions of users. We recognize there is a significant underreporting of adverse events in postmarketing settings, however, physicians are well aware that adapalene belongs to the class of teratogenic retinoids, and in case there was a pregnancy outcome suggesting potential retinoid embryopathy, there is a good likelihood that this case would have been reported, given the product has been on the market for over 20 years with millions of uses.
As submitted studies have shown, adapalene would be used by pregnant females but the data available provides us with a high degree of confidence that the risk of teratogenicity with the use of topical adapalene is very low and the benefits would outweigh the risks.
Other adverse events of adapalene including redness, scaling, dryness, itching, and burning will occur in 10-40% of patients as has been shown in clinical trials throughout development program. However those adverse events are reversible upon discontinuation of therapy. Itching or burning immediately after application will occur in approximately 20% of patients, and an apparent exacerbation of acne may occur during the early weeks of therapy. However, these adverse events are not worrisome and can be managed with appropriate labeling.

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/s/

TATIANA OUSSOVA
06/21/2016

Clinical Investigator Financial Disclosure
Review Template

Application Number: 20380/ S-010

Submission Date(s): September 10, 2015

Applicant: Galderma Laboratories, L.P.

Product: Adapalene Gel, 0.1%

Reviewer: Ryan Raffaelli, M.D.

Date of Review: June 15, 2016

Covered Clinical Study (Name and/or Number): Protocol RD.06.SPR.18254 (PK study)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 3		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Clinical Investigator Financial Disclosure
Review Template

Application Number: 20380/ S-010

Submission Date(s): September 10, 2015

Applicant: Galderma Laboratories, L.P.

Product: Adapalene Gel, 0.1%

Reviewer: Ryan Raffaelli, M.D.

Date of Review: June 15, 2016

Covered Clinical Study (Name and/or Number): Protocol 13049: Juno Trial

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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/s/

RYAN M RAFFAELLI
06/15/2016

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	20380/S-10
Priority or Standard	Standard
Submit Date(s)	September 10, 2015
Received Date(s)	September 10, 2015
PDUFA Goal Date	July 10, 2016
Division / Office	DNDP/ ODE IV
Reviewer Name(s)	Ryan Raffaelli, MD
Review Completion Date	June 9, 2016
Established Name	Adapalene Gel, 0.1%
(Proposed) Trade Name	Differin® Gel
Therapeutic Class	Naphthoic acid/Retinoid
Applicant	Galderma Laboratories, L.P.
Formulation(s)	Topical gel
Dosing Regimen	Once daily
Proposed Indication(s)	Acne treatment
Intended Population(s)	12 years and older

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

Clinical Review
Ryan Raffaelli, M.D.
NDA 20380/S-010 (Differin® Gel (adapalene) 0.1%)

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This is the clinical review evaluating Galderma Laboratories' supplemental NDA to switch Differin® Gel (adapalene) 0.1% from prescription (Rx)-only to over-the-counter (OTC) marketing status. If approved, the 0.1% gel formulation will be fully switched for the same indication as approved for Rx use, treatment of acne. Two other topical adapalene formulations, lotion and cream, a higher strength product, 0.3%, and a combination product, Epiduo® (adapalene/benzoyl peroxide), will remain available by prescription only. Based on this reviewer's evaluation of the data, **I recommend, from the clinical perspective, approval to allow Differin® Gel (adapalene) 0.1% to be marketed in the OTC setting for treatment of acne in adults and children > 12 years of age**. This recommendation is contingent on the applicant's acceptance of labeling revisions to support safe and proper use in the OTC setting.

The specific focus of this review, and major contribution to the final recommendation on approval, is the Actual Use Trial (Project Juno, "Juno Trial;" Protocol 13049). That trial provided significant evidence that consumers are both unlikely to overuse the product, and likely to only apply the product to acne-involved skin. Notably, pregnant women appear likely to use the product regardless of any label warning to seek the advice of a healthcare professional before use, and absent any warning to stop use and seek medical advice if users become pregnant while using it. Details on the actual use trial are found in **Sections 6 Review of Efficacy** and **7 Review of Safety**. While FDA considered an actual use trial necessary to support this application, our greatest concern during development of this product for OTC use regarded the decisions made by pregnant women who might choose to use this retinoid-like product and potentially risk congenital effects with embryonic exposure. These decisions are better evaluated in label comprehension and self-selection studies. We also reviewed postmarketing safety data submitted by the applicant and requested a consult review by divisions within the Office of Surveillance and Epidemiology to assess the evidence of teratogenicity due to use of adapalene in the Rx setting.

Use of some oral (isotretinoin) and topical retinoid drug products (tazarotene) are contraindicated in pregnancy. Other topical retinoids, or a retinoid-like product such as adapalene (Pregnancy Category C), are not contraindicated in that population, but cautious use is recommended where the benefits outweigh the potential risks. This often follows thoughtful discussion between the patient and a learned intermediary in the Rx setting. Since OTC availability of a retinoid-like drug such as adapalene removes the learned intermediary from the point-of-purchase decision to buy and use the drug, it is necessary to understand how well labeling is comprehended and adhered to and whether risk can be sufficiently mitigated such that this drug available OTC can be used safely and properly by consumers. There are OTC drugs identified as

Pregnancy Category C (i.e., evidence exists of teratogenic effect in animals, but no controlled trials in humans; e.g., guaifenesin and bismuth subsalicylate) or D (i.e., evidence exists of teratogenic effect in humans, but the benefits may outweigh the risks; e.g., non-steroidal anti-inflammatory drugs (NSAIDs) used in third trimester)[1]. The nonclinical data available for adapalene provided evidence of a wide exposure margin by the oral and topical route, but no adequate trial had been conducted to evaluate systemic exposure in humans following maximal usage as defined in recent literature[2]. Thus, that trial was conducted to support Galderma's supplementary application and the data supported a wide exposure margin, i.e., maximal exposure (a single outlier with exposure approximately 3.5 fold higher than the mean) supported a 70 fold margin. Regarding teratogenic potential, it is unclear how sensitive humans may be to adapalene, since no controlled trials have been conducted to investigate, or how well the animal data predicts effects in humans, although, the margin of exposure is wide. Therefore, this reviewer concludes that data combined from the biochemistry of the adapalene compound, i.e., how it differs from true retinoids, nonclinical development of the drug substance, a maximal usage pharmacokinetics trial and the determined exposure, or safety, margin, consumer behavior data (label comprehension testing, self-selection study and actual use trial) and postmarketing safety data provide support for the safe use of this product by pregnant women in the OTC setting. For details, see the relevant subject matter specific reviews and **Section 9.3 Advisory Committee Meeting** where a unanimous (16-0) decision supporting approval was made following a thorough review and discussion of the available data. Note that the Committee's decision was also contingent on the applicant revising the Drug Facts labeling to reflect all of the important warnings, precautions and directions to support safe and effective use. This reviewer agrees (see **Section 9.2 Labeling Recommendations**).

If the consensus opinion is that labeled use of adapalene by pregnant women in the OTC setting is not a safety concern with regard to congenital effects, then the only other safety consideration is for skin-related effects. Adapalene users are instructed to avoid applying the product to damaged skin, near mucus membranes, if skin is unprotected from sun or ultraviolet light exposure and if other topical acne medications are used concomitantly. The reason for the warnings is to limit the risk and extent of skin irritation; however, the remedy is to simply stop using the product and to see a healthcare professional if irritation persists or is severe. Such a warning is well understood by OTC drug consumers and a reasonable method to limit the risk. Since acne is not a serious medical condition requiring management to limit risk for morbidity or mortality, stopping use and seeking an alternative treatment is a simple mitigation. There are several retinoid and non-retinoid topical and oral products similarly indicated to treat the range of acne severity.

[1] Black RA, DA Hill, 2003, Over-the-counter Medications in Pregnancy, *Am Fam Physician*, 67(12): 2517-2524.
[2] Bashaw ED, DC Tran, CG Shukla, X Liu, 2014, Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products, Ther Innov Regul Sci, 49: 108-115.

1.2 Risk Benefit Assessment

Acne is a pervasive dermatologic condition resulting from various mechanisms, e.g., androgen effects, neuropeptide activity, and environmental or genetic factors contributing to hyperseborrhea, an epithelial hyperproliferation in the sebaceous duct, and stimulated development of comedones and inflammatory lesions. Bacterial strains of Propionibacterium acnes (P. acnes) stimulate cytokine synthesis maintaining inflammation on the skin surface. Acne begins in the post-pubertal period with prevalence peaking in adolescence and high rates maintained throughout the 3rd decade of life. Up to 40% of cases may persist beyond age 25, particularly for women. Clearly, any teratogenic risk must be heavily considered since this includes the population of women of childbearing potential. Some exogenous factors may also contribute to acne severity, including use of hormone treatments, sports participation, nicotine use and poor glycemic control. The natural history of acne is gradual development of visible disease lasting months, or up to a year, followed by occasional flares and slow regression into the 3rd decade of life. Because acne is a chronic, recurring disease, maintaining suppression of microcomedone formation with topical retinoids, for example, is deemed effective. Severity of disease can vary and, in worst cases, can result in permanent facial scarring. Increased severity of disease can have a significant psychological impact and improved access to an effective acne treatment could have a significant public health impact as well.

With regard to the efficacy of adapalene, to support approval of the original NDA, the applicant conducted five controlled clinical trials comparing the product to the vehicle or an active control, tretinoin gel, 0.025%, in subjects with mild to moderate acne vulgaris. Other trials compared the product with isotretinoin gel as well, demonstrating significant improvement of both noninflammatory and inflammatory acne lesions compared to the vehicle. Under typical design as well-controlled trials investigating acne treatment, improvement of acne lesions was assessed at 12 weeks. There were no new efficacy trials required for this proposed switch to OTC marketing status, and the efficacy of the product is not questioned here.

The Juno actual use trial was conducted to assess use behaviors of acne sufferers in a naturalistic setting. It was a 6-week, open label, multi-center (N= 31 geographically dispersed pharmacy sites) trial in subjects self-reporting acne. Subjects (N= 1277) entered the trial and 947 were included in the actual use population – those who gave informed consent/assent, purchased the drug and applied at least one dose. The trial demonstrated a successful proportion of correct use by the primary and main secondary endpoints for the trial's user population overall. In the population, 65% of enrollees were female, 68% of eventual users were female, and 76% of the female users were of childbearing potential. The mean age of users was 29.9 years with the population made up of acceptable proportions of adolescents (21.4%) and users with acne and eczema (1.5% - to evaluate potential for off-label use). The proportion of low literacy subjects was lower than recommended (13.8% - adults; 10.8% - adolescents), but did not appear to have a significant impact on the results. The eligibility criteria were appropriate,

including my assessment of those subjects excluded from the use phase of the trial at the investigator's discretion (i.e., subjects who might have been harmed or who were unlikely to follow the trial procedures).

All rates of correct use were above the *a priori* success thresholds and there were no clinically relevant differences in usage rates by relevant subgroups (age, gender, literacy). The primary endpoint assessing once daily use on the same skin location found 89.1% of subjects doing so. Over 99% (more precisely, 99.3%) of subjects used the product only on sites of acne, another primary endpoint, and 97.5% (secondary endpoint) used the product on undamaged skin and avoided eyes or mucus membranes (lips, mouth). Mitigations were reasonably applied by the applicant. With regard to incorrect use by the major endpoints, 43% (N=44) of misusers reported that they misused (applications > once daily) to seek greater or faster benefit, or to treat subjectively "severe" breakouts. Only seven subjects reported using the product on non-acne conditions (e.g., psoriasis, skin discoloration). Seven subjects were identified as applying the product "like a lotion, all over the face." Regarding clinically relevant subject eligibility to enter the use phase of the trial, nine subjects did not report having acne, six were < 12 years of age, 10 were pregnant or breastfeeding and 25 were excluded based on a variety of reasons under the Investigator's judgment. None of the reasons for exclusion raised safety concerns regarding OTC availability of the drug. Use in pregnancy and additional safety considerations are addressed in greater detail below and in **Section 7 Review of Safety**.

There were some important limitations in the design of the Juno trial, but none raise concern for this reviewer that could not be addressed in labeling. Actual use trials are not true measures of use in the OTC setting, but can provide a window into how a product is *likely* to be used by the general OTC consumer. The Juno trial was only six weeks in duration, providing a somewhat limited picture of how consumers are likely to use the product, particularly pregnant users. A final limitation of the trial was that it was not, as the applicant contended, a true "all comers" trial. The recruitment and advertising material was focused on acne sufferers. If the product is approved, it is reasonable to assume that acne sufferers will be the target of advertising and product placement on pharmacy shelves will have that same focus, but for the purpose of evaluating off-label use or misuse on non-acne skin conditions, the Juno Trial was lacking. While an assessment of off-label use potential may be limited, and the product likely to be used by OTC consumers for a variety of skin conditions, the quantity and duration of use may also be limited by lack of efficacy, adverse skin-related events and small tube sizes at premium OTC pricing, at least in the short term before a market for generics emerges.

European Guidelines[3] and the American Academy of Dermatology[4] (AAD) strongly or moderately recommend adapalene, as first line monotherapy for mild comedonal acne,

3 Nast A, B Dreno, V Bettoli, K Degitz, R Erdmann, AY Finlay, et. al., 2012, European Evidence-based (S3) Guidelines for the Treatment of Acne, *J Eur Acad Dermatol Venereol*, 26 (Suppl 1): 1-29.
4 Zaenglein AL, AL Pathy, BJ Schlosser, A Alikhan, HE Baldwin, DS Berson, et. al., 2016, Guidelines of

or in combination with benzoyl peroxide and/or topical/systemic antimicrobials, as first line treatments for comedonal and moderate to severe inflammatory, papulo-pustular acne. Adapalene is the preferred topical retinoid where those types of drugs are indicated. The recommendations highlight the efficacy and safety profile of adapalene as its availability is considered for use in the OTC setting for treatment of acne. Notably, while the AAD advises that female patients be counseled on pregnancy risks before healthcare providers prescribe adapalene and identifies treatment of acne in pregnant women as a research gap, Gollnick, et. al., citing the European Guidelines in making recommendations for treatment of acne, in a blanket statement, advised that no topical retinoid products be used by women during pregnancy[5].

In the Juno trial, several subjects were pregnant when they sought to purchase the product. Five of nine pregnant subjects incorrectly said "Yes" to the purchase question, i.e., they did not indicate, as per the label, that they would seek medical advice prior to use. During the trial, four subjects became pregnant and continued using the product. None spoke with their doctors about using adapalene during pregnancy, however, the proposed labeling does not include and instruction to do so. One did not know she was pregnant until the end of the trial, one subject chose to terminate her pregnancy for personal reasons and one subject had already applied her last dose so she chose not to discuss use of the drug. Based on available information, one healthy newborn was born, but the remaining two pregnancies were lost to follow-up. See comments in **Section 1.1 Recommendation on Regulatory Action** with regard to pregnant women using adapalene in the OTC setting.

There appears to be a wide exposure margin and a lack of evidence (case reports, controlled trials or postmarketing experience) of a critical exposure threshold for congenital effects in humans. However, an assessment of likely exposure to the drug in the OTC setting could be informative to further support safe use. With regard to usage in the clinical trials, subjects in the MUsT applied an average of 1.95 g per day (~ ¾ tsp) over an average body surface area of 1865.7 cm^2. Extended over the 29 day duration of that trial, usage would average 56.5 g (1 ¼ tubes) applied over approximately 10% body surface area (average BSA for adult males and females ranges 16000-19000cm^2; thus, 1865.7 cm^2 is about 10-11% BSA). Note that systemic exposure, and, hence, the exposure margin, followed from the instructions for application of adapalene in the MUsT. In the Juno trial, I estimate that subjects averaged about 0.6 g applied per day. Based on weights of returned tubes at the end of the trial, subjects averaged about 24.3 g used in the use phase of the trial. Nearly 94% of subjects only used the contents of one tube of the product. Subjects remained in the trial for a mean of 41.4 days, with over 93% staying in the trial for at least five weeks. Thus, 24.3 g used over 41 days is approximately 0.6 g of product applied daily, or about 30% of the average daily usage evaluated in the MUsT (1.95 g/day). Thus, based on likely use in the OTC setting, the

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Care for the Management of Acne Vulgaris, *J Am Acad Dermatol*, http://dx.doi.org/10.1016/j.jaad.2015.12.037.
5 Gollnick HP, CC Zouboulis, 2014, Not All Acne is Acne Vulgaris, *Dtsch Arztebl Int*, 111: 301-312.

margin appears widened even further. Additionally, there were no major differences in mean quantity used by age, gender or literacy.

Only 6.4% (N= 61) of users purchased more than one tube of the product and only four subjects purchased the maximum of three tubes over the duration of the trial. With proposed package quantities of 15 g and 45 g, **this reviewer recommends that approval of adapalene also be contingent on availability of a 45 g tube maximum to help maintain the exposure margin by limiting the opportunity for overuse, e.g., by application over large BSA.** Regarding pregnancy exposures in the Rx setting, 239 instances are contained within the applicant's pharmacovigilance database. Very few congenital malformations are reported and none describe the pattern of major malformations consistent with retinoid embryopathy (ear malformations, cleft palate, micrognathia, conotruncal heart defects, ventricular septal defects, aortic arch malformations and brain anomalies).[6] With an estimated annual rate of 2-4% of major congenital malformations reported in the United States,[7,8,9] it would be difficult to determine any degree of causality between using adapalene and sporadic reports without evidence of the recognized pattern. The applicant also commissioned a medical geneticist's review of pregnancy exposures reported to the applicant. She concluded there was no suggestion or evidence that use of adapalene was associated with any pattern of anomalies. Nor did reviews of available postmarketing safety databases (FAERS, WHO) identify any pattern of congenital anomalies. This reviewer finds that labeling can adequately communicate the caution that should be reasonably exercised by pregnant women who are determining whether it is okay to first use, or continue to use adapalene (**Section 9.2 Labeling Recommendations**).

The applicant estimates that over 40 million patients have been prescribed adapalene gel at strengths of 0.1% or 0.3% since its international birthdate in 1992. This provides a denominator to weigh the impact of the postmarketing safety experience of adapalene used in the Rx setting. From 1998 through 2014, 4176 postmarketing safety reports were submitted by users (~235 reports/year), with skin-related AEs accounting for 70% of those reports. In total, only 70 reports (1.6%) were serious. With regard to skin-related events, the most frequently reported AEs were "dry skin" and "erythema" (25-30% of AEs). Another small number of cases (N=48) suggested some degree of possible photosensitivity. These included skin irritations or burns following sun exposure. The events were generally local, mild and, where reported, resolved on their own. The applicant also conducted a search of possible drug interactions between adapalene and topical acne drug products containing sulfur, resorcinol or salicylic acid,

6 Lammer EJ, DT Chen, RM Hoar, ND Agnish, PJ Benke, JT Braun, et. al., 1985, Retinoic Acid Embryopathy, *N Eng J Med*, 313 (14): 837 – 841.
7 CDC, 2008, Update on Overall Prevalence of Major Birth Defects – Atlanta, Georgia 1978 – 2005. *MMWR Weekly*, 57 (1): 1-5.
8 Nelson K, LB Holmes, 1989, Malformations Due to Presumed Spontaneous Mutations in Newborn Infants, *N Eng L Med*, 320 (1): 19-23.
9 Correa A, JD Cragan, JE Kucik, CJ Alverson, SM Gilboa, R Balakrishnan, et. al., 2007, Reporting Birth Defects Surveillance Data 1968-2003, *Birth Defects Res A Clin Mol Teratol*, 79 (2): 65-186.

since caution, noted in adapalene Rx labeling, is recommended with concomitant use. It identified 50 cases of exposure. As expected, the cases included frequently reported events such as dry skin, irritation and erythema. There were 34 reports of off-label use with the most frequent number of reports for use to "brighten," "lighten," or "whiten" the skin (N=8). None of the off-label uses were serious and no AEs, overall, raised any safety issues.

With regard to other safety data resulting from the clinical trials (Juno trial and MUsT) conducted to support this application, there were no serious adverse events, deaths or discontinuations due to events that raised any clinical concern as to the safety of adapalene used in the OTC setting. There were no important differences in the event reporting by age or gender. Most events (88%) in the Juno trial were mild, although 49.7% of subjects reported at least one, with the most common being headache, dry skin and erythema. Skin-related events accounted for four of the top seven Preferred Terms reported. Notably, none of the seven highest quantity users (> 91 g) reported any skin-related events. Only 2% of users reported applying the product to damaged skin or non-acne sites and 3% reported sunburn. Nearly all reported events by these subjects were mild and many noted that continuing application of the product did not worsen skin irritations. Most recognized, through labeling, that adapalene may be irritating during the first few weeks of use.

This reviewer concludes that the benefit-risk profile is favorable for approval to switch adapalene gel 0.1% to OTC marketing status. In an abundance of caution, without evidence of known, or probable, congenital risks that would preclude marketing the product OTC, this reviewer finds that labeling can guide pregnant women to use the product safely. Labeling can also guide users to properly seek medical advice if skin irritation, representing the most commonly reported adverse events, persists or becomes severe. If adapalene is approved in the gel form, there are considerations that must be made as other retinoid products are brought forth with applications for OTC switches. Some formulations of topical retinoid drug products, i.e., creams, lotions or ointments, may have greater systemic exposure under maximal usage conditions, or over large BSA, and the differential risk with pregnancy exposure must be considered on the basis of each individual drug's nonclinical, pharmacokinetic and clinical safety profile. Finally, because acne is a potentially chronic and recurring condition, the potential risks with long term exposure to retinoid drug products were taken into consideration when this reviewer assessed the benefit-risk profile of this product and recommended labeling.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

Adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid) is a naphthoic acid derivative with retinoid-like and anti-inflammatory properties. It is a receptor-selective retinoid analogue binding preferentially to retinoic acid receptor beta (RAR-β), and retinoic acid receptor gamma (RAR-γ), the latter predominantly expressed in the epidermis. Topical adapalene is purported to normalize the differentiation of follicular epithelial cells, resulting in decreased microcomedone formation.

Acne is a common dermatologic condition and its topical treatment is a well-established OTC indication. Topical products including benzoyl peroxide, resorcinol and resorcinol monoacetate (when combined with sulfur), salicylic acid and sulfur alone are allowed for use under a Final Monograph (21 CFR 333, Subpart D). The applicant posits that adapalene is a safe and effective acne treatment with labeling that would support safe and proper use in the OTC setting.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple prescription-only (Rx) and over-the-counter (OTC) topical (Rx and OTC) and systemic (Rx only) drug products available for treatment of acne (**Table 1**). **Table 2** shows the comparative dermatologic and antimicrobial safety profiles of some commonly used topical acne therapies. Notice that adapalene appears to be the least irritating of the listed nonantimicrobial products. Frequently, several of these products are used in combination, depending on the severity, type and extent of acne, the availability of treatments, and the prescribing physician's preference.

Table 1: Available Rx and OTC Drug Treatments for Acne Vulgaris

Ingredient/Treatment Class	Drug Product
Topical	
Benzoyl peroxide	Several products
Salicylic acid	Several products
Azelaic acid	Several products
Antimicrobial/ keratolytic	Sulfur, Sulfur/resorcinol
Sulfa products	Sulfacetamide, Sulfacetamide/sulfur
Antibiotics	Clindamycin, Erythromycin
Retinoids	Adapalene, Tazarotene, Tretinoin
Systemic (oral)	
Antibiotics	Erythromycin, Doxycycline, Tetracycline, Minocycline
Retinoids	Isotretinoin
Oral contraceptives	Several products

Table 2: Common Side Effects of Some Topical Acne Therapies

Drug	Erythema	Sting/ Burn	Desquamation	Xerosis	Bacterial Resistance
Tretinoin 0.05%[1]	+++	++	++	++	-
Tretinoin 0.025%[1]	++	++	+	+	-
Adapalene	**+**	**+**	**+**	**+**	**-**
Azelaic acid	(+)	++	-	+	-
Benzoyl peroxide 2.5%[2]	+	+	+	++	-
Benzoyl Peroxide 5%[2]	++	++	+	++	-
Erythromycin[3]/ Clindamycin[3]	-	-	-	-	+++/ ++(+)

Source: Modified from Table 3, p. 5 (Gollnick, et al. (2014))
[1]Newer formula ions are less irritating
[2]Newer formula ions are less irritating
[3]Resistance occurs with monotherapy; ( ) uncommon

2.3 Availability of Proposed Active Ingredient in the United States

Adapalene is approved as an Rx product for the topical treatment of acne vulgaris in patients 12 years of age and older. The applicant has marketed the following:

- 0.1% solution (NDA 20338) – approved May 31, 1996; withdrawn (effective June 16, 2006)
- 0.1% gel (NDA 20380) – approved May 31, 1996; subject of this efficacy supplement for OTC marketing status
- 0.1% cream (NDA 20748) – approved May 26, 2000
- 0.3% gel (NDA 21753) – approved June 19, 2007

- Adapalene 0.1%/ benzoyl peroxide 2.5% gel (NDA 22320) – approved December 8, 2008
- 0.1% lotion (NDA 22502) – approved March 17, 2010
- Adapalene 0.3%/ benzoyl peroxide 2.5% gel (NDA 207917) – approved July 15, 2015

2.4 Important Safety Issues with Consideration to Related Drugs

Adapalene, though structurally distinct from retinoic acid, is considered a retinoid since it acts at retinoic acid receptors (see **Section 4.4 Clinical Pharmacology**). Humans appear to be highly sensitive to 13-Cis-retinoic acid (isotretinoin) and its teratogenic effects (see discussion in **Section 1.2 Risk Benefit Assessment**). Drugs in the same class as isotretinoin are related to retinol (vitamin A) which contributes to vision, reproduction and development and epithelial cell differentiation and turnover[10]. Professional guidelines recommend retinoids as first line therapies for all severities of acne, either alone or in combination with other topical or oral agents for more severe disease. Of the retinoids, only tazarotene and isotretinoin are known to cause birth defects in humans. Oral isotretinoin prescriptions require including a medication guide and registry with a pregnancy prevention program as part of a Risk Evaluation and Mitigation Strategy (REMS).

Retinoids are known skin irritants and teratogens. Use of these products may also make for heightened sun sensitivity because the products may decrease the number of protective layers of stratum corneum. Further, sun protection is important because retinoids are known to increase tumorigenic risk in animals following ultraviolet light exposure. While the significance of these findings in humans is unknown because photocarcinogenicity trials have not been conducted, animal studies may not be predictive, and human sensitivity to the drug is unknown, labeling recommends that sun and artificial ultraviolet light exposure be minimized or avoided.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Galderma and FDA have interacted on several occasions to support development of adapalene for OTC marketing status. Those interactions are summarized below:

On March 12, 2013, FDA held a Pre-IND meeting with Galderma to discuss overall development. FDA advised the applicant conduct several studies including label comprehension, self-selection, actual use and a pharmacokinetics assessment under maximal usage conditions, a MUsT. FDA specifically requested that warnings against use in pregnancy and for sun avoidance be tested in label comprehension. FDA raised concerns about teratogenicity and carcinogenicity potential as identified in animal studies and postmarketing experience for retinoid drug products. FDA advised that the applicant test selection decisions by pregnant women, women seeking to become

10 Nau H, Retinoid Teratogenesis: Toxicokinetics and Structure-specificity, HM Bolt et. al. (eds.), Archives of Toxicology: Use of Mechanistic Information in Risk Assessment (Vol. 16), p. 118-127.

pregnant and women of child-bearing age, also requesting information on usage and counseling of these women in clinical practice (e.g., prescribe oral contraceptive drugs, advise to stop use if become pregnant, avoid prescribing if pregnant). FDA advised the applicant primarily test adherence to the approved indication, thus identifying extent of possible off-label use for wrinkles or other skin lesions, for example; and could address concerns about accidental or non-accidental overuse, by quantity used, body site, frequency of use and duration of use. FDA also requested data from postmarketing experience from various sources with particular focus on teratogenicity (retinoid embryopathy), fetotoxicity and carcinogenicity.

On January 6, June 30 and October 22, 2014, FDA offered further advice on studies. We stated that, if Galderma chose not to conduct the targeted self-selection study to assess decisions in the context of pregnancy, it would need a strong rationale supporting their decision and addressing the risk of teratogenicity. The applicant was encouraged to enrich the study with enough women of reproductive age, pregnant women and female adolescents so that conclusions could be interpreted adequately. We repeated that systemic exposure data were missing or inadequate to support safe use of the product by adolescents (not enrolled in PK trials) and over larger body surface areas (larger than 1000 cm^2 or 15% BSA). We advised that a minimum of 16 subjects from 12 to 17 years of age be enrolled in any MUsT.

Reviewer's comments: The applicant conducted all requested trials. On July 10, 2014, the applicant submitted a protocol to open an IND, "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." That trial was considered safe to proceed.

We advised that off-label usage would need to be a primary objective in the actual use trial. Therefore, the protocol should incorporate an "all-comers" recruitment approach, versus targeting acne patients, and adequate documentation procedures on the extent of application, frequency, duration and reasons for use. A cohort of eczema patients needed to be recruited. Note that on June 13, 2014, the applicant submitted a protocol for their actual use trial, Study 13049 "Actual Use Study for Adapalene Gel, 0.1%." FDA's recommendations on the initial protocol were sent on October 22, 2014 and the applicant submitted a revised protocol on November 18, 2014.

On June 10, 2015, FDA and the applicant held a pre-NDA meeting to discuss content and format of an application and the studies and trials that had been conducted. FDA began by raising doubt as to the acceptability of adapalene for OTC marketing status due to its retinoid-like behavior. The applicant was tasked with providing a very strong, well-supported rationale that the product could be used safely and properly in the OTC setting. There were several deficiencies noted in the protocol for the actual use trial, namely a missing pre-specified analysis of women excluded due to pregnancy, no clinical justification for the thresholds established to determine the primary objectives, diaries lacking adequate space to document extent of product application and

description of site where product was applied, no recording of concomitant acne treatments and no procedure to document reasons why subjects chose to use the product. FDA noted that some key safety language was not translated from the Rx to OTC label. FDA also stated that any claim (b) (4) would require additional clinical data to support it. Finally, FDA expressed concerns about some mitigations for certain endpoints. We noted that the acceptability of mitigations would be a review issue.

Reviewer's comments: Galderma commented on each of the above deficiencies and addressed them in the application. The firm did not pursue a claim (b) (4) *maintaining both the original approved Rx claim for treatment of acne and a proposed claim consistent with the Final Monograph for topical acne products, "clears up acne pimples and acne blemishes."*

FDA informed Galderma that only the gel formulation was supported by data from a MUsT and that without similar data to support an application for the 0.1% lotion and 0.1% cream formulations, fileability of the application would be an issue if the applicant chose to pursue a switch to OTC status for all three formulations. The Integrated Summary of Safety needed to address the teratogenic risks. Datasets would be submitted for all studies and trials conducted.

2.6 Other Relevant Background Information

Adapalene gel 0.1% is approved for Rx use in many countries worldwide including the United Kingdom, Canada, Japan and Australia. In 2001, the product was approved for OTC use in Russia for adults and children 12 years of age and older.

Reviewer's comments: Upon filing the supplementary application, FDA asked the applicant to provide English translation of labeling for the OTC product marketed in Russia. The applicant submitted the translation by email on December 4, 2015. It appears to be an insert provided in the package.

Labeling for the Russian version of adapalene identifies the ingredient as a "metabolite of retinoid." While the labeling also states that absorption is low, it is not recommended for use during pregnancy. Russian labeling for OTC use differs generally from the U.S. Drug Facts in that it contains more specific pharmacology and safety information. In addition to the caution against using the product when pregnant, labeling differs from the proposed Drug Facts in the following ways:

Russian Labeling	Proposed U.S. Labeling
1) Users are instructed to apply once daily at bedtime; label recommends using other acne treatments during the day if necessary 2) Labeling provides a 4-8 week expectation of visible effect, with a statement that sustained benefit may be observed after three months of treatment 3) It is labeled as safe for use during breastfeeding, but "in order to avoid contact exposure with the child," it is not recommended to apply gel to the breast. 4) Labeling recommends users to avoid using cosmetics with drying and irritating effects	1) No instruction to use only at bedtime 2) A proposed insert states that (b) (4) 3) Women who are breast-feeding are instructed not to use before speaking with a (b) (4) 4) No warning about using nonacne treatments with drying or irritating effects

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the quality of the submission was adequate. It was reasonably well-organized and labeled, and the hyperlinks were in working order and accurate. At our request, the applicant submitted timely minor amendments to the application when needed for review. The datasets supporting the final report for the Juno trial contained all required data and the integrity of the data appeared without question.

3.2 Compliance with Good Clinical Practices

The central Institutional Review Board (IRB), (b) (4) approved the protocol, advertising and recruitment materials, Informed Consent/Assent, and all pharmacy sites contracted to conduct the Juno trial. The applicant asserts that all trial procedures complied with Good Clinical Practice Guidelines and principles under the Declaration of Helsinki, as well as all applicable laws and regulations. The final versions of the Informed Consent and Assent forms and Case Report Forms were adequate and without biases. There were no protocol violations reported. There was one protocol amendment that did not significantly alter the design of the trial.

Reviewer's comment: The Informed Consent and Assent forms appropriately disclosed all potential risks associated with use of adapalene gel.

On November 13, 2015, DNDP consulted the Office of Scientific Investigations to conduct an audit of the Juno trial. We identified two pharmacy sites and the headquarters of the Contract Research Organization (CRO), (b) (4) The CRO processed and stored all data and records from the Juno trial. Two sites with highest enrollment were audited, #17 (Kroger, Houston, TX; 80 subjects) and #28 (Ralph's, Los Angeles, CA; 88 subjects). A sample of records at two additional sites was also reviewed (#05 and #13). No action was indicated, based on the review, whereby no significant violations or major deficiencies were identified that would have impacted the conduct of the trial or the integrity of the data submitted.

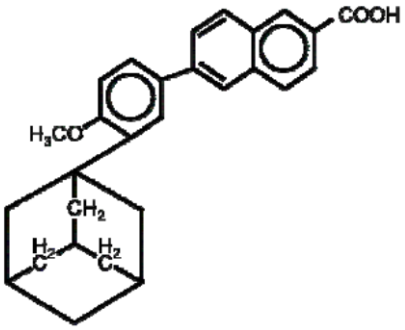
3.3 Financial Disclosures

There do not appear to be any financial relationships between the applicant and the trial sites, or CRO that could have impacted the conduct or results of the Juno trial submitted to support this supplemental NDA. FDA Form 3454 was submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Adapalene has the molecular formula $C_{28}H_{28}O_3$ and the following structural formula:



The formula differs from retinoic acid by replacement of double bonds with naphthoic acid aromatic rings, increasing stability. The applicant notes that the phenoxy adamantyl portion of the molecule results in decreased systemic exposure. There are no proposed changes to the drug substance, drug product or container closure

compared to the product currently marketed under the NDA, and no Module 3 is submitted. Table shows the composition of the drug product.

Table 3: 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		

Source: Applicant's submission; Module 2.3.P, Table 1

The applicant proposes to market the product as a 2 gram consumer sample tube, and in market-size tubes of 15 grams and 45 grams. The Office of New Drug Quality Assessment finalized their review, recommending approval, on April 29, 2016 and May 16, 2016. A categorical exclusion from an environmental assessment was granted. The approval recommendation followed submission of revised labeling with required storage conditions and no proposed changes to the drug substance or product that had been originally approved.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

Dr. Cindy Li's nonclinical review was finalized on June 6, 2016. The applicant submitted no new nonclinical data. Dr. Li determined that there are no data impeding the approvability of the product for OTC use, although, as also stated elsewhere in this review, the level of exposure in humans required to cause teratogenicity, and the predictive capacity of animal data to predict risk to humans, are unclear. Adapalene is

well characterized pharmacologically, without specific nonclinical pharmacology, carcinogenicity, mutagenicity or reproductive toxicity studies required to support this supplemental application. The applicant relies on prior studies conducted to support the original NDA. As per the Rx label, no teratogenic effects were seen in rats at oral doses of adapalene up to 5 mg/kg/day, 120 times the maximal daily topical dose in humans. By the cutaneous route, teratology studies in rats and rabbits up to 6 mg/kg/day, 150 times the maximal daily topical dose in humans, showed no fetotoxicity and only small increases in supernumerary ribs in rats. There are no well-controlled trials of teratology in humans. As noted in **Sections 1.1 Recommendation on Regulatory Action** and **1.2 Risk Benefit Assessment**, this nonclinical data in concert with data from the MUsT provide a level of confidence in the safety of the drug available in the OTC setting.

Prescription labeling describes studies conducted to assess topical and oral exposure with doses up to 75 times the maximal daily human topical dose. In an oral study in rats, follicular cell adenomas, thyroid carcinomas and pheochromocytomas had dose-related increasing incidence. No photocarcinogenicity studies have been conducted with adapalene, but when retinoids and UV radiation are combined, animal studies demonstrate increased tumorigenicity. It is not clear how this data translates to informing risk in humans.

Another OTC topical acne product has raised concern in the past regarding carcinogenic potential. Benzoyl peroxide is allowed under a final monograph to treat acne in products with concentrations ranging from 2.5 to 10% (75 FR 9767; March 4, 2010). Assessment of its carcinogenic potential and continued OTC availability of products containing the ingredient deserve further discussion. In 1991, a Proposed Rule (PR) was issued re-categorizing benzoyl peroxide as category III (more data needed) due to safety concerns. Available information at that time suggested that benzoyl peroxide may initiate tumor formation and promote tumor development in animals. FDA found further studies necessary to assess the carcinogenic and tumor-promoting potential of the ingredient. An Advisory Committee was convened in 1992 whereupon the committee, while determining that the data were inconclusive but concerning, recommended new photocarcinogenicity studies and inclusion of animal data in product labeling. The committee determined, and FDA agreed, that continued marketing of Rx-only and OTC benzoyl peroxide products, with updated labeling, was acceptable while additional data were gathered. *In vitro* genotoxicity studies, tumor promoter studies, carcinogenicity studies, including photocarcinogenicity, have been conducted and demonstrate that benzoyl peroxide appears to be able to promote tumor growth and conversion in the presence of a tumor initiator (e.g., chemical exposure, but not necessarily UV radiation exposure), but data do not support it being a carcinogen. In humans, several epidemiological studies have failed to discover a link between use of benzoyl peroxide and tumor development. Recommendations for labeling of adapalene that could mitigate risk can be found in **Section 9.2 Labeling Recommendations**.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

According to the Rx label, adapalene, a third generation poly-aromatic topical retinoid, binds to specific retinoic acid nuclear receptors (RAR), RAR-alpha, RAR-beta and RAR-gamma, but not to cytosolic receptor proteins. RAR-gamma receptors are the predominant receptor in epidermal cells. Biochemical and pharmacological profile studies have demonstrated that adapalene bound to RARs modulates cellular differentiation, keratinization and inflammatory processes (also see **Section 9.1 Literature Review/References**, Czernielewski, et al. (2001)). However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne is unknown, but suggests normalization of the differentiation of follicular epithelial cells, thus decreasing microcomedone formation.

4.4.2 Pharmacodynamics

Not known.

4.4.3 Pharmacokinetics

Based on results in acne patients applying the product long-term in controlled clinical trials, absorption through human skin is low (< 0.25 ng/mL). Excretion appears to be by the biliary route. To address concerns about off-label use, e.g., use on skin without acne or large areas of skin, FDA asked the applicant to conduct a MUsT to investigate systemic exposure under such conditions. The MUsT, "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," was conducted in 24 adults and children > 12 years of age across three research sites from August 21, 2014 to November 17, 2014. Eighteen subjects (75%) were < 18 years of age. The treatment period was 29 days' duration and trial personnel administered a single daily application to the face, shoulders, upper chest and upper back of enrolled subjects. Personnel recorded the total daily amount applied and consistently applied the same quantity daily. Plasma concentrations were quantifiable in all subjects and concentrations reached steady state by Day 15.

Safety and tolerability data are described in **Section 7 Review of Safety**. Notably, eight subjects reported 17 AEs. None were serious or resulted in discontinuation from the trial. There were no deaths.

The clinical pharmacology review was finalized on May 18, 2016. The conclusion was that the results of the MuST were acceptable. Data from the MUsT was considered with that from prior nonclinical studies assessing the NOAEL for adapalene and potential risk

for systemic exposure in humans. An exposure margin was calculated and is addressed in Dr. Li's review with data described in Dr. Shukla's review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: List of Studies - Differin Gel, 0.1% for OTC Marketing Status

Type	Trial ID	1° Objective	Design	# Subjects	Diagnosis	Duration
LCS (U.S.)	100544	Comprehension – once daily; not on healthy skin	MC, label evaluation	586 (12-70 years); 130 low literacy; 282 12-18y	All comers	Single visit
SSS (U.S.)	103439	Self-selection in pregnant or BF women - advice seeking behavior	MC, label evaluation	293 (13 – 54 years); N= 2(< 18y)	Pregnant or BF; 91 pregnant (37%)	Single visit
SOCS* (U.S.)	1022234	Prescribing, counsel and care information by prescribers/ patients	Survey (qualita-tive)	233 (13 – 69 years)	Differin users and prescribers	N/A

Source: Applicant's submission, Module 5 and Module 1.14; ID – Identification; 1° - Primary; LCS – Label Comprehension Study; MC – Multicenter; SSS – Self-selection Study; BF – Breastfeeding; SOCS – Standard of Care Study; N/A – not applicable

*This study does not contribute to our assessment of the benefit-risk profile of Differin Gel used in the OTC setting. It had many limitations which are described in Ms. Cohen's review and in the background material in preparation for the April 15, 2016 Advisory Committee Meeting. It is included here only for completeness.

Table 5: List of Clinical Trials – Differin Gel, 0.1% for OTC Marketing Status

Type	Trial ID	Objective	Design	# Subjects	Diagnosis	Duration
PK (U.S.)	18254	Assess maximal usage PK	R,MC,OL	24 (18 were 12 – 17 years)	Acne vulgaris	29 days
Actual Use (U.S.)	100931	Use in OTC setting	MC,OL	947 (12 – 73 years); N=203 < 18	Report acne vulgaris	6 weeks

Source: Applicant's submission, Module 5.2 – Tabular listing of all clinical studies; ID – Identification; PK – Pharmacokinetics; R – Randomized; MC – Multicenter; OL – Open Label

5.2 Review Strategy

This reviewer provided details on the regulatory background of development of this product for OTC marketing status. I reviewed the Actual Use Trial (also reviewed by Dr. Scott Komo – Office of Biostatistics), safety data from the Maximal Usage Trial (MUsT) and postmarketing safety data submitted to support the application. Dr. Chinmay Shukla from the Office of Clinical Pharmacology reviewed the MUsT. Since this is a proposed switch to OTC marketing with the same approved indication, treatment of acne, there is no need to review the original safety and efficacy trials conducted to support initial approval; however, the findings from the Actual Use Trial will be reported in **Section 6 Review of Efficacy** and **Section 7 Review of Safety** due the ease of utilizing the relevant section headings. From the perspective of the prescription division that currently manages the NDA, Dr. Amy Woitach from the Division of Dermatology and Dental Products provided a general assessment and recommendation on the appropriateness of adapalene marketed in the OTC setting. In her review, Dr. Woitach recommended that adapalene remain available by prescription only. Her main concern was with regard to risk for teratogenicity and data lacking to support the safety of adapalene used in the OTC setting. See her review for details (DARRTS; June 1, 2016).

Assessment of safety data from the original trials is in the Rx label and the important warnings and precautions necessary for safe and proper use of the product will be translated to the Drug Facts Label. My review also includes comment on the relevance of nonclinical data with regard to the pharmacokinetic data when the product was applied under maximal usage conditions and the clinical relevance of the remainder of the consumer behavior program, including the label comprehension and self-selection testing (see **Section 5.3 Discussion of Individual Studies/Clinical Trials**). Ms. Barbara Cohen and Dr. Komo will review those studies in full.

5.3 Discussion of Individual Studies/Clinical Trials

Ms. Cohen's review of the label comprehension and self-selection studies, and the survey study, was not completed at the time this review was finalized. For the LCS, she concluded that the primary communication objectives, "use once daily" and "do not use on damaged skin," generally tested well overall. The pregnancy/breastfeeding (BF) warning was not tested such that understanding of the warning to seek medical advice before using adapalene is unclear, although, the targeted self-selection study and the actual use trial also addressed this concern.

Regarding the targeted self-selection assessment, considered important to address behavior by pregnant acne sufferers, only 37% of the subjects were actually pregnant (the remainder was breastfeeding, consistent with the proposed label warning). Only two were adolescents (these subjects were recruited through teen pregnancy centers and support groups) and the recruitment was somewhat suspect in that adult subjects in mall intercepts had to "appear" between 18 and 50 years of age, to have acne, to be

visibly pregnant, or were accompanied by a child appearing less than 18 months of age. Only if subjects self-reported acne and affirmed pregnancy or breastfeeding were they enrolled in the study. The study did not demonstrate, to a significant degree, that pregnant women would seek medical advice before choosing to use the product. The lower confidence bound for the entire study population was 68.4%, over 20 percentage points below the 90% *a priori* target threshold. For only the pregnant subjects, 70% correctly stated they would seek medical advice. The lower confidence bound was 58.7%. Notably, several who made incorrect decisions stated that they did not see the warning. No conclusions can be made on how adolescents, likely the population with highest usage potential, who are pregnant, would determine whether the product was right for them. Finally, the sponsor conducted a "standard of care" survey study to gather information on prescribing, counseling and management of patients using adapalene and HCPs who prescribe the drug. Ms. Cohen describes several limitations of this study and it is not included in our overall assessment of the benefit-risk profile of adapalene to support OTC marketing status.

6 Review of Efficacy

Efficacy Summary

Because this supplementary application is for approval for a switch from Rx to OTC marketing status, the applicant relies on efficacy data from the original NDA approval for Rx marketing of adapalene gel, 0.1%. For that approval, the applicant conducted five controlled clinical trials comparing the product to the vehicle or an active control, tretinoin gel, 0.025%, in subjects with mild to moderate acne vulgaris. Other trials compared the product with isotretinoin gel as well, demonstrating significant improvement of both noninflammatory and inflammatory acne lesions compared to the vehicle. Under typical design as well-controlled trials for the claimed indication, improvement of acne lesions was assessed at 12 weeks. There were no new efficacy trials required for this proposed switch to OTC marketing status, and the efficacy of the product is not questioned here. The applicant intends to market the product for the same indication as approved for Rx-only use, treatment of acne. Notably, acne treatment is a well-established OTC indication and there are several topical ingredients available for use allowed under a Final OTC Monograph.

FDA did require an actual use trial (Protocol 13049: Pivotal Actual Use Study for Adapalene 0.1% Gel – Project "Juno" (Juno trial)) to assess usage and adherence to precautions and directions for use in the OTC setting, i.e., an assessment of generalizable effectiveness (proper use) and safe use. Two primary endpoints, frequency of use (once daily at same acne location) and use on acne only, were assessed. The main secondary endpoints were set to assess self-selection decisions by pregnant or breastfeeding women (a safety endpoint – see **Section 7 Review of Safety**) and use of the product on correct body areas (i.e., undamaged skin and avoidance of eyes, lips and mouth). The Juno trial is reviewed here. Other consumer behavior studies were conducted to support the adequacy of labeling to ensure proper

use in the OTC setting, that is, whether the drug can be used as intended for treatment of acne in the OTC setting. Ms. Barbara Cohen and Dr. Scott Komo, social science analyst and statistician, respectively, reviewed the label comprehension and separate self-selection studies elsewhere. Dr. Komo's deemed the statistical assessment of the data in the Juno trial to be acceptable. He noted that, based on the data from the consumer behavior studies, pregnant women are likely to use the product without consultation with an HCP and that approvability would depend on the acceptability of the exposure margin to support marketing in the OTC setting.

The Juno trial demonstrated a high proportion of correct use by the primary and main secondary endpoints assessing usage. The investigators enrolled a diverse population of subjects with females and adolescents adequately represented. While the low literacy population was low (13.8% adults; 10.8% adolescents), there were no apparent differences in adherence to important labeling messages by subgroup analysis of that population. Of those subjects who said "Yes," they wanted to purchase the product, 14.5% (161/1108) were excluded from purchasing and entering the use phase of the trial. The majority of these subjects (64.6%; 104/161) did not meet eligibility criteria to enter the use phase. Reasons why subjects did not meet eligibility criteria included 1) no acne; 2) < 12 years of age; 3) pregnant or breastfeeding; 4) investigator's judgment. These categories are discussed in more detail in subsections below; however, none of the reasons for exclusion raised any concerns over selection to use the product in the OTC setting, although, it seems clear that pregnant women will use the product and may continue to use it while pregnant (see **Sections 6.1.5 Analysis of Secondary Endpoints(s), 7.6.2 Human Reproduction and Pregnancy Data** and **9.3 Advisory Committee Meeting**). The remainder (N=57) of excluded subjects did not show to purchase the product, were female and unable to provide an adequate urine sample, or were excluded for administrative reasons.

The point estimates for the primary endpoints were 89.1% and 99.3% for once daily use and acne only use, respectively. The applicant set success thresholds at > 85% for the lower bounds of the 2-sided 95% confidence intervals. The lower bounds for the respective endpoints were 87% and 98.5%. The point estimate for the main secondary endpoint was 97.5%. There were no significant differences in use with any subgroup analyses by age, gender or literacy. The applicant established a few mitigation criteria which it applied to categories of incorrect use, as per the endpoints, and reconsidered them as correct. The criteria were reasonable and did not significantly impact the results of the trial. FDA agreed on the primary and main secondary endpoints and on various design elements of the trial, however, there were some important limitations. Actual use trials are not true measures of use in the OTC setting, but do provide a window into how a product is *likely* to be used by the general OTC consumer. The Juno trial was only six weeks in duration providing a somewhat limited picture of how subjects are likely to use the product. One related concern raised at the Advisory Committee meeting on April 15, 2016 was that such a product may be used chronically, without oversight of a learned intermediary, and that the safety of such use is unclear. The Juno trial demonstrated that a vast majority of subjects used the

product for at least five weeks which is consistent with the duration required to see visible improvement (4-12 weeks of daily use). See **Section 9.2 Labeling Recommendations** for comments on how labeling should provide consumers with an expectation of benefit when using the product. A final limitation of the trial was that it was not, as the applicant contended, a true "all comers" trial. The recruitment and advertising material was focused on acne sufferers. If the product is approved, it is reasonable to assume that acne sufferers will be the target of advertising and product placement on pharmacy shelves will have that same focus, but for the purpose of evaluating off-label use or misuse on non-acne skin conditions, the Juno Trial was lacking. This is evidenced in the extremely high rate of correct usage by the "acne only" primary endpoint.

The most commonly reported reasons for incorrect use are described in the relevant sub-sections below, but none raised any safety concerns. Of greatest concern, for any of the categories of incorrect use, is skin irritation with overuse or misuse. As is well-established in OTC labeling for topical drug products, warnings for skin irritation can be adequately labeled and are well understood by consumers. Users who may have skin that is sensitive to irritating substances can choose to test a small area or avoid use all together, while users who may experience irritation while using the product are instructed to stop use and seek medical advice if irritation is severe. There are no known risks associated with continued application to irritated skin if a user chooses to continue applying the product.

6.1 Indication

The proposed OTC indications are "for the treatment of acne" and "clears up acne pimples and acne blemishes." The former is consistent with the prescription indication, "treatment of acne vulgaris." The latter is not an approved indication for the Rx product, but is allowed under the Final Monograph for topical acne drug products. The monograph includes definitions of both acne pimples and acne blemishes which are considered general skin findings of acne treated under the umbrella claim "treatment of acne." See **Section 9.2 Labeling Recommendations**.

6.1.1 Methods

The Juno trial was a 6-week, open label, multi-center (N= 31 geographically dispersed pharmacy sites) trial in subjects self-reporting acne, a well-established OTC indication. The primary investigator was William Miller, MD who appeared qualified to lead the trial. All comers with acne were eligible to enroll. The trial was conducted from January 23, 2015 to May 2, 2015.

Initially, the applicant proposed that 1200 would enter and 800 would complete the trial. The low literacy target was 20-25%. Ultimately, 1277 subjects entered the trial and 947 were included in the actual use population – those who gave informed consent/assent,

purchased the drug and applied at least one dose. This group also constituted the safety population for analysis. The major inclusion/exclusion criteria were as follows:

- Self-report acne
- Age 12 years to adult (assent required for children 12 to 17 years of age)
- Subject is pregnant – urine pregnancy test conducted in all female subjects of childbearing potential
- Self-reports breastfeeding
- Self-reports allergy to adapalene or any inactive ingredient

Reviewer's comments: The protocol was designed so that all comers would be allowed to make a selection decision. After subjects made a selection decision, if subjects were found to be pregnant or reported breastfeeding or allergy, they were excluded from the use portion of the trial in the event they desired to use the product. The applicant ascertained their reasons for decisions to purchase. These subjects would be documented as "purchase decision failures." This reviewer notes that outright exclusion of pregnant or breastfeeding subjects is acceptable, but not in keeping with the proposed labeling warning to ask a doctor before use. Adherence to the warning is addressed both as a secondary endpoint, and separately in the self-selection study (see Ms. Cohen's review).

Potential subjects were recruited by advertising and underwent minimal screening to exclude those who had participated in studies in the past 12 months or worked in a healthcare related field. Upon arrival at a participating pharmacy site, subjects enrolled in the trial were offered the product package and asked to make a purchase decision. The cost of one box containing one 45 gram tube was 7.00$. Subjects were allowed to purchase a maximum of two boxes per pharmacy visit, and three boxes over the duration of the trial. Those who said "Yes" (selectors) to the purchase decision gave informed consent/assent and female subjects of childbearing potential were required to self-administer a urine pregnancy test. All of the selectors underwent further medical screening to determine whether it was appropriate to use the drug. A healthcare professional participating as a screener would make the final decision on enrollment for each subject. These subjects then completed the Rapid Estimate of Adult Literacy in Medicine (REALM) to determine literacy. Once the product was purchased, subjects were given basic instructions on completing the diary, contact information and when to schedule the next visit. Subjects were not provided information on how to use the product or for what conditions it should be used. Subjects who chose not to purchase (non-selectors) or who were found ineligible due to labeling contraindications or other exclusions (e.g., pregnancy) underwent a truncated screening to collect data on demographics, targeted medical history and clarification of the reason not to select or purchase the product for use.

*Reviewer's comments: The Drug Facts Label on the test product package was nearly identical to the label proposed for the to-be-marketed product (**Section** **9.2Labeling Recommendations**). The only difference is that the* (b) (4)

(b) (4)

claim is not on the proposed labeling.

The healthcare professionals conducting the enrollment interviews used "their own medical judgment to clarify any responses." There were no scripts or algorithms to follow. The subjects' responses and the probing follow-up questions may have introduced bias into the decisions why a subject did or did not choose to continue into, or be barred from, the Use phase of the trail. For example, if an interviewer asks follow-up questions to inquire why a subject gave a certain response, the act of simply asking such a question could cue a subject to reconsider the response to potentially err on the side of safety, i.e., comment that they would ask a doctor first or choose not to use the product.

On visit 2 (Study close-out day; End-of-trial (EOT)), subjects were expected to return diaries and unused product. All but one subject who attended visit 2 returned a completed diary. Another subject, #30006, reported a situation whereby her roommate, subject #30005, took her diary and copied entries. Subject #30006 was discontinued from the trial at Visit 2, and her diary discounted, due to potentially fraudulent data, since subject #30005 had completed her EOT visit the day before.

Female subjects of childbearing potential undertook repeat urine pregnancy testing and all subjects filled out body charts to document the body areas where drug was applied. They also completed EOT medical histories and answered any outstanding questions about their usage patterns or adverse event reporting. All subjects were reimbursed for their time and travel, but not for product purchases. Subjects were not made aware of the reimbursement arrangement at the time of first visit. This is typical of AUTs.

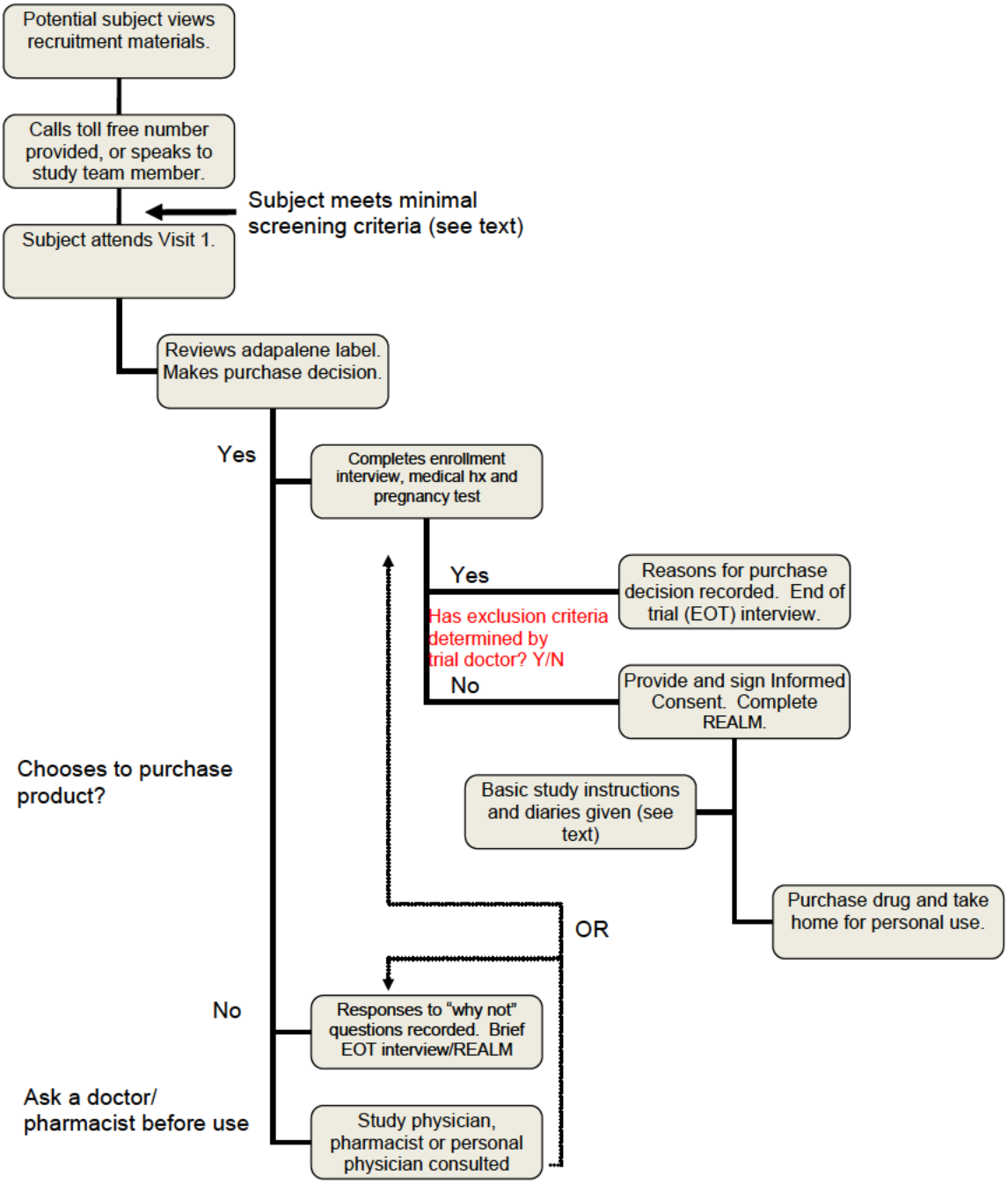


Figure 1: Juno Trial Enrollment

6.1.2 Demographics

Based on discussions between the applicant and FDA, Galderma set a quota of ≥ 10% of the enrollees to be children 12 to 17 years of age. Subjects who were younger than 12 were allowed to make the screening visit (with a parent/guardian), but were not allowed to purchase the drug. Their reasons for interest were documented. See **Table 6**.

Table 6: Subject Demographics (Juno trial – Use Population)

Variable	All Subjects (N=947)	
Age (years)		
Mean (SD)	29.9 (12.72)	
Median	28	
Min, Max	12, 73	
Age subgroup, n (%)		
12 to 17 years	203 (21.4)	
≥ 18 years	744 (78.6)	
Sex, n (%)		
Male	304 (32.1)	
Female	643 (67.9)	
Race, n (%)		
White	492 (52)	
Black or African American	321 (33.9)	
Other	88 (9.3)	
Asian	25 (2.6)	
American Indian or Alaska Native	12 (1.3)	
Native Hawaiian or Other Pacific Islander	6 (0.6)	
Refused	3 (0.3)	
REALM Score, n (≥ 18 years)	**Normal Literacy (%)**	**Low Literacy (%)**
744	641 (86.2)	103 (13.8)
REALM-Teen Score, n (12 to 17 years)	**Normal Literacy (%)**	**Low Literacy (%)**
203	181 (89.2)	22 (10.8)

Source: Modified from applicant's submission, Module 5.3.5.2, Synopsis – Table 4, p. 5-6, and Module 5.3.5.2, 'Synopsis,' Table 2, p. 3.

Table 3 shows a wide-ranging population enrolled in the trial by age, sex and race. The young mean and median ages are expected. The applicant also captured an acceptable proportion of adolescent subjects (21.4%) and a majority female population (67.9%) to capture behaviors, as advised by FDA, potentially based on pregnancy or breastfeeding status. The status of the actual use population (users) indicates that a lower proportion of the trial population was considered low literacy (adults and adolescents) than FDA advised (20-25%). This population is further defined in **Table 7**.

Also based on prior discussions, the applicant attempted to enrich the trial to ensure that a proportion of subjects self-reported acne and eczema and chose to purchase the drug. This was intended to further evaluate the potential for off-label use, extensive use and potential exposure on damaged skin that may increase potential for systemic absorption and raise concerns about exposure in pregnancy and while breastfeeding. According to the applicant, 37 subjects reported a history of eczema but chose not to purchase and use the drug. Of those, three reportedly made the decision not to purchase *because of* their eczema. The applicant reports that 14 subjects reported eczema and participated in the treatment phase. Only two (subject #s 18024 and 31043) reported applying the product to eczema if "it might help." Subject #18024 determined that her eczema rash may have been an effect of the drug only after having continued applying through the treatment period. No others applied to sites where acne and eczema were commingled.

Reviewer's comments: Based on users' responses to the questionnaires, this reviewer identified a total of 48 subjects who stated at some point during the trial, from screening to the EOT interview, that they had either a history of eczema or were currently experiencing an exacerbation. Of those, 23 had said "yes" to purchase. Only 14 subjects participated in the treatment phase because nine were excluded due to other "actual use screen failures," i.e., the subjects had eczema but not acne. This reviewer cannot explain the discrepancy between the 48 subjects identified and the 60 subjects with eczema that were identified by the applicant (37 who chose not to purchase + 14 who chose to use the product + nine who were excluded at screening). The interpretation of the findings were not impacted by this.

There was no enrichment for pregnant women in the actual use trial since there was a dedicated self-selection study conducted on that population (see Ms. Cohen's review). Since the actual use trial was open to enroll all-comers, the women likely to be interested in using the product were also more likely to be of child-bearing potential since acne typically affects adolescents and younger adults. Ultimately, 43.9% of the enrolled population (**Table 7**) was women of childbearing potential (12 to 54 years of age) where such status was bracketed by menarche and menopause or defined by post-surgical status (e.g., post-hysterectomy, post-tubal ligation). Data were collected on the selection/purchase decisions of women who were determined to be pregnant or breastfeeding during screening. Assessment of these women was a secondary objective of the trial. FDA previously noted to the applicant that the six-week trial duration was likely too short to capture an adequate number of interim pregnancies to analyze the behaviors of those women, i.e., whether they would stop use or seek the advice of a healthcare professional.

6.1.3 Subject Disposition

Table 7: Subject Disposition - Juno trial

Category	All Subjects	Normal Literacy[a]	Low Literacy[a]
Enrolled[b]	1277	1047 (82%)	189 (14.8%)
Actual Use/Safety Population	947	822 (86.8%)	125 (13.2%)
Excluded from Use	330 (%)		
Purchase Decision = 'No'	169 (51)[d]	119	35
Actual Use Screen Failure[c]	104 (31)	71	18
No Show[e]	41 (12.4)	30	11
Other[f]	14 (4.2)	3	0
Subject Withdrew Consent	1 (0.3)	1	0
Adverse Event	1 (0.3)	1	0
Study Staff Decision	0	0	0
Purchase Decision = 'Yes'	919 (97%)	795	124
Ask a Health Professional First	28 (3%)	27	1
Study Doctor, PA, Nurse	7	6	1
Pharmacist	20	20	0
Personal Healthcare Professional	1	1	0
Completed Use Phase	938	813	125
Discontinued Use Phase Early	9	9	0
Adverse Event	8	8	0
Other (#30006)	1	1	0

[a]The literacy status of 41 subjects (3 2%) was undetermined. Those subjects are not included in these columns and were not entered into the trial.
[b]Enrolled subjects were hose who answered the adver isements and passed he initial, minimal screening – identified as label evaluators
[c]Screen failures would have been subjects meeting any exclusion criteria including the discretion of the healthcare professional during telephone screening
[d]The percentage is of those excluded from use (N=330)
[e]"No shows" were subjects who left the site wi hout purchasing and never returned
[f]Nearly all subjects excluded as "other" either did not sign Informed Consent or were unable to provide a urine sample with a positive/nega ive result for pregnancy testing. Some tests were "inconclusive."
PA = Physician's Assistant
Source: Modified from Applicant's submission, Module 5.3 5.2, 'Synopsis,' Table 2.

Table 7 shows the subject disposition of the Juno trial. The number of enrolled subjects was similar to the proposed study size to address the primary endpoints. The low literacy cohort in the enrolled population (14.8%) is well below the proportion initially proposed for the trial (20-25%). The majority of subjects who were "excluded from use" (N=330) had decided not to purchase the drug after viewing the package (N=169). Of the 104 subjects who failed the screening (including those who incorrectly selected to purchase the product), this reviewer found the following trends:

- Seven potential subjects were younger than 12 years of age:
  - Due to his age, one of these subjects reported that he would not purchase
  - Five subjects were within 12 months of their 12th birthday. They wanted to purchase and their decisions were mitigated. One subject was 10 years old

  - The subjects who wished to use the product simply wanted to improve their acne and had been unsuccessful using other products
- One subject reported an allergy to adapalene or other ingredients
- Twenty subjects reported that they did not have acne:
  - Nine (0.7%; 9/1277) of these subjects selected to purchase but were excluded
    - These subjects stated that they did not have acne, but wanted to, for example, "prevent acne," "unclog pores," or "remove the blemishes" and "even out the skin tone"
    - None commented that they wanted to use the product for non-acne conditions such as eczema, psoriasis, or age-related wrinkling or other skin changes
- Several subjects (N=16; 1.3%, 16/1277) reported that they were pregnant (N=4) or breastfeeding (N=10), or were determined to be pregnant upon screening (N=2). Several (N=10) initially chose to use the product while pregnant or breastfeeding. On probing, subjects reported:
  - Not seeing the warning
  - Not considering the seriousness of the warning, for example, stating "all medications say ask a doctor before use"
  - Not considering use while breastfeeding to be a risk
    - The topical formulation appeared to ease concern versus use of oral drugs
  - Discussing use with the pharmacist and believing there was minimal risk (lack of absorption) associated with use of the topical formulation
  - Deciding to use regardless of pregnancy status, either because of prior discussions with a doctor or pharmacist, or on their own volition

Reviewer's comment: See Ms. Cohen's review of the self-selection study in pregnant women for a more detailed assessment of decisions to use adapalene. Of the pregnant or breastfeeding subjects who rightly chose to seek medical advice first, several asked their trial site's pharmacist whether the product was okay to use. Some subjects chose to use the product even after speaking with the pharmacist indicating, in one instance, that they were not concerned, that the product would not be "fully absorbed so there shouldn t be any effects" (Subject 24038). This subject noted that "since she won't be applying study drug to her breast it's okay." Responses from pharmacists regarding risks with use in pregnancy or while breastfeeding ranged from, for subject 24038, "no human data available" to "best thing would be to ask pediatrician [if passes through breast milk]," and "it's not [okay to use while breastfeeding]." See ***Section 9.2 Labeling Recommendations*** *for comments based on these findings. This reviewer believes physicians or other medical providers are best equipped to discuss the potential risks of use of retinoids by women who are pregnant or who may become pregnant.*

- Twenty nine subjects were excluded based on the judgment of the investigator conducting the Visit 1 screening

On January 11, 2016, at FDA's request, the applicant provided a more detailed account of the investigator's judgment to exclude these 29 subjects. Of them, all but four (N=25) wanted to purchase the product. Two subjects either stated they were pregnant (but pregnancy test was negative), or reported missing two menstrual cycles and being concerned about possible pregnancy (negative test). Both indicated they were interested in purchasing the product for use. Three subjects had inconclusive pregnancy tests and were excluded. Another subject refused to provide a urine sample for the pregnancy test. A subject had a positive pregnancy test but reported having had an elective termination just prior to the screening visit.

Six subjects were excluded due solely to "interest in money" for participation in the trial. Two more subjects were considered to be under the influence of drugs or alcohol during the screening visit. Finally, nine subjects did not appear to comprehend the instructions for use, understand interview questions, or raised concerns for staff over compliance with protocol.

Three of the pregnant women offered information on the progress of their pregnancies. They were under the care of medical professionals and reported no issues.

6.1.4 Analysis of Primary Endpoint(s)

The primary objectives of the Juno trial were to evaluate the frequency of use (labeled for once daily use) and to determine off-label use (i.e., non-acne use). Subjects who used the product even once were to be included in the final analysis. The applicant determined the proportion of correct users as the number of subjects who had an overall correct behavior for the primary objectives out of the entire number of users. Correct behavior was defined as initial behavior (no more than once daily use at same location and acne use only) including behavior mitigated *a priori* and behavior mitigated *post-hoc*. The adequacy of the derivation and statistical support for the endpoint will be determined by the statistical reviewers from the Office of Biostatistics.

Reviewer's comments: Although FDA encouraged the applicant to include an endpoint to evaluate "off-label" use, we acknowledge that the recruitment for this trial for use with acne (Recruiting Ad: "Do you have acne? People of all races and ages get acne. If so you may qualify for a study. Please call 1-800-xxx-xxxx") may limit the non-acne use of the product as subjects with such conditions may self-exclude based on advertising and placement of the product on acne treatment shelves at pharmacy sites. Other materials including the questionnaires and informed consent/assent may also cue subjects that the product is an acne treatment, thus potentially resulting in self-exclusion. The investigators collected data at the end of the trial on uses for reasons other than acne treatment, and proposed to enrich the trial with eczema sufferers. The generalizability of the data to support proper use of the product as intended for treatment of acne needs strong consideration here. Additionally, the three-box purchase limit may have

impacted subjects' decisions on how extensively to apply the product. A higher purchase limit may have allowed a better assessment of the likelihood of off-label use.

Regarding mitigations, the applicant set conditions whereupon initially incorrect responses would be considered "correct." Two conditions for the two primary endpoints captured those subjects who 1) either reported that they mistakenly used the product > once daily only one time with an explanation that they changed their use after the single mistake, or 2) had been prescribed the product for a non-acne (off-label) indication by a healthcare provider. *Post-hoc* mitigations were utilized based on subjects' responses to use inquiries by trial staff. Five mitigating circumstances were established for three endpoints (two primary and one main secondary):

- Use product no more than once daily in same location (Primary)
  - Subjects who changed their application schedule or applied the product at night and the following morning
  - Subjects who re-read the directions and changed behavior
- Use only for acne (Primary)
  - Acne is in the same area as another skin condition
- Apply to correct body area (Secondary; see next section)
  - Subjects used the product near a 'warning' area
  - Subjects reported using the product on damaged skin which they later understood to be a known effect of the medication, e.g., dryness.

The applicant determined the point estimate and lower bounds of the two-sided 95% confidence limit. **The thresholds for success were lower bounds > 85% for each primary endpoint; frequency and indication for use (Table 8).** The applicant considered the thresholds consistent with those "commonly set for primary endpoints in consumer studies," also stating that it had no clinically relevant concerns about overuse or off-label use based on the history of marketing of adapalene in the Rx setting. Certain subgroups were also analyzed. These included age group cutoffs at 12 to 17 years and ≥ 18 years and low literacy (REALM < 60 or equivalent for children and adolescents). The applicant proposed to capture duration of exposure as consecutive days with categories from < one (1) week to > six (6) weeks.

The applicant established the statistical analysis plan following the first amendment of this protocol (January 29, 2015). Missing data were not imputed for assessment of any of the endpoints.

Table 8: Primary Endpoint 1 - Analysis of Once Daily Use in Same Location

Endpoint 1: Statistics	All Subjects (N=947)	Normal Literacy (N=822)	Low Literacy (N=125)	12 to 17 years (N=203)	≥ 18 years (N=744)
Subjects who used product no more than once daily in same location[a]					
N (%)	844 (89.1)*	732 (89.1)	112 (89.6)	184 (90.6)	660 (88.7)
95% CI	(87.0, 91.0)	(86.7, 91.1)	(82.9, 94.3)	(85.8, 94.3)	(86.2, 90.9)

CI = Confidence Interval; * = endpoint met lower bound of two-sided 95% confidence limit for *a priori* threshold
[a] Final corrected use = number of subjects wi h overall correct behavior (uncorrected use + *a priori* mitigation + post-hoc mitiga ion) divided by actual use population.
Source: Modified from Applicant's submission, Module 5.3.5.2, 'Synopsis,' Table 5, p. 7.

The proportions of misusers did not differ much by literacy level or age. Of the 844 subjects considered by the applicant to correctly use the product only once daily (**Table 8**), 61 subjects had use mitigated by an *a priori* criterion, and 16 subjects had use mitigated by *post-hoc* criteria as described above. Seventeen (22%; 17/77) of these subjects were in the 12 to 17 year old age bracket. There were no trends raising concern about the potential for misuse due to younger age. For the subjects whose use was mitigated by the *a priori* criterion, the applicant determined that all used the product more than once daily only a single time (N=61).

Reviewer's comments: While the product may have been used by these subjects more than once per day only one time over the treatment period, the reasons for misuse are such that it is not unlikely that they would be repeated over a course of treatment. For example, subjects reported reapplying after showering, having a bad "breakout" on a particular day and hoping it would work faster or better, or forgetting the first application. More frequent use may not be uncommon based on similar circumstances, but it does not raise significant safety concerns (see ***Section 2.5 Summary of Presubmission Regulatory Activity Related to Submission****). Since systemic absorption appears to be minimal even under conditions of maximal usage (see Dr. Chinmay Shukla's review), the likely risks due to systemic exposure appear similarly minimal. Skin-related adverse effects can be addressed in labeling and users with more severe effects are likely to stop use and seek advice from a healthcare professional.*

For the subjects whose use was mitigated by the *post hoc* criteria, 12 subjects' use was mitigated by a work/school/schedule change whereby the subjects used the product late at night followed by use the next day < 24 hours later. The other four subjects' use was mitigated because they re-read the directions and changed their use behavior.

Reviewer's comments: The applicant summarized the findings of those subjects whose behaviors were mitigated, but did not provide a rationale for the codes it established to define the reasons why mitigations were appropriate. Therefore, this reviewer evaluated the verbatim reasons given by subjects whose use was mitigated post-hoc. On January 14, 2016, the applicant responded to a request for data on subjects' verbatim responses that determined acceptability of mitigation. The applicant utilized responses to probing questions at visit 2, in addition to the EOT medical history and the subject's diaries. The responses to probing questions aided in identifying core themes and resulted in assignments of verbatim reason codes to categorize incorrect usage and determine mitigations.

Some subjects reported variable work/life schedules that resulted in their occasionally applying the product late at night on a particular date and, as typical of their pattern otherwise, early in the morning with < 24 hours between applications. Or, if they

typically applied the drug at night, applications on consecutive nights may have been < 24 hours apart. These subjects, and those who mistakenly believed the product was to be applied twice daily, but who corrected their usage after reviewing the directions, do not appear to signal any concern for overuse and were appropriately mitigated.

Subjects who used the product incorrectly without a mitigating factor (N=103) most frequently reported using it whenever they showered or washed their face, i.e., sometimes twice daily (34%; 35/103), sought to achieve greater, or faster, benefit (24.3%; 25/103), in an attempt to treat "severe" acne (18.4%; 19/103), or because they misread the directions or used it as per "my routine," usually twice daily (8.7%; 9/103). Reasons for misuse by these subjects and the remainder (N=12) did not identify any safety concerns.

Regarding the second primary endpoint, the proportion of subjects who used the product only for acne, **Table 9** shows that the applicant met the *a priori* success threshold (lower bound of 2-sided 95% CI > 85%). The proportions within sub-populations stratified by health literacy (REALM scores) and age were similarly well higher than the threshold.

Table 9: Primary Endpoint 2 - Analysis of Acne-only Use

Endpoint 2: Statistics	All Subjects (N=947)	Normal Literacy (N=822)	Low Literacy (N=125)	12 to 17 years (N=203)	≥ 18 years (N=744)
Subjects who used product only for acne[a]					
N/M[b] (%)	938/945 (99.3)*	814/820 (99.3)	124/125 (99.2)	202/203 (99.5)	736/742 (99.2)
95% CI	(98.5, 99.7)	(98.4, 99.7)	(95.6, 100)	(97.3, 100)	(98.2, 99.7)

CI = Confidence Interval; * = endpoint met lower bound of two-sided 95% confidence limit for *a priori* threshold
[a] Final corrected use = number of subjects wi h overall correct behavior (uncorrected use + *a priori* mitigation + post-hoc mitiga ion) divided by actual use population.
[b]M is the number of subjects who used the product and had no missing assessments (two subjects had missing assessments – both had normal health literacy as per REALM testing and were ≥ 18 years of age)
Source: Modified from Applicant's submission, Module 5.3.5.2, 'Synopsis,' Table 6, p. 8.

Proportions of misusers did not differ by literacy level or age. No subjects misuse was mitigated due to having a prior prescription for adapalene for a non-acne condition. Five subjects misuse was mitigated post-hoc. They reported using the product on a non-acne condition because they also had acne on the same location. Only seven subjects misused on areas without acne. Those subjects reported using the product for psoriasis (1), anti-aging (1), "dark spots" (1), "eye puffiness" (1), "reduce pore size" (1), and "eczema" (two subjects # 18024 and 31043). All of them thought using the product would help their conditions.

Reviewer's comments: As noted above, the recruitment and advertising clearly specified that the product was intended for acne. This likely biased the determination of

this endpoint, although the number of subjects who misused is impressive in how few it was.

With regard to use of adapalene for non-acne conditions, although no subject reported using adapalene gel at the time they entered the trial, based on interviews, 41 subjects reported having received a prior prescription for the gel. All reported being prescribed and using the product for acne except for two ('skin discoloration' and 'hormonal breakout'), and the duration of use ranged from approximately one month to more than five years, with most subjects using the product for less than one year (eight reported using adapalene for less than two months).

6.1.5 Analysis of Secondary Endpoints(s)

The secondary objectives were 1) to evaluate the body areas where subjects applied the product, 2) to determine whether pregnant or breastfeeding women would ask a health professional before use as instructed on labeling, and 3) to assess adverse events (AE) in a naturalistic environment. The endpoints were the proportion using on the correct body areas (no damaged skin and avoiding contact with eyes/lips/mouth) and adherence to the pregnancy/breastfeeding warning. While a point estimate and confidence interval were calculated for the "body area" endpoint, no *a priori* threshold was set.

Reviewer's comments: The statistical analysis plan implies that the secondary endpoint addressing selection decisions by pregnant or breast-feeding women is intended to determine <u>complete</u> adherence to the DFL warning.

Similarly as for the primary endpoint, the applicant set conditions for mitigating usage and selection decisions. They include the following:

- Subject unintentionally applied product to eyes, lips or mouth once or twice and with minimal exposure
- Subject unaware of pregnancy until after choosing to purchase product, i.e., subject had a positive pregnancy test after making a selection decision (Visit 1)
- Subject unaware of pregnancy during use phase of trial, i.e., subject had a positive pregnancy test at the EOT (Visit 2)
    - Because this type of trial is intended to simulate a naturalistic environment, contact between investigators and subjects is intentionally kept to a minimum. Although there were four subjects who became pregnant during the trial, there was no mechanism for contact, to inform the investigator, after subjects discovered they were pregnant. The product labeling is intended to provide all necessary information for safe and proper use in the OTC setting (see **Section 9.2 Labeling Recommendations**).
- Subject was pregnant or breastfeeding and had previously been prescribed the product, by their physician, under same conditions

- Subject reports having eczema and acne, but eczema is at a different location and subject applies product to acne sites only
- Subject reports having eczema at the same sites as acne, but understands to use the product for acne only

Reviewer's comments: A final mitigation, seemingly unrelated to the secondary endpoints but included with those above, was to consider correct those selection decisions by subjects 11 years of age whose caregiver consulted with a physician prior to use.

*Regarding the pregnancy-related mitigations, there was no information on whether those subjects who used the product, and who discovered their pregnancy while on-treatment, actively took any precautions to prevent pregnancy based on the labeling. Based on responses at the EOT, (**Section 7.6.2 Human Reproduction and Pregnancy Data**) pregnant subjects were not alarmed about using adapalene while pregnant. Without any label warnings to stop use and seek medical advice, women who become pregnant while using the product are unlikely to stop using adapalene if they deem it effective for acne treatment. Although the data appear to support safe use during pregnancy (**Section 1.2 Risk Benefit Assessment**), there is still likely benefit to discussing use of the drug with a healthcare professional to ensure that the benefits, proper use and potential risks of use are properly aired, such that an informed decision can be made on whether to continue using the drug. Pregnant women are keenly aware that there are drugs that are contraindicated for use or recommended against unless the benefits outweigh the risks. However, additional instructions may support safe and proper use with regard to adapalene and pregnancy (**Section 9.2Labeling Recommendations**). Also see Section **9.3 Advisory Committee Meeting**.*

Table 10 demonstrates high proportions of application to the correct body areas, those areas that subjects self-reported the presence of acne. There were no great differences based on literacy level or age. Of the 921 who correctly used the product, nine had usage mitigated based on criteria established *a priori*, and four were mitigated by post-hoc criteria. Eight of the first nine mitigated subjects unintentionally applied the product near their eyes, ears or mouth, or did so because their acne was near those sites, but only once or twice. The ninth subject applied the product to damaged skin at the site of acne, but only once due to stinging skin. The final four mitigations were for application to acne sites near the lips (N=3) and on an area of dry skin (N=1), an apparent effect of the drug product on the acne site. Therefore, 96% (908/945) were initially correctly using the product. Of the incorrect users (N=24), 17 reported applying the product to damaged skin either because they had acne at the site, the damage was considered mild, or the drug did not cause further irritation. The remaining seven subjects were "applying the product like lotion; all over the face" as categorized under the applicant's "core themes." By subgroups, there were no apparent differences in the reasons why subjects misused.

Table 10: Analysis of Use on Correct Body Area – Secondary Endpoint (SE) 1

SE 1: Statistics	All Subjects (N=947)	Normal Literacy (N=822)	Low Literacy (N=125)	12 to 17 years (N=203)	≥ 18 years (N=744)
Subjects who used product on correct body areas[a]					
N/M[b] (%)	921/945 (97.5)	799/820 (97.4)	122/125 (97.6)	194/203 (95.6)	727/742 (98.0)
95% CI	(96.2, 98.4)	(96.1, 98.4)	(93.1, 99.5)	(91.8, 98)	(96.7, 98.9)

CI = Confidence Interval
[a] Final corrected use = number of subjects wi h overall correct behavior (uncorrected use + *a priori* mitigation + post-hoc mitiga ion) divided by actual use population.
[b] M is the number of subjects who used the product and had no missing assessments (two subjects had missing assessments – both had normal health literacy as per REALM testing and were ≥ 18 years of age)
Source: Modified from Applicant's submission, Module 5.3.5.2, 'Synopsis,' Table 7, p. 8.

As discussed in **Section 6.1.3 Subject Disposition**, while several women who were pregnant or breastfeeding wished to purchase and use the product, the assessment of women of childbearing potential is better addressed in the targeted self-selection study and Ms. Cohen's review.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

There did not appear to be any significant differences in assessment of the stated objectives by age, gender or literacy level. More specific details are provided in the relevant sections of this review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

Since approval, the safety profile of adapalene is well-characterized and continues to support its current Rx marketing status. In clinical trials, 5,414 subjects have been

exposed to adapalene up to maximum dose strength of 0.3%. Skin-related adverse events are most commonly reported with erythema, scaling, dryness, pruritis and burning topping the lists (up to 40% of trial subjects). A similar pattern of events were reported in the clinical trials conducted to support OTC marketing status. In the MUsT, 33% of subjects reported at least one adverse event. In the Actual Use Trial, nearly 50% reported at least one event. None of them were serious and 88% were mild in severity. In both trials, the majority of events were skin related and there were no major differences in event reports by age or gender. Half of the users who applied the product more than one time daily also reported adverse events. They, too, were mostly skin-related events. Twenty (2%) and 29 (3%) subjects reported using the product on damaged skin with co-located acne or suffering mild sunburn, respectively. Most of these subjects continued applying the product through the mild irritation, seemingly understanding that acne can appear to worsen both early in the treatment process and with sensitization due to sun exposure.

In review of the MUsT and Juno trial, this reviewer considered whether the extent of application may impact the safe use and risk for pregnant women. If consumers use the product in greater quantity or more frequently than recommended, the most likely outcome may be skin irritation at the application sites. The applicant's proposed labeling both cautions that irritation is more likely early in treatment and when other topical products are used concurrently, and warns to stop use and ask a doctor if irritation becomes severe. Such warnings are common to topical OTC drug products and well understood by OTC consumers. If adapalene is associated with congenital anomalies in humans, and neither my review nor other reviews of the original data supporting the Rx application or postmarketing safety data revealed evidence of any link, the potential risk for pregnant women could increase in circumstances where subjects are using quantities of the product that may increase systemic exposure to some critical degree. However, the nonclinical and clinical pharmacology data provide evidence of a significant exposure margin that would require significant overuse on large body surface area (BSA). The biochemistry and receptor binding of adapalene also appears to differ from other retinoids such that even addressing risk for teratogenicity may be unnecessary (see **Section 9.1 Literature Review/References**; particularly Czernielewski, et. al.). Also, the proposed to-be-marketed product quantities are small, 15 gram (g) and 45 g tubes, and likely to have premium pricing limiting the likely extent of use in the OTC setting. Limiting the package sizes available on the OTC market is a reasonable safety measure to ensure limits on application and potential exposure to the drug.

With regard to usage in the clinical trials, subjects in the MUsT applied an average of 1.95 g per day (~ ¾ tsp) over an average body surface area of 1,865.7 cm^2. Extended over the 29 day duration of that trial, usage would average 56.5 g (1 ¼ tubes) applied over approximately 10% body surface area (average BSA for adult males and females ranges 16,000-19,000cm^2; 1,865.7 cm^2 is about 10-11% BSA). In the Juno trial, I estimate that subjects averaged about 0.6 g applied per day. Based on weights of returned tubes at the end of the trial, subjects averaged about 24.3 g used in the use

phase of the trial. Nearly 94% of subjects only used the contents of one tube of the product. Subjects remained in the trial for a mean of 41.4 days, with over 93% staying in the trial for at least five weeks. Thus, 24.3 g used over 41 days is approximately 0.6 g of product applied daily and 30% of the daily usage evaluated in the MUsT (1.95 g/day). Regarding quantity purchased over the duration of the Juno trial, 61 subjects purchased > 1 tube, but 77% bought that quantity at the 1st visit. Only two returned during the last week of the trial to purchase more tubes, and only four subjects purchased the maximum of three tubes. However, 17% of children < 18 years and nine of the top 13 highest quantity users reported > 40 g and > 80 g used, respectively. Yet, none of the seven highest quantity users (> 91 g) reported any skin-related events. Notably, there were no major differences in mean quantity used by age, gender or literacy.

Acne, a prevalent condition for post-pubertal children, adolescents and young adults, is similarly common for females of childbearing potential. Due to their position as first line treatments in mild to moderate acne, topical retinoids, or retinoid-like products such as adapalene, available without prescription would likely be highly utilized by such women to treat acne. The potential risks to unborn fetuses may be increased particularly because retinoids appear to be most damaging during those first few weeks of pregnancy[11], often before a woman is aware she is pregnant. While oral and some topical forms of retinoids are contraindicated for use by pregnant women and women who do not commit to effective birth control measures, adapalene is not contraindicated for use by that population. At the time of approval, the drug was considered a Pregnancy Category C drug. The benefits of the drug as an acne treatment must be weighed against potential risks, e.g., congenital defects. Those risks have been evaluated such that nonclinical data support a wide exposure, or safety, margin for use of the topical product. They are further supported by comparison of the extent of use demonstrated in the Juno trial (see **Section 6 Review of Efficacy**) and use in the MUsT which determined the margin (see Dr. Shukla's and Dr. Li's respective reviews for details). Postmarketing experience and the biochemistry of the drug also support safety. While the assessment of the benefits versus any potential risk have so far been part of the discussion between provider and patient when adapalene is prescribed, it does not appear that OTC consumers are likely to be unduly at risk for harm by using the product without the input of a learned intermediary.

The applicant evaluated, as a secondary endpoint, behaviors by pregnant or breastfeeding women who were considering purchase of the product in the Juno trial. This reviewer does not find any significant safety concern for breastfeeding women except if they apply the product to their chest and the drug transfers to a feeding infant, but this seems an unlikely occurrence. Based on the systemic exposure findings in the MUsT, it is unlikely that a feeding infant will be exposed to the drug through breastmilk, but it is unknown if that quantity of oral exposure would raise any safety concerns.

11 Kaplan YC, J Ozsarfati, F Etwel, C Nickel, I Nulman, G Koren, 2015, Pregnancy Outcomes Following First-trimester Exposure to Topical Retinoids: A Systematic Review and Meta-analysis, *Br J Dermatol*, 173: 1132-1141

Therefore, this reviewer focused on those pregnant women who chose to use the product or who became pregnant during the Juno trial. Five of nine pregnant women who inquired about enrolling in the Juno trial incorrectly said "Yes" to select to use the product, i.e., they did not intend to speak to a doctor first. Two of the women had negative urine pregnancy tests, but continued to state that they were or might be pregnant. The other three reported not seeing the warning, or that the pregnancy did not change their decision, or that "all labels" contain the warning, but they did not consider adapalene a safety concern for their pregnancy. One subject who said "No" to purchase was made aware that pregnancy was an exclusion criteria and it is unclear how she would have responded without that knowledge.

Once the trial was underway, four women, all over age 18 years, became pregnant during the six week use phase. One woman only discovered she was pregnant at the end-of-trial interview when she had a positive urine pregnancy test. The other three women confirmed pregnancy during the trial, but none spoke with their doctors about using adapalene. One had already applied her last dose, so she found it moot to disclose. Another later terminated her pregnancy for unrelated personal reasons. The fourth subject continued using the product. Notably, there is no proposed label warning to stop use and seek advice from a HCP if a female consumer becomes pregnant. Of the three pregnancies that were ongoing after completion of the trial, only one outcome is known, an uneventful birth.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

- MUsT – 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
- Actual Use Trial – Pivotal Actual Use Study for Adapalene 0.1% Gel

Reviewer's comments: This reviewer provided an assessment of the entire Juno trial. For the MUsT, an assessment of the safety of the trial is provided here. See Dr. Shukla's review for details on the pharmacokinetics' findings. Also see ***Section 8 Postmarket Experience*** *for additional details on the safety of adapalene when used in the prescription setting.*

7.1.2 Categorization of Adverse Events

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. Treatment emergent AEs were summarized by System Organ Class (SOC), Preferred Term (PT) and for related AEs, serious AEs (SAE) and discontinuations. The applicant's definitions of AEs, serious AEs, determination of relatedness of AEs to the test drug, severity and other description of the safety

monitoring are acceptable and were recorded on subject's CRF. The applicant reported that the small comparative number of low literacy subjects (125 vs. 822) and adolescents (12 to 17 years; 203 vs. 744), made difficult any conclusions based on those subgroups, although, on their face, there did not appear to be any significant differences in the AEs reported. Adverse events in this review will be assessed by frequency overall.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In all phase 2/3 trials worldwide in which the applicant has so far evaluated the safety of adapalene gel, 2,121 subjects have applied the drug at least once, with 661 treated in trials (up to 12 months' duration) to support original approval of the NDA. In the MUsT, 24 subjects were enrolled. Eighteen were < 18 years of age, with six over age 18. Thirteen were male and 11, female. All 24 received the study drug. On average, subjects applied 1.95 g/day ranging 1.2 to 2.9 g. Three subjects applied daily doses > 2.5 g. Mean dose applied by adolescents was less than that applied by adults > 17 years of age (1.85 g/day vs. 2.24 g/day). The total treated body surface area (BSA) averaged 1864.7 cm^2 (range 1387.4 – 2893.9 cm^2). BSA was greater in adults vs. adolescents (2022.5 cm^2 vs. 1812.2 cm^2). All exposures were over 1300 cm^2. The applicant provided a table (**Table 11**) with maximum concentrations and areas under the curve following trial exposures of up to 2 g 0.1% adapalene applied daily for 30 days with different formulations. The applicant indicates that normal daily use may provide maximum exposure of 0.5 g per day, such that a 15 g tube is equivalent to a 30-day supply.

Table 11: Maximum Systemic Exposure in Trials with Adapalene 0.1% Formulations

Formulation	Clinical Study#	Subjects	N	N quantifiable (at steady state)[a]	Most exposed subject	
					AUC_{0-24h} (ng.h/mL)	C_{max} (ng/mL)
Epiduo gel, 0.1%	SRE.18097	Adults	12	1	1.99	0.13-0.21
Monad adapalene, 0.1 %	SRE.18097	Adults	12	1 to 2	2.65	0.16
Adapalene Lotion, 0.1%	SRE.18108	Adults	14	1	2.00	0.13
	SRE.18190	Adolescents	13	5	4.93	0.24
Adapalene 0.1 % Gel	SRE.18115	Adults	25	4 to 7	3.47	0.20-0.31
	SRE.18254	Adults Adolescents	24 (6 adults +18 adolescents)	21 to 24[b]	2.90	0.17

a Steady state: PK sampling dates varied across studies from Day 10/15 to Day 28/30
b LOQ=0.02 ng/mL for study SRE.18254 only; LOQ=0.1 ng/mL for other studies
Source: Applicant's submission, Integrated Summary of Safety, Module 5.3.5 3, Section 4.2.2.5, Table 24, p. 69.

The applicant assessed exposure in the naturalistic setting of the Juno trial. The mean duration of treatment was 41.4 days (median 42 days), with 93.1% of subjects (882/947) remaining in the trial for at least five weeks. This length of daily use should have provided the average subject the opportunity to see some improvement, thus supporting the effectiveness of the product as an acne treatment in the OTC setting.

Reviewer's comment: AUTs are not typically designed or powered to adequately evaluate the effectiveness of a drug product for its intended purpose. The interview at the EOT did not include questions inquiring about subjects' improvement; however the five weeks' average duration of use in this six-week trial may support a noticeable improvement for those subjects who used for that time. The applicant reported, however, that nearly 86% of subjects used less than one tube of the product (see below). As noted in ***Section 9.2 Labeling Recommendations****, evidence supporting the original Rx approval indicates that noticeable improvement may occur by* (b) (4) *weeks of daily use.*

As indicated above, a 45 gram tube was available for purchase and subjects could purchase a maximum of three tubes (135 g). The directions on the DFL are to apply a "thin layer" over the entire affected area. There is no maximum dose. Based on subject body chart reporting and tube weights at the EOT visit, mean use of the product was 24.3 g (standard deviation 16.87) with a maximum reported use of 129.5 g. Overall, 85.7% (812/947) used less than one tube of the drug product (< 40 g). Stratified by literacy level, low literacy subjects had a slightly higher mean usage (26 g), median usage (26.3 g vs. 22.2 g) and similar range of quantities used (1.4- 116 g). By age, subjects ≥ 18 years had a slightly lower mean usage (24.1 g vs. 25.1 g), but higher median usage (22.8 g vs. 20.6 g) than subjects 12 to 17 years of age. There were no trends in total quantity used when subjects were stratified by alternative age brackets (12 to 17 years, 18 to 29, 30 to 39, 40 to 49 and 50+). By gender, women used slightly less (23.4 g) than men (26.2 g) over the duration of the trial.

In the total user population, 13 subjects (1.37%; 13/947) used more than 80 g, or close to two tubes of adapalene over the six-week treatment phase. Nine were in the 12-29 year age bracket and five were women of childbearing potential. Of these subjects, the seven greatest users (> 91 g) reported no AEs that appeared related to use of the drug (skin-related). A few other high users did report skin-related AEs such as dry, red or pruritic skin, but all were mild and only one reported reducing the dose applied.

Reviewer's comments: The applicant notes that it is common in naturalistic trials for some, often small, proportion of subjects to save drugs used in the trials particularly if the subjects find them effective. This is one possible explanation for seemingly high usage, particularly without reports of moderate to severe skin irritation or dryness. Such irritation would be likely with thicker or more extensive application than directed by labeling. The fact that 77% of subjects who bought > 1 tube did so at the first visit and that very few subjects returned to purchase in the last week of the trial may be counter to the notion that subjects bought only to store for use after the trial.

This reviewer also noted six subjects who were identified as "applying the product like lotion," potentially using a larger quantity than directed. Three reported mild skin-related AEs, peeling, dryness and burning sensation. All resolved on their own.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

In the MUsT, hematology, biochemistry and urine pregnancy and drug screen laboratory panels were tested at screening for all subjects. EOT labs were tested where indicated. In addition, tolerability was assessed with scales for erythema, scaling, dryness and stinging/burning. There were no significant trends, compared to baseline, in lab values over the duration of the trial. While subjects reported some skin changes in the tolerability assessments, none were severe and none resulted in discontinuation.

Urine pregnancy testing was the only routine diagnostic test conducted in the Juno trial. Women of childbearing potential performed the test twice, prior to entering the Use phase of the trial and at the EOT.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The potential adverse events associated with use of topical retinoid products are well established and were not addressed in the application or this review.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in either clinical trial.

7.3.2 Nonfatal Serious Adverse Events

There were no serious AEs reported in either clinical trial.

7.3.3 Dropouts and/or Discontinuations

There were no dropouts from the MUsT. Following a request by FDA (November 25, 2015), the applicant submitted (December 18, 2015) the CRFs for all subjects (N=9) who were excluded from or discontinued the Juno trial due to AEs (see **Table 12**).

Table 12: Findings for Discontinued Subjects - Juno trial

Subject	Demographics	Medical History	Usage History	Adverse Events
17047	18 years; M; normal literacy	NC	3/10/15 – 4/3/15; 32 g	Pruritis, redness at application site
20054	15 years; M; normal literacy	NC	3/22/15 – 3/25/15; 1 g	Redness, irritation at application site
24012	34 years; F; normal literacy	NC; Negative pregnancy test x 2	2/19/15 – 3/23/15; 7.4 g	Cold virus; peeling at application site
25008	14 years; F; normal literacy	NC; Negative pregnancy test x 1	Diary incomplete; ND	Rash, burning at application site
25012	14 years; F; normal literacy	NC; Negative pregnancy test x 2	3/10/15 – 4/16/15; 20.3 g	Sleepiness; increased acne
26043	27 years; F; normal literacy	NC; Negative pregnancy test x 2	3/15/15 – 4/8/15; 11.9 g	Worsening acne
26047	13 years; F; low literacy	NC; Negative pregnancy test x 2	3/15/15 – 4/15/15; 21 g	Virus; dry skin
27045	26 years; F; normal literacy	NC; post-hysterectomy	3/26/15 – 4/16/15; 19.7 g	Peeling skin* at application site
30020	51 years; F; normal literacy	NC; post-menopausal	3/9/15 – 3/22/15; 3 g	Increased blemishes

Source: Applicant's amendment, Module 5.3.5.2, Case Report Forms (Discontinued Subjects).
M/F: Male/Female; NC: Non-contributory; ND: No data; *Subject 27045 was the only one to report AE not resolved.

Reviewer's comments: None of the AEs or any other circumstances of discontinuation raised any safety concerns.

Subject 30006 was discontinued from the trial after nearly six weeks. The subject was female, > 18 years of age and with negative pregnancy tests at screening and EOT, although she did not complete the EOT interview. Her circumstances are described in **Section 6.1.1 Methods**.

7.3.4 Significant Adverse Events

None were considered significant that are not elsewhere discussed, e.g., pregnancy.

7.3.5 Submission Specific Primary Safety Concerns

The proposed labeling warns users not to apply to damaged skin including where "cuts, abrasions, eczema, sunburned" skin is present. In total, 80 users reported having damaged skin during the treatment phase. Reports ranged from sunburn and other accidental burns to cuts/abrasions and dry, scaly or peeling skin. Twenty (25%) reported using the product on those areas, mostly because their acne was in the area as well. Most of these users indicated that their skin was only mildly irritated and not worsened by application, or reported understanding that some irritation was likely early in the treatment period. Some subjects who reported stinging or irritation stopped applying the product to those areas, but even these subjects reported only mild effects.

In the Rx setting, users with sunburn are advised not to use the product until "fully recovered." The Drug Facts Label instructs users not to use on sunburned skin, to avoid excess sun exposure and tanning beds, and to use sunscreen. In the Juno trial, 29 subject users (3%; 29/947) reported "sunburn." All events except one (moderate) were considered mild, and 11 subjects were reported to either interrupt (N=6) using the product or reduce (N=5) their applied dose.

Reviewer's comment: Based on review of data in the submission, it is difficult to know how the dose was 'reduced,' and of those reported as "interrupting" their daily regimen, only three had diary data that supported the interruption in use, i.e., they stopped use over the time they reported suffering sunburn. Regardless, the reported AEs were nearly all mild and resolved without intervention.

This reviewer identified four subjects (05013, 15004, 20032, and 31021) who used adapalene on non-acne sites and reported AEs. These subjects thought the product may help with their skin conditions, e.g., rosacea and psoriasis. None raised safety concerns, and all but skin dryness, for one subject, were resolved or resolving by the EOT. Another notable circumstance is when subjects continue using other topical acne drugs, or drugs with potential for skin irritation, while also using adapalene. Concomitant topical acne drugs include various marketed products containing ingredients such as benzoyl peroxide, salicylic acid, and dapsone. In such cases,

irritation may worsen. These subjects reported a total of 63 AEs, mostly skin-related AEs or headache. Nearly all were mild. As stated elsewhere, users of adapalene who continue to use other topical acne products are likely to stop their regimen and seek medical advice if skin irritation becomes severe or persists.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the MUsT, eight subjects (33.3%) reported 17 AEs. None were serious and all were mild to moderate in severity. The most frequently reported AEs (N=3 each) were "skin irritation," "pruritis," and "headache."

The applicant indicates that skin-related AEs (erythema, scaling, dryness, pruritis, burning) may occur in up to 40% of product users as per the Rx labeling. The frequency of these AEs generally declines after the first month of daily use and the conditions typically improve spontaneously after drug discontinuation. In total, 471 (49.7%; 471/947) subjects in the user population reported at least one AE (N=1012 AEs). Over 88% were mild in severity and none were serious. There were no significant differences in the types of AEs reported when comparing subjects less than, to those greater than 18 years of age. **Table 13** demonstrates the most frequently reported (>2%) AEs in the Juno trial. In some instances, included AEs are closely related to the listed PT, e.g., nasal congestion and nasopharyngitis.

Table 13: Frequency of AEs (>2% total; N=1012) in Juno trial

System Organ Class Preferred Term (PT)	All Subjects, N; (% AEs)
Headache	179 (17.7)
Dry Skin	106 (10.5)
Erythema	46 (4.5)
Dysmenorrhea	40 (3.9)
Nasal congestion/rhinitis	39 (3.9)
Skin burning sensation	39 (3.9)
Skin exfoliation	39 (3.9)
Seasonal allergies	37 (3.7)
Acne	30 (3.0)
Sunburn	29 (2.9)
Back pain	23 (2.3)
Abdominal pain/discomfort	21 (2.1)
Rash/papular rash	21 (2.1)

Source: Modified from applicant's submission, adverse event datasets for Juno trial.

Reviewer's comments: The majority of AEs reported were skin-related disorders which is expected and included in labeling for adapalene. Users who experience "severe irritation" are directed to stop use and seek medical advice. This is a common warning for topical OTC drug products with dryness or irritation potential. None of the other reported AEs raise any safety concerns. Sunburn is discussed elsewhere.

This reviewer identified those subjects (N=88) who reported AEs and who applied the test product more than once daily, i.e., those subjects considered as incorrect users by one of the primary endpoints (see **Section 6.1.4 Analysis of Primary Endpoint(s)**). Of all subjects who used the product more than once daily (N=180), 49% (88/180) reported an AE (N=190). None of the AEs were serious, and rarely even moderately severe, and the most frequently reported events were grouped under the System Organ Classes (SOC) Skin and Subcutaneous Tissue Disorders (N=64; 33.7%), Nervous System Disorders (N=31; 16.3%) and Injury, Poisoning and Procedural Complications (N=20; 10.5%). The frequent AEs were skin conditions (e.g., dry skin, peeling skin, burning skin sensation, red/erythematous skin), headaches and seasonal or multiple allergies. Notably, sunburn (N=7) is categorized under the Injury, Poisoning and Procedural Complications SOC.

7.4.2 Laboratory Findings

No significant findings or trends in MUsT or any other trials conducted to support initial or worldwide approvals.

7.4.3 Vital Signs

No significant findings in MUsT or any other trials conducted to support initial or worldwide approvals.

7.4.4 Electrocardiograms (ECGs)

Not applicable.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See **Section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**.

7.5.2 Time Dependency for Adverse Events

Time dependency for AEs was not formally addressed in this application. Skin-related AEs are most likely to occur with regular use.

7.5.3 Drug-Demographic Interactions

See discussion of pregnancy-related concerns elsewhere.

7.5.4 Drug-Disease Interactions

See discussion of AEs and exposure under conditions of damaged skin.

7.5.5 Drug-Drug Interactions

None.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable. The Rx labeling for adapalene products notes that no human photocarcinogenicity trials have been conducted with adapalene, but animal studies have shown an increased risk of skin neoplasms with use of other retinoid drugs when exposed to UV irradiation or sunlight. Adapalene users are instructed to avoid or minimize exposure to sunlight or other sources of UV irradiation when using the drug.

7.6.2 Human Reproduction and Pregnancy Data

No subjects became pregnant during the MUsT and all women of childbearing potential committed to abstinence or use of approved contraceptive drugs during the trial. Pregnancy is not generally considered an AE, but any birth defects, congenital anomalies or other seemingly adverse outcomes (e.g., spontaneous abortion) reported by women who were pregnant or who became pregnant during use of a test product during clinical trials were considered SAEs. However, in the Juno trial, the applicant identified pregnancies as an AE since the labeling instructs to seek advice from a health

professional before use, and female users of childbearing potential are expected to be aware to take adequate precautions when determining to use the drug. During the trial, four women (subjects # 05008, 10016, 15007 and 28002), all over 18 years of age, became pregnant. All findings were reported, although, as noted above, the trial did not include a mechanism to report pregnancies to the investigators in lieu of a labeled instruction to do so.

Of the women who became pregnant, two had coincident AEs, headaches and dry skin. Three spoke with a doctor during the trial to confirm pregnancy, but none of those women discussed use of adapalene with their doctors. Two did not stop using the product afterward (the third had already applied her final dose and did not think disclosure of its use was relevant). One of the two chose to terminate the pregnancy for unrelated personal reasons. Subject 15007 had not seen a doctor because she only discovered she was pregnant at the EOT visit (positive urine pregnancy test). The applicant and primary investigator attempted on multiple occasions to contact (by email, telephone and letter) these women, finding that one delivered a healthy newborn. There is no information on the final outcomes of the other two pregnancies.

Reviewer's comments: Taking an opportunity to further discuss pregnancies in adapalene trials, in a phase 3, long-term (12 month), open-label safety trial conducted in Japan (Study 27006), of 357 subjects who completed the trial, 14 pregnancies were reported. Nine resulted in normal deliveries, two were premature deliveries (> 36 weeks gestation), and one each resulted in miscarriage, stillborn death (placental abruption) and elective termination. None of the 11 newborns had any congenital anomalies. One female subject withdrew from the trial after one month due to pregnancy. Approximately one month later, she suffered miscarriage (at 13 weeks). No other details were collected. The subject who reported stillborn death had used the drug for 84 days and stopped once pregnancy was confirmed. Fetal demise occurred six months later in gestation after drug discontinuation. The subject who terminated her pregnancy chose to do so on her own accord. She had withdrawn from the trial six months after enrolling, due to her pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Adapalene is not intended for OTC use by children under 12 years of age. Because there is no change to the approved formulation, indication, dosing regimen or route of administration, the Pediatric Research Equity Act (PREA) is not triggered. However, on February 19, 2016, in an overall assessment of the safety and effectiveness of adapalene without prescriber oversight, reviewers from the Division of Pediatrics and Maternal Health (DPMH) proposed considering making adapalene available for use by children from 9 to 12 years of age, thus expanding the indication to capture post-pubertal children who are likely to suffer acne and benefit from available treatment[12].

[12] Eichenfield LF, AC Krakowski, C Piggott, J Del Rosso, H Baldwin, SF Friedlander, et. al., 2013, Evidence-based Recommendations for the Diagnosis and Treatment of Pediatric Acne, *Pediatrics*, 131 (Suppl 3): S163-S186.

They note that more recently approved drugs for treatment of acne include safety and efficacy trials with pubertal patients as young as 9 years, whereas older drugs were not required to study children younger than 12 years. Some applications predated PREA and others were not considered to represent a meaningful therapeutic benefit over existing therapies. While there are no data from clinical trials supporting the safety and effectiveness of adapalene as a single ingredient product, nor any data from the consumer behavior program demonstrating that children 9 to < 12 years of age could use the product without a learned intermediary, DPMH rightly notes that, without labeling to the contrary, children < 12 years may be likely to use the product off-label. Regarding safety in younger children, the DPMH review states that "the safety profile [in controlled clinical trials for approval of Epiduo®] in patients 9 years to 11 years of age was comparable to that observed in older patients 12 years of age and above both in the nature and frequency of the observed events."

Reviewer's comments: The efficacy of adapalene as a single ingredient product can likely be extrapolated to a pubertal pediatric population < 12 years of age (the mechanism of acne formation does not differ). There may be adequate safety data from development of adapalene combination products (Epiduo®) to support use by younger children. However, the applicant is not seeking to expand the population to children < 12 years, we have no consumer behavior data demonstrating that younger children could select for and use the product safely and properly in the OTC setting, and the other formulations of single ingredient adapalene products (lotion and cream) would remain available by prescription only for use by children > 12 years.

There is no regulatory pathway to approve a wider target population without an application seeking such a claim. Even if there were, it could set a precedent whereby an OTC product would be available to a wider population than other single ingredient Rx-only formulations (lotion and cream) of the same drug for the same indication. This would occur if data were not also available to support approval of the same age expansion for the lotion and cream forms for Rx use. If FDA were inclined to expand the population, the applicant would need to first submit an application with supportive data since FDA is not empowered to force such a submission (e.g., through a postmarketing requirement pathway). Most likely it would be the applicant's prerogative, or may be encouraged through a Written Request.

Concerns about teratogenicity and congenital abnormalities (i.e., retinoid embryopathy) are addressed elsewhere in this review. In addition, see consult reviews by DPMH and the Office of Surveillance and Epidemiology.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

At FDA's request, the applicant submitted additional postmarketing safety analyses on December 18, 2015. The analyses included assessment of dermal safety including photosensitivity and irritation, AEs associated with concomitant use of topical acne products containing sulfur, resorcinol or salicylic acid and an analysis of scientific literature addressing safety of adapalene. The review of this data is in **Section 8 Postmarket Experience**.

8 Postmarket Experience

The applicant addressed the potential toxicity of adapalene on reproduction and fetal development with focus on teratogenicity and fetotoxicity. It also addressed carcinogenicity and analyzed postmarketing reports of skin-related toxicity and drug interactions. The applicant estimates that over 40 million patients have been prescribed adapalene gel at strengths of 0.1% or 0.3% since its international birthdate in 1992. From 1998 through 2014, 4,176 postmarketing safety reports have been submitted by users (~235 reports/year), with skin-related AEs accounting for 70% of those reports. Only 70 reports (1.6%) were serious. In the entire postmarketing period (through July 1, 2014), the applicant has received 239 reports of pregnancy exposure to adapalene. It also provided an assessment of the teratogenicity risk including a review of the characteristics of the adapalene molecule, its retinoid-like properties, a summary of retinoid-related teratogenicity with animal toxicity data and a review of the safety margin based on systemic exposure. The risk may be further assessed by Dr. Cindy Li, DNDP toxicologist, and reviewers from the Division of Pediatric and Maternal Health (DPMH).

Resulting from the applicant's focus as described above, four malignancies were identified, including two thyroid cancers, from search of the applicant's database, FDA Adverse Event Reporting System (FAERS) and the World Health Organization safety database (WHO VigiBase). The narratives contained limited information and the applicant noted that, in particular, thyroid cancer is not described in the literature following exposure to any form of retinoid drug.

The applicant also conducted a survey study (#102234) to understand current practices in physician-patient relationships when prescriptions are provided for adapalene products and other retinoids for acne. Both physicians (N=151) who prescribe adapalene and patients (N=147) with acne who used retinoid products were queried. Fifty percent (50%) of the enrolled physicians were dermatologists. The objectives were to ascertain practice patterns for treating acne and discussing treatment options, counseling for precautions and warnings and other management (e.g., pregnancy testing), as well as patient-reported experiences when managing acne and interacting with providers. Over one-third (36%) of physicians reported discussing potential risks of using a topical retinoid while pregnant, but only 6% of patients recalled discussing such information. See Ms. Cohen's review for further details on this survey study.

The applicant commissioned a review of their pharmacovigilance data to investigate pregnancy cases[13]. Dr. Gnansia, an expert in medical genetics and teratology, highlighted 276 pregnancy cases found in the applicant's database through September 2014 and including use of both adapalene single ingredient products and Epiduo® (adapalene/benzoyl peroxide). The reported outcomes (N=17) were varied, e.g., prematurity, hydrops fetalis, neurofibromatosis type 1, kidney malformation, and none appeared to describe patterns of anomalies consistent with retinoid embryopathy or provided information to support any significant causal association with use of adapalene ("Other outcomes;" **Table 14**).

Reviewer's comment: One case (# 3968610) identified some findings that have been seen with retinoid embryopathy. It included report of a woman who was four months pregnant and whose fetus was diagnosed by ultrasound with cleft lip/palate, "brain anomalies, no stomach, cardiovascular problems and bowel problems." She was 34 years old and reported no history of substance abuse. She reported using Differin® Gel for six months and commented that she would "probably have to terminate the pregnancy." There was no further information provided. While Differin® is the only drug identified, and the constellation of anomalies include some that have been identified following use of retinoid drugs, i.e., clefts, cardiac and brain anomalies, information is limited (other risk factors for anomalies, chromosomal aberrations) and the background rate of congenital anomalies in the U.S. population must be considered.

Because postmarketing data relies on spontaneous reporting, the author notes that it is unlikely that the number of pregnancy exposures reflects the actual number. In addition, there is likely bias towards untoward outcomes since normal pregnancies are unlikely to be reported to great extent. The circumstances resulting in "lost to follow-up" outcomes are not elucidated further.

Table 14: Pregnancy Outcomes from Galderma's Pharmacovigilance Database

Outcome	Postmarketing surveillance
Ongoing at time of report	27
Lost to follow-up	126
Healthy baby	83
Elective termination	7
Miscarriage	16
Other outcomes	17
Total	**276**

Source: Applicant's submission, Footnote 2, Table 1.

Galderma searched for cases using the following Standardized MedDRA Queries (SMQ): Normal Pregnancy Conditions and Outcomes, Pregnancy and Neonatal Topics, Neonatal Exposures via Breast Milk, Pregnancy and Neonatal Topics, and Pregnancy-

13 Gnansia E, 2015, Review of Exposures to Topical Adapalene Gel, Cream, Lotion During Pregnancy.

related Hepatic Disorders. It identified eight cases that contained information on pregnancies following exposure to adapalene. One case was of an adult female who appeared to have a history of congenital anomalies (micrognathia, kidney malformation) rather than a neonate following maternal exposure. The second case described adapalene as one of 44 drugs mentioned where the suspect drug, associated with autism, craniosynostosis and strabismus in a newborn, was sertraline. A third case described various cardiac anomalies and adapalene and sertraline included in a list of 11 medications. It was unclear to the applicant whether the subject was a neonate following maternal exposure. Three cases reported exposures only, and two reported only fetal growth restriction and induced abortion, without further details.

The applicant noted that postmarketing reports of skin-related AEs mirrored the findings from the Juno trial and the well-established safety profile of topical retinoids and other topical products indicated for treatment of acne. Regarding photosensitivity, the applicant points to only a single case of sun-exposure sensitization in all clinical trials conducted to support original approval. In postmarketing data, the most frequently reported skin-related AEs are “dry skin” and “erythema” (25-30% of AEs). In 15 total cases of overdose, or use of adapalene more than once daily, users generally reported local skin effects, mostly erythema, exfoliation and worsening acne. The applicant notes that in a few cases (N=15), dermatitis was confirmed as local hypersensitivity by positive patch testing to adapalene or the final formulation. Another small number of cases (N=48) suggested some degree of possible photosensitivity. These included skin irritations or burns following sun exposure. The events were generally local, mild and, where reported, resolved on their own. Nine cases reported concomitant use of tetracyclines, common inducers of photosensitivity. Presumably due to limited data in the reports, it is unclear in several of the cases describing sun exposure what role adapalene played in potentially increasing sensitivity. There were no reports of adapalene and photosensitization found in the scientific literature. The applicant conducted a search of possible drug interactions between adapalene and acne drug products containing sulfur, resorcinol or salicylic acid, since caution, in adapalene Rx labeling, is recommended with concomitant use. It identified 50 cases of exposure. As expected, reports included frequently reported events such as dry skin, irritation and erythema. None were serious and no AEs raised any safety issues.

The applicant submitted a Periodic Safety Update Report (PSUR) covering the period August 2013 through July 2014. In it, 215 medically-confirmed AEs were reported following over two million presumed patient exposures. Of these, two were serious (congenital anomalies – clubfeet and miscarriage) and the most frequent AEs were skin-related. The applicant notes that only 71 serious, unlisted AE reports have been collected since marketing of adapalene began (over 40 million patient users). Skin-related AEs are most expected compared to other events that may be seen following use of oral retinoids since systemic exposure following topical application is minimal (see **Section 4.4.3 Pharmacokinetics**). There were 34 reports of off-label use with the most frequent number of reports for use to “brighten,” “lighten,” or “whiten” the skin (N=8). Three of these cases included skin irritation as an AE. There were no apparent

safety concerns, raised over the reporting period, prompting the applicant to revise the Core Data Sheet or labeling of marketed adapalene 0.1% products. Also see the consult review by evaluators in OSE who provided a thorough investigation of the available postmarketing data and medical literature relevant to pregnancy outcomes following adapalene exposure (DARRTS; March 14, 2016).

9 Appendices

9.1 Literature Review/References

As requested, on December 18, 2015 the applicant submitted a summary table of nonclinical and clinical literature with details on study designs, population, test products, duration of exposure and results. The table included 17 articles. Important articles are summarized below.

Reviewer's comments: This reviewer identified the following references relevant to the important safety issues, including those concerns with pregnancy exposures.

Clewell HJ 3rd, ME Andersen, RJ Wills, L Latriano, 1997, A Physiologically Based Pharmacokinetic Model for Retinoic Acid and its Metabolites, *J Am Acad Dermatol*, 36 (3 Pt. 2): S77-S85. This study intended to create a model of topical 0.05% tretinoin pharmacokinetics across species and routes of administration. Oxidation and glucuronidation metabolism of tretinoin are described and glucuronidation is more prominent in primate species after topical dosing. Notably, once the glucuronide is formed, the placenta becomes impassable. Maximal plasma concentration, concentration over time and extent of distribution were determined. Systemic exposure appears minimal after topical application versus oral administration. For example, in monkeys given oral doses resulting in teratogenic effects, the ratio of areas under the curve for therapeutic topical facial doses in humans was 450,000:1 (5960 ng*hr/mL vs. 0.013 ng*hr/mL).

Cunliffe WJ, M Poncet, C Loesche, M Verschoore, 1998, A Comparison of the Efficacy and Tolerability of Adapalene 0.1% Gel vs. Tretinoin 0.025% Gel in Patients with Acne Vulgaris: A Meta-analysis of Five Randomized Trials, *Br J Dermatol,* 139 (Suppl 52): 48-56. This meta-analysis compared five well-designed, randomized clinical trials (N=900 subjects) to investigate differences in efficacy and safety of topical forms of adapalene or tretinoin for treatment of mild to moderate acne. The authors found that adapalene had equivalent, but more rapid (by week 1 assessments in 12-week trial duration periods) effect compared to tretinoin, but it was also more tolerable (erythema, scaling, dryness, burning and pruritis) at all evaluation points. The investigators also point to explanations for adapalene's tolerability, including less potential for irritation from breakdown products upon exposure to light (tretinoin is less chemically stable). The formulations may also have a role as

adapalene gel is aqueous compared to tretinoin's alcohol-based form. Tolerability factors could also contribute to improved compliance and better efficacy over the treatment period.

Reviewer's comments: Any significant difference in tolerability is a factor to consider for future Rx-to-OTC switches of topical retinoids. With greater possible incidence of side effects, including the potential for worse skin irritation, tretinoin, and other retinoids, must be compared to adapalene regarding the safety profiles if adapalene is approved for OTC use. With concerns over pregnancy exposures, significant skin irritation that may impact compliance to a treatment regimen could imbalance the benefit-risk profile for considering some products for OTC marketing status. If subjects do not use the products for a duration long enough to give the opportunity for effect, they would be only exposing themselves to potential safety risks.

Czernielewski J, S Michel, M Bouclier, M Baker, C Hensby, 2001, Adapalene Biochemistry and the Evolution of a New Topical Retinoid for Treatment of Acne, *J Eur Acad Dermatol Venereol*, 15(Suppl 3): 5-12. The authors, Galderma employees, describe the history of Galderma's development of adapalene for topical treatment of acne. The drug is described as one with the efficacy of available retinoids "while minimizing the burden of retinoid-associated irritation" and, thus, treatment compliance. Some tretinoin degradation products, due to poor stability of the molecule particularly in the setting of sun/UV radiation exposure or when applied concomitantly with benzoyl peroxide (an oxidizing agent)[14], were found to be irritating. In the development of the adapalene molecule, tretinoin's double bonds are replaced by naphthoic acid aromatic rings, resulting in greater molecular stability (**Figure 2**). In several trials comparing adapalene to tretinoin, the authors have found that adapalene has a lower irritation potential. This finding persisted when adapalene was compared to monotherapy and in combination with antimicrobial acne treatments, benzoyl peroxide, erythromycin and clindamycin.

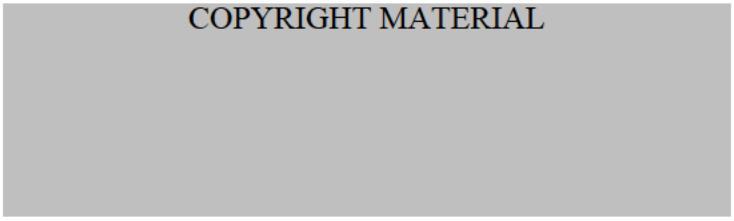


Figure 2: Chemical Structures of Adapalene and Tretinoin

Source: Figure 1 (Czernielewski, et al., p. 6)

Kaplan YC, J Ozsarfati, F Etwel, C Nickel, I Nulman, G Koren, 2015, Pregnancy Outcomes Following First-trimester Exposure to Topical Retinoids: A Systematic

[14] Martin B, C Meunier, D Montels, O Watts, 1998, Chemical Stability of Adapalene and Tretinoin when Combined with Benzoyl Peroxide in Presence and in Absence of Visible Light and Ultraviolet Radiation, *Br J Dermatol*, 139 (Suppl 52): 8-11.

Review and Meta-analysis, *Br J Dermatol*, 173: 1132-1141. This study reviewed all available reports of exposure, including in the first trimester, to topical retinoids to determine any association between drug exposure and risk of adverse pregnancy outcomes. The authors searched several major databases with independent review of reports describing retinoid exposure in a total of 654 pregnant women (590 births) compared to 1,375 unexposed women (1,278 births). Two reports identified adapalene exposure (Panchaud (2012) and Autret (1991)). The authors detected no significant increased rates of major congenital malformations, spontaneous abortions, stillbirths, elective terminations, low birthweight or prematurity after pregnancy exposures; nor did they detect significant heterogeneity between studies. Also, the authors did not consider any of the reported major congenital anomalies consistent with those typical of retinoid embryopathy. The authors did not conclude, however, that there were *no* risks associated with use of topical retinoids. They cite animal studies demonstrating skeletal variations, low birth weights and fetal demise following exposure. They also cite sporadic case reports, but no randomized trials or other epidemiological studies, in human pregnancies describing findings such as holoprosencephaly and other central nervous system anomalies, ear malformations, cardiovascular and optical tract anomalies. These are findings consistent with retinoid embryopathy.

Kawashima M, S Harada, P Andres, Y Miyachi, 2007, One-year Efficacy and Safety of Adapalene Gel 0.1% Gel in Japanese Patients with Acne Vulgaris, Skin Res, 6: 504-512. These authors investigated the long-term safety and efficacy of adapalene in 357 Japanese subjects (83% female) 12 to 35 years of age who completed one year in a trial. The drug, used daily as directed on the face, was safe and well tolerated for treatment of acne. The majority of adverse events occurred in the first two weeks with 79% reporting skin-related AEs in the first month. Of 2,450 AEs in total, only 13 were serious (no deaths). Nearly 60% were skin-related and nearly three-fourths were mild. Three subjects discontinued due to adverse events during the first six months and only one additional subject did so during the second half of the trial. Urine pregnancy tests were conducted at baseline, at six months and at the end of the trial; 14 subjects discontinued due to pregnancy. Nine resulted in normal deliveries, two premature deliveries, and one each of miscarriage, intra-uterine death and elective abortion. There were no congenital malformations. No “per-protocol” population was defined for this long-term trial, so the safety population, “all patients treated,” was defined as all subjects who applied the product at least once.

Reviewer’s comments: This long-term trial provides limited details on pregnancies that occurred during the trial, but demonstrates no signal for retinoid-related birth defects in subjects who may have been taking the product for up to one year for facial acne. Reported adverse events do not raise clinical concerns and the drug appears to be well-tolerated over long-term treatment.

Panchaud A, C Csajka, P Merlob, C Schaefer, M Berlin, M De Santis, et. al., 2012, Pregnancy Outcome Following Exposure to Topical Retinoids: A Multicenter Prospective Study, *J Clin Pharmacol*, 52: 1844-1851. While adequate clinical data

on the safety of topical adapalene used in pregnancy are lacking, these authors sought to ascertain the range of adverse birth outcomes following first trimester exposure to topical retinoids, including adapalene. Eleven teratology services enrolled pregnant women exposed to topical retinoids whose doctors sought advice from the service between 1992 and 2006. These services are typically contacted by obstetricians and cases are reviewed by teratology experts. The authors compared the frequencies of outcomes (e.g., congenital defects, spontaneous abortion and elective termination) to pregnancies of women without exposure to topical retinoids or known teratogens. The control group (1:2) included pregnant women who were taking drugs deemed nonteratogenic, who were matched at the same clinical service site, and matched by age and gestation. Twenty four subjects (10.2%; 24/235) reported using adapalene, while the majority of subjects used topical tretinoin (N=143). Nearly all subjects were using a retinoid prior to or at the time of conception (mean 1.8 gestational weeks), and most women stopped using the products when pregnancy was confirmed, although mean drug exposure was 8.1 weeks. Most pregnancies resulted in birth of healthy newborns (85%). The only significant difference between groups was by the frequency of elective terminations (15 vs. 7; $p < 0.001$), but details on reasons for termination were not reported. There were no other significant differences between the two groups, including gestational age at birth (39.4 weeks for both groups). No children had features of retinoid embryopathy and there were no significant differences in the frequency of major or minor birth defects between the two groups (OR 1.8; 0.6-5.4 and 1.3; 0.4-3.7, respectively). The authors found no increased risk of adverse birth outcomes in pregnant women using topical retinoids in the first trimester, likely due to limited systemic bioavailability.

Reviewer's comments: The authors did not provide many details on drug exposure (extent of use), or a drug-specific assessment of birth outcomes, likely due to the small numbers, but this study lends support to the safe use of topical retinoids, including adapalene, in the OTC setting. Many women would be expected to stop using adapalene once pregnancy is confirmed. This is evidenced in behavior under the advice of a learned intermediary. Even outside the setting of a clinician's office, OTC labeling that warns women who are pregnant to speak to their doctors first and to stop use and see a doctor if they become pregnant while using adapalene gel appears to be an acceptable alternative.

Stancil SL, M Miller, H Briggs, D Lynch, K Goggin, G Kearns, 2016, Contraceptive Provision to Adolescent Females Prescribed Teratogenic Medications, *Pediatrics*, 137: e20151454 [ePub ahead of print]. This retrospective review describes pediatrician behaviors when prescribing known teratogenic drugs to adolescent and young adult patients (14 to 25 years of age). There are studies demonstrating that adult females of reproductive age are not commonly prescribed contraceptives if taking teratogens. The drugs (N=59; commonly prescribed in pediatric medical centers) were classified as Pregnancy Category D or X. Data were collected on provision of contraceptives and history-taking for menstrual and sexual activity. The investigators

queried ICD-9 diagnostic codes or key word searches in electronic medical records and orders to capture visit interactions (N=4,172). Over a five year period (2008 to 2012), 1,694 female patients were prescribed 4,506 teratogenic medications. Most frequently, specialists in neurology, hematology-oncology and dermatology prescribed the drugs. Contraceptive provision or counseling was documented in 28.6% of visits (1,194/4,172). Dermatologists accounted for the highest proportion (46.9%) of counseling or contraception. Drugs with risk mitigation systems in place, e.g., isotretinoin, were more likely to prompt provision of contraception (RR 2.09, 95% CI, 1.88-2.32; adjusted OR 3.33, 95% CI 2.69-4.11), but there was less documentation of menstrual or sexual history discussion in those circumstances. From 2013 national data, 35.2% of adolescent females were classified as sexually active. Thus, the authors conclude that adequate precautions are not being taken by healthcare providers to mitigate risks with teratogenic medications in the studied population.

Reviewer's comments: The only acne treatment queried was oral isotretinoin. It was the fourth most frequently prescribed medication (6.7%; 275/4172). No topical products were identified in this review. The authors cite published studies demonstrating that women of reproductive age are not more likely to receive any form of contraceptive intervention if prescribed teratogenic medications than women who are not prescribed such drugs.

Schwarz EB, DA Postlethwaite, Y-Y Hung, MA Armstrong, 2007, Documentation of Contraception and Pregnancy when Prescribing Potentially Teratogenic Medications for Reproductive-age Women, Ann Intern Med, 147: 370-376. The objective of this one year (2001) retrospective review was to assess pregnancy rates and documented frequency of counseling when women of reproductive age were prescribed drugs classified as pregnancy category D or X. This review was conducted among a cohort of women (N= 488,175) in an HMO in northern California. Internists and family practitioners prescribed 48% of all class D or X medications to women in the study. Of those women who received these prescriptions (scripts), 48% of women filling scripts for class D drugs and 47% of women getting class X drugs had no documentation of counseling, contraceptive use or sterilization within the two years prior to receiving the scripts. There were similar proportions of class D or X drug scripts and class A or B drug scripts filled (37% vs. 39.4% respectively) by women who also filled a contraceptive prescription or had been sterilized. Additionally, women who filled scripts for class D or X drugs were only slightly less likely than those who filled scripts for class A or B drugs to have a positive pregnancy test within three months of filling the scripts. The authors found that women prescribed teratogenic medications were no more likely to receive any counseling than women who were not.

9.2 Labeling Recommendations

(b) (4)

Figure 3: Proposed Adapalene Drug Facts Label

As noted in **Figure 3**, the applicant proposes (b) (4)

Reviewer's comments: (b) (4)

(b) (4)

On May 2, 2016,

the applicant submitted revised labeling (b) (4)

.

Regarding the pregnancy warning in the DFL, there are many OTC drug products, including monograph-allowed topical acne products such as those containing benzoyl peroxide or salicylic acid, with a Category C classification as adapalene is classified. The applicant acknowledges FDA's concerns about the potential risks to fetal development following retinoid exposure, proposing to include the warning (21 CFR 201.63(a)) "If pregnant or breast-feeding, ask a health professional before use." This warning is intended for drugs with systemic absorption, so the applicant notes that it is "proposing to incorporate a heightened warning for precaution statement" (Module 5.3.5.2, Protocol, Section 2.1, p. 16). **This reviewer recommends that the warning be modified to state "If pregnant or breast-feeding, *ask a doctor* before use."** This revision may encourage a more robust discussion between the user and their healthcare provider regarding the potential reproductive risks associated with use of adapalene. Such a discussion may be more beneficial to the user than what may come of a briefer encounter with pharmacy staff at the point of purchase. Based on data submitted in the application, the term "health professional" may be too vague in this instance.

This reviewer also recommends a warning to "Stop use and ask a doctor" if a user is trying to become pregnant or becomes pregnant while using the product. It is expected that such a warning may also prompt a conversation between the user and a healthcare provider on the benefits and risks of using adapalene while pregnant. Because acne may be chronic and recurring, and a product like adapalene may be used for an extended period, such a precaution is important to ensure that pregnant women have a conversation with their HCP about use of the product. There was no similar warning on the tested labels, likely contributing to continued use by pregnant women in the Juno trial. There was no reason for them to stop use. While there is no established link between teratogenicity and use of topical adapalene, and there are a variety of other reasons outlined in this review and supportive of OTC marketing status for adapalene gel, it is reasonable for a pregnant or interested consumer to be prompted to speak with their HCP if they have questions about use of this product, retinoids in general, and risks for teratogenicity.

Additional items that appear to be inadequately addressed in the proposed labeling, and are recommended for inclusion can be found in **Section 9.4 Additional Labeling** in marked up versions of the proposed DFL and consumer leaflet:

- The Rx label warns that concomitant use of adapalene and "other potentially irritating topical products" may cause more than mild skin irritation. It may be prudent to delay use of adapalene until other effects have improved or resolved
    - Consumers may be instructed to use only one acne treatment at a time
- Add a bullet cautioning consumers not to use more than directed since that will not result in faster or better results
    - The statement may include a reminder not to use the product more than one time per day
- Add a bullet informing consumers that moisturizers containing alpha hydroxy and glycolic acid ingredients should be avoided to limit skin irritation. This is in the patient information of Rx labeling
    - The label should indicate to consumers that the worsening of acne early in the treatment course is normal. Rather than stating (b) (4) the label may instruct consumers to continue using unless irritation becomes severe
- Based on Rx labeling, findings from the development program and comments made in **Section 4.3 Preclinical Pharmacology/Toxicology**, this reviewer recommends the DFL address the following under the subsection "Directions" saying:
    - Use the product at night
    - Direct consumers how to protect from the sun if they must apply the product during the day
- Users should have some expectation of the timing of benefit. Rx labeling states that "[t]herapeutic results should be noticed after eight to twelve weeks of treatment." In the applicant's core data sheet, evident clinical improvement is expected after four to eight weeks of daily use. The proposed Consumer Leaflet (**Figure 4**) needs revision on this point
    - If consumers get no improvement by 12 weeks of daily use, the DFL needs to direct them to stop use and ask a doctor

On the Principal Display Panel (PDP), this reviewer has additional recommendations:

- (b) (4) I recommend the (b) (4) be deleted
- The (b) (4) needs to be removed
- Several claims require substantiation including (b) (4)
    - (b) (4) The claim is misleading and I recommend removal. (b) (4)
    - (b) (4)

[redacted] I find the terms confusing and potentially misleading [redacted] The applicant is no longer seeking a [redacted] claim.

- I recommend the statement [redacted] be revised to "Once-a-day" acne treatment consistent with the consumer leaflet
- Whether the product can claim it is oil-free and fragrance-free requires input from reviewers in ONDQA
- There are no data provided that consumers understand what [redacted] means or whether the data support adapalene as [redacted]
    - See **Section 9.4 Additional Labeling** for comments on moisturizers that may be avoided
- The applicant needs to substantiate the claim that the drug is "dermatologist developed [redacted]," otherwise I recommend it be deleted
- This reviewer finds that the statement [redacted] while truthful, may mislead consumers [redacted] but what that means to consumers is unclear. Further discussion about retinoids in the insert may be warranted
    - The statement must be revised to "First FDA approved over-the-counter retinoid for acne use." If the statement is considered acceptable, this reviewer recommends that an asterisk be added after "retinoid" referring pregnant consumers to the relevant section of the information leaflet (see comment in **Section 9.4 Additional Labeling** on "What should I know before using the product?")
    - The asterisk could be followed by a statement such as "if pregnant, see the Drug Facts and the consumer information leaflet inside the package and talk to your doctor first for more information on adapalene (Differin) and retinoid drugs"

Reviewer's comment: After additional discussion with the review team, the statement following the asterisk was recommended for revision to read "IMPORTANT: (in red font) Read the carton and enclosed consumer information leaflet before using this product. Keep this carton and consumer information leaflet. They contain important information."

For the Drug Facts and Consumer Information Leaflet, this reviewer has recommended revisions that are provided in the sideline comments and tracked changes in **Section 9.4 Additional Labeling**.

9.3 Advisory Committee Meeting

This product is the first of a new class of drug to be introduced to the OTC consumer. While the topical treatment of acne is an indication well established in the OTC setting, retinoid drugs, as a class, are associated with teratogenicity. Although adapalene is a Pregnancy Category C drug and there is no evidence of retinoid embryopathy with its topical use, an Advisory Committee meeting was convened to discuss approval for OTC marketing status. At the meeting, FDA presented Rx postmarketing safety data and results of analyses from a variety of studies and trials including a MUsT, label comprehension and self-selection studies and an actual use trial. FDA also presented nonclinical data that, when considered in light of MUsT data, supported a wide exposure margin. The Committee was made up of members of the Nonprescription Drug Advisory Committee, and dermatology and reproductive toxicology specialists and the meeting was held on April 15, 2016.

Overall, the committee found the safety profile acceptable to support availability of adapalene in the OTC setting. The committee unanimously voted (16-0) in favor of OTC use of the product for treatment of acne by adults and children > 12 years of age. The committee was split on the extent of labeling precautions important for safe use by pregnant women and women of childbearing potential. Several also proposed uncoupling the breastfeeding warning from the pregnancy warning, and removing it, since they deemed there were no safety issues with use while breastfeeding. Some wanted the proposed precaution (If pregnant or breastfeeding, ask a healthcare professional before use) removed because the available data did not support the precaution and they were concerned that it would be misunderstood and that providers may unnecessarily advise against use of the drug or for birth control measures, and may have concerns about risks to a fetus that are unsubstantiated. Other members proposed that the precaution remain and that the Consumer Information Leaflet (CIL) contain information on how adapalene differs from other retinoids and that providers have safety information available to appropriately counsel their patients.

Regarding other precautions and warnings on Drug Facts labeling, the committee made several recommendations including, with general agreement, the following:

- Improve clarity of the direction on where the product should be applied (whole face vs. affected area) and how frequently (consider, for example, “use once in a 24 hour period”)
    - Consider revising the direction not to use another topical acne medication to within 24 hours of using adapalene
    - Ensure that the DFL and CIL communicate the same messages
- Improve clarity on how to prepare the affected area before applying, i.e., cleaning and drying the area
    - Be more specific on the types of facial moisturizers that can be used for dryness
- Consider a maximum duration of use because efficacy trials were only 12 weeks’ duration

    - Beyond the maximum, direct consumers to first consult a physician
- Specifically caution that sun/ UV light exposure may increase skin sensitivity
- Consider more specificity on the direction to apply a "thin layer" which may limit against over-applying
- Make the CIL clearer with regard to explaining "severe" skin irritation

The committee also cautioned that something like a CIL is typically discarded so clarity within the DFL box is important, acknowledging size limitations and readability. Notably, the Principal Display Panel was not available to the committee for discussion, so there were no recommendations made on the information proposed there.

Reviewer's comments: This reviewer has addressed many of the proposed labeling revisions in my labeling recommendations, and generally agrees with the committee's considerations. I agree with the committee members who preferred that the pregnancy warning remain in the label. I also considered that the breastfeeding warning be uncoupled and removed since, although the Rx label states that there are no data on exposure in breastmilk, systemic exposure is minimal, there is no evidence of risks associated with breastfeeding, and it seems unlikely that women would apply the product directly to their breasts resulting in more localized exposure through absorption on the breast or by transfer to the skin of a feeding baby. Also, topical OTC drug products do not typically include pregnancy/breastfeeding warnings in labeling. However, the warning was discussed internally by the review team and this reviewer is now of the opinion that it remain as a precaution for both pregnant and breastfeeding women in order to encourage safe use and interaction with a doctor to discuss the full benefit and risk profile for those populations of potential users.

Other proposed revisions that I do not agree with are labeling to explain the quantity of a "thin layer" application. The small package size that we would allow to be marketed and the data from the actual use trial support the safe use of the product and a "thin layer" application. I am not confident that evaluating consumer understanding of the direction to apply a "thin layer" would result in a quantity that could be universally understood and measured by all OTC consumers of this product. Also, consumers are likely to understand severity of skin irritation, a common warning on topical OTC drug labels.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RYAN M RAFFAELLI
06/09/2016

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M E M O R A N D U M

Date: May 26, 2016

From: Amy Woitach, DO, Medical Officer, DDDP

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CC: Tatiana Oussova, MD, Deputy Director of Safety, DDDP
Lydia Springs, Regulatory Health Project Manager, DDDP

Re: DDDP Consult 1709: NDA 020380/S-010 Differin (adapalene) gel, 0.1%

Background: DNDP has received a supplemental New Drug Application (sNDA) for NDA 020380/S-010 Differin (adapalene) gel, 0.1%. The supplement proposes an Rx to OTC switch for this product strength. DDDP associated reviewers have been asked to provide collaborative input as subject matter experts.

Material Reviewed:

1. Consult request
2. Application NDA 020380/S-010
3. Differin Gel, 0.1% Prescribing information
4. May 31, 1996 Clinical Team Leader Review of NDA 020380
5. DMPH consult responses
6. Clinical pharmacology review
7. OSE Postmarketing Safety Reviews
8. Advisory Committee Meeting Materials

Review:

Regulatory History

The Agency initially approved adapalene as a new molecular entity in 1996, under the trade name Differin. Five topical dosage forms containing adapalene at 2 different strengths (0.1% and 0.3%) have been approved in the US. Adapalene is approved as a single agent for the topical treatment of acne vulgaris in patients 12 years of age and older as:

- 0.1% solution (NDA 20-338), approved 5/31/1996, now discontinued
- 0.1% gel (NDA 20-380), approved 5/31/1996
- 0.1% cream (NDA 20-748) approved 5/26/2000
- 0.3% gel (NDA 21-753), approved 6/19/2007
- 0.1% lotion (NDA 22-502) approved 3/7/2010

Adapalene 0.1% is also approved (NDA 22320) in combination with Benzoyl Peroxide 2.5 % as a topical gel (Epiduo). It was approved on 12/8/2008 for the topical treatment of acne vulgaris in patients 12 years of age and older and the indication was revised to include patients nine years of age and older in February 2013 based on clinical studies conducted in this pediatric population.

Another adapalene/benzoyl peroxide combination product, Epiduo Forte (NDA 207917), was approved on 7/15/15 for the topical treatment of acne vulgaris. The product contains adapalene 0.3% gel and benzoyl peroxide 2.5% and was evaluated in patients 12 years of age and older.

At this time, adapalene 0.1% Gel is available as a nonprescription drug only in Russia. In January 2016, Germany's Federal Institute for Drugs and Medical Devices considered and recommended against releasing adapalene gel 0.1% (in 25 gram packages) from medical prescription [redacted] (b) (4)

Teratogenicity

Adapalene is not a true retinoid but exhibits retinoid like clinical effects, and competes in the marketplace with other topical retinoids such as topical tretinoin. All retinoids, including adapalene, are known to have teratogenic effects in animals. Animal studies do not always predict effects in humans, and the actual threshold for an effect in humans may be different (higher or lower) than the species tested. The human sensitivity to retinoid is unknown. However, it has been suggested that humans may be a more sensitive species for teratogenic effects of retinoids. Some retinoids, both oral and topical, have been associated with congenital anomalies suggestive of teratogenic effects in humans.

Toxicology data clearly demonstrate a teratogenic signal with oral adapalene and the findings are consistent with other drugs in the retinoid class. When given orally, adapalene is teratogenic in both rats and rabbits at doses of 25 mg/kg or greater. Findings in the rat include cleft palate, microphthalmia, encephalocele and skeletal abnormalities. Findings in the rabbit include in umbilical hernia, exophthalmos, and kidney and skeletal abnormalities. When given topically, adapalene did not induce malformations, but there were increases in supernumerary ribs in both species and delayed ossification in rabbits.

The margin of exposure for teratogenic effects of adapalene is estimated to be approximately 70 times for rats and 357 times for rabbits. This is based on a calculation comparing the animal data with the highest value observed from human PK data measured in subjects who dermally applied what is considered to be maximal use of adapalene 0.1% gel.

Reviewer comment: It is this reviewer's opinion that the margin of exposure calculation should not be used to make a determination of human safety as it does not take into account other factors that could increase the absorption rate over that seen in the maximal use trial. These could include use on damaged skin, concomitant use of substances/ dressings that increase absorption, simultaneous use of vitamin A-containing dietary supplements or cosmetics, heavy application of product, frequent application of product and application to a larger body surface area. Additionally, the unknown sensitivity of humans to adapalene-related teratogenicity precludes the margin of exposure from being a surrogate for safety determination \. Without a learned intermediary to limit the likelihood of achieving increased absorption, in both clinical judgment as well as limiting the amount of prescribed product, and without a known threshold for teratogenic risk, the predicated "safety margins" are unlikely to fully inform human teratogenic risk to allow ad libitum use in the OTC setting.

Of note, a literature report describes a case in which it appears that under certain conditions, it may be possible for topically applied adapalene to achieve a dosage that can have systemic effects. Albeit the indication is not acne, in the OTC setting there will be no limitation on how the product is used. A brief description of the case is as follows:

> *A 55-year-old female with Darier disease had a history of hepatitis with long term acitretin (oral retinoid) use. Approximately 10 months later, she was treated with adapalene 0.1% cream daily for the relapse of Darier disease. Overall, 15 tubes of 30 g adapalene were applied on approximately 15% of her body surface from January 2012 to September 2012 (8 months). She developed hepatitis. Hepatitis is an unlabeled event for adapalene, but labeled for oral retinoids. This case supports a probable association between adapalene and hepatitis based on temporality, clinical presentation, laboratory values, positive dechallenge, and absence of other causes of hepatitis. The use of a large dose of adapalene on her lesions may have resulted in an increased absorption of adapalene resulting in toxicity.*

While this reviewer understands that others have found the margin of exposure to reassuring, considering it a "safety margin", there remains uncertainty in the applicability of the calculated multiple of exposure in the OTC setting. It is this reviewer's opinion that it is a misapplication to rely on the margin of exposure, typically used to estimate a safe human starting dose, as a surrogate for teratogenic risk in the OTC setting. Thus, this reviewer finds that the role of the learned intermediary is important for ensuring that systemic exposure continues to fall within the safety limits

that have been characterized in clinical trials and as a governor of dispensed amounts of product in the prescription post-marketing setting.

Human Pregnancy Exposure

As stated above, retinoids are teratogenic when an unknown systemic exposure threshold is achieved in humans. Characteristics of congenital anomalies that are consistent with retinoic acid embryopathy have been reported in infants exposed to both oral isotretinoin and topical tretinoin. Retinoic acid embryopathy is associated with various craniofacial defects, cardiovascular defects, and central nervous system defects as well as thymic, parathyroid, and skeletal abnormalities. Additionally, some affected infants may present with neurocognitive effects such as below average intelligence and learning disabilities, but no major structural abnormalities.

There have been no clinical trials assessing the teratogenic risk of adapalene in pregnant women. Post-marketing safety data from 20 years of prescription use demonstrate few cases of abnormal pregnancy outcomes with no clear-cut cases of teratogenic effects due to adapalene. The Division of Pharmacovigilance (DPV) identified 18 cases of adapalene associated abnormal pregnancy outcomes in FAERS reported from May 2006 through November 17, 2015. These cases included reports of miscarriage (9), congenital anomalies (5), abortion (2), preterm birth (1), and hemorrhage (1). The assessment of such analyses is limited by underreporting, lack of clinical data in individual cases, and reporting biases. Also, FAERS is not the ideal database to detect adverse events that have a latency period of expression, such as congenital anomalies.

Reviewer comment:
The absence of reports does not necessarily translate to an absence of events. Underreporting, especially of nuanced events such as spontaneous abortions and neurocognitive effects, limits interpretation. Also, practitioner experience with the retinoid class may affect prescribing patterns of acne treatments for pregnant patients.

While not optimal for an assessment of teratogenicity, the post-marketing data supports that when used as prescribed, the risk of teratogenicity is likely to be low. However, it is not clear to this reviewer as to how the post-marketing prescription information can adequately support adapalene use in the OTC setting. When available OTC it is expected that adapalene will likely be used in many more pregnancy women based on the actual use experience and for some, there is a strong possibility of achieving higher levels of systemic exposure. Because the threshold for teratogenicity in humans in not known, it is this reviewer's opinion that there is currently not enough safety data available on the use of adapalene in pregnant women to support an OTC switch.

Submission:

No new non-clinical data were submitted with this sNDA. Also, no new data pertaining to efficacy were submitted. To support OTC use, Galderma conducted a multiple-dose pharmacokinetic study under maximal use conditions to evaluate absorption through the skin in an adolescent and adult population. The applicant also conducted three consumer

studies in support of the OTC use of adapalene: a label comprehension study, a self-selection study in pregnant and lactating women, and an actual use study.

Efficacy

The applicant intends to rely on the efficacy from the original submission. The risk benefit of the product was adjudicated at the time of approval in 1996. The Division has no additional information to the contrary that the product is effective when dispensed as a prescription product and used as labeled. In order to answer questions from DNDP regarding the original approval, below are excerpts based on the 4/21/1994 statistical and 4/12/1996 team leader reviews.

A total of five controlled clinical studies were conducted with adapalene gel 0.1% in subjects with mild to moderate acne vulgaris, two of which were vehicle-controlled. Primary assessments were at 12 weeks. Table 1 below provides a summary of the results and a description of the study designs and outcome follows.

Table 1

Study Number		Week 12 % Reduction from baseline			
		Adapalene 0.1%	Retin-A 0.025%	Vehicle	p Value or 95% Conf Interval
C-89-61	Non-inflammatory lesions	**48%**	39%	35%	**.059**
	Inflammatory lesions	**46%**	44%	36%	.138
9105-CD271G-EV	Non-inflammatory lesions	26%		1%	**.001**
	Inflammatory lesions	34%		12%	**.01**
	Global Grade	1.21		1.34	**.058**
CR88091	Non-inflammatory lesions	73%	**81%**		-18,2
	Inflammatory lesions	65%	**71%**		-20,9
	Global Grade	**77%**	74%		-8,14
CR89064	Non-inflammatory lesions	63%	**64%**		-1,1
	Inflammatory lesions	55%	**60%**		-16,6
	Global Grade	54%	**57%**		-11,6
CR 89-32	Non-inflammatory lesions	**46%**	33%		**.2,26**
	Inflammatory lesions	**48%**	38%		-2,22

Vehicle controlled

1. Study C-89-61 a multicenter, randomized, double-blind, parallel study of 180 subjects randomized 2:2:1 to adapalene 0.1%, Retin-A and vehicle. In this study, adapalene failed to beat the vehicle and was not therapeutically equivalent to Retin-A.

2. Study 9105-CD 271G-EV a multicenter, randomized, double-blind, parallel study of 256 subjects randomized 1:1 to adapalene 0.1% gel and vehicle. The study provides statistical evidence to support that adapalene 0.1% gel is therapeutically better than vehicle ($p>0.05$) for the primary efficacy variables, inflammatory and non-inflammatory lesions.

Dose-ranging

3. Study CR 88051is a controlled, randomized, investigator masked, three arm, 2 center study 0.03% adapalene gel, adapalene 0.1% gel, 0.025% Retin-A gel. 89 subjects demonstrated that adapalene 0.1% was not therapeutically equivalent to Retin-A based on efficacy, but better tolerated than Retin-A based on local safety assessments.

Active-control

4. Study CR 89064 (European Study) is a multicenter, 268 subject, 2- arm active-control trial wherein the primary objectives are to demonstrate therapeutic equivalency of adapalene 0.1% gel, 0.025% Retin-A gel for both inflammatory and non-inflammatory lesions. Adapalene 0.1% was not therapeutically equivalency to Retin-A based on inflammatory lesions, was therapeutically equivalent based on non-inflammatory lesions, and better tolerated than Retin-A based on local safety assessments.
5. Study CR 89-32 is a multicenter, randomized, investigator masked parallel group study comparing adapalene 0.1% gel and 0.025% Retin-A gel in 290 subjects. The primary objectives are to demonstrate therapeutic equivalency of adapalene for both inflammatory and non-inflammatory lesions. Adapalene 0.1% was statistically better than Retin-A based on non-inflammatory lesions, was therapeutically equivalent based on inflammatory lesions, and better tolerated than Retin-A based on local safety assessments.

Approval was granted based on totality of the data showing a favorable risk/ benefit for adapalene gel 0.1%

Reviewer comment: The Agency has determined that adapalene gel 0.1% demonstrates efficacy for the treatment of acne vulgaris. It is not clear to this reviewer that adapalene gel 0.1%, which is often prescribed to be used in combination with other products, and has demonstrated marginal efficacy in some clinical trials, would provide a substantial benefit in the OTC setting despite having a different mechanism of action. However, it is this reviewer's opinion that the current supplemental application for OTC-switch is not dependent on whether adapalene is safe and/or effective, but whether consumers are able to adequately self-diagnose and treat acne, in the absence of a learned intermediary which I do not take issue with, but more importantly whether there are essential safety concerns that should preclude its OTC use.

The applicant is seeking the indications of:

- For the treatment of acne
- Clears up acne pimples and acne blemishes

Reviewer comment: There is no data to support a claim for pimples and blemishes from the prescription drug development program. It is this reviewer's opinion, that treatment of pimples and blemishes would encompass an expansion of the indication to include minimal disease for which a benefit/ risk calculus has not been determined.

Maximal Use PK Study

Pharmacokinetics data were provided as part of the original application. However in these studies, the application of adapalene 0.1% gel was over a limited body surface area and adolescents were not included in the assessment. To support OTC use, Galderma conducted a multiple-dose pharmacokinetic study under maximal use conditions to evaluate absorption through the skin in an adolescent and adult population.

Study RD.06.SRE.18254 was a multi-center, open-label study to assess the systemic exposure to adapalene 0.1% topical gel in adolescents and adults with moderate to severe acne under maximal use conditions over 4 weeks. Twenty-four subjects including 18 adolescents (10 males and 8 females, 13-17 years of age) and 6 adult subjects (3 males and 3 females) were treated with adapalene once daily for 29 days, applied as a thin layer to the face, shoulders, upper chest and upper back. Three 24-hour PK profiles were performed on Day 1, Day 15, and Day 29.

All 24 subjects completed the trial. The mean daily medication usage was 1.95 g (range 1.21 to 2.92 g), with a mean percent treated body surface area of 9.2% (range 6.8% to 13.0%). By Day 29, adapalene plasma concentrations were quantifiable in all subjects, and steady state appears to have been achieved by Day 15. The highest individual human exposure was 2.9 ng·h/mL expressed as $AUC_{0\text{-}24h}$ by one subject (a 16-year-old male) at Day 24, with a mean value of 0.83 ng·h/mL.

The PK information obtained from the MUsT can help identify potential safety concerns and help determine whether an adequate safety margin exists for an active ingredient based on toxic effects seen in animal studies. In order to provide the most conservative safety margin calculation, the highest individual human exposure (2.9 ng·h/mL) was used for the calculation rather than the mean value. The 70-fold safety margin represents the safety margin assuming the PK trial assesses maximum human exposure.

The clinical pharmacology team made a cross-trial comparison of PK data from other approved adapalene-containing products. This type of analysis is for qualitative purposes only due to the fact that trials have been conducted in different populations using different study designs, different formulations and different bioanalytical validation methods. The team concludes that the results from the MUsT appear to be within the systemic concentration range observed with the adapalene 0.1% strength products.

Reviewer comment: The most exposed subject (#8139-006) was a 16 year old male. He received 1.89 gram of study medication on 1899 cm^2 BSA daily. This subject did not use the maximum dose of product based on amount used (use was below the mean) or body

surface area covered (at the mean). Thus, there appears to be other, undefined factors increasing the systemic exposure in this subject's case.

Maximum PK values (Cmax and AUC) achieved in subjects treated with 0.1% gel in the MUsT appear to overlap with the mean values obtained from PK studies supporting the 2015 approval of Adapalene 0.3% / Benzoyl peroxide 2.5% but are lower than the mean values obtained from PK studies supporting the 2007 approval of Adapalene 0.3%. Although the studies cannot be conclusively quantitatively compared, the possible overlap brings into question whether, under certain conditions, systemic exposure to the 0.1% product could achieve similar levels as that of the 0.3% product. If under controlled conditions, there is overlapping exposure between products with a 3 fold difference in strength, what levels could be achieved in the OTC setting when factors such as use on damaged skin, concomitant use of substances/ dressings that increase absorption, simultaneous use of vitamin A-containing dietary supplements or cosmetics, heavy application of product, frequent application of product and application to a larger body surface area are not controlled? And is it possible to surpass the threshold for teratogenic risk? Because of the uncertainty of exposure that could be reached in the OTC setting and the unknown threshold for human teratogenicity, this reviewer supports maintaining the status quo by maintaining adapalene for prescription use.

Consumer Safety Studies

The OTC indication is supported by three consumer studies—a label comprehension study, a self-selection study focusing on pregnant and lactating women, and an actual use study.

Label comprehension study

The primary objective of the label comprehension study was to test the instruction "Use once daily" and the secondary objective was to test "Do not use on damaged skin." Overall, 515 of the subjects were of normal literacy and 130 (22%) were low literacy. Respondents did reasonably well for both objectives, although subjects with low literacy did worse on the primary objective. For "Use once daily," 96.5% of normal literacy [Lower Bound of the Confidence Interval (LCB) 94.4%] and 86.9% of low literacy (LCB 79.9%) subjects answered correctly. For "Do not use on damaged skin," 97.4% (LCB 95.5%) of normal literacy and 99.2% (LCB 95.8%) of low literacy subjects answered correctly.

Reviewer comment: Subjects with low literacy appear to have a more difficult time than normal literacy subjects in comprehending instructions to use the product once daily. This raises the potential concern that low literacy patients may be at risk for greater systemic exposure if they are to use the product more frequently.

Self-selection study

The primary objective of the self-selection study was to assess whether pregnant or breastfeeding women with acne would ask a health care professional prior to use of adapalene, as per the directions on the Drug Facts Label (DFL). Overall, women

generally did poorly when asked if they would consult a doctor prior to use of adapalene. In the pregnant only group, 70% of women (LCB 58.7%) said they would ask a doctor before use. Rationales given by subjects for incorrect self-selection suggest that women believe that topical products cannot hurt a developing infant and that OTC products are safe to use during pregnancy. In addition, a subgroup (N=15) stated that they did not see the warning on the label.

Reviewer comment: The data demonstrate that if adapalene were available OTC, the product would be used by pregnant women due to the low perceived risk of OTC products in general and topical products in particular. Additionally, pregnancy females would be unlikely to discuss adapalene use with their physician(s).

Actual use trial

The actual use trial was a 6-week, open label, multi-center trial in 947 adolescent and adult subjects with self-reported acne. All women were tested for pregnancy before being allowed to purchase study drug; subjects were also pregnancy tested at completion of the 6-week study period. The major inclusion/exclusion criteria were as follows:

- Self-reported acne
- Age 12 years to adult (assent required for children 12-17 years of age)
- In the judgment of the investigator or designee, the subject was likely to be harmed by participating in the study, or the subject was unlikely to follow the study procedures
- Subject was pregnant – urine pregnancy test conducted in all female subjects of childbearing potential
- Self-reported breastfeeding
- Self-reported allergy to adapalene or any inactive ingredient

The cost of one box containing one 45 gram tube was $7.00. Subjects were allowed to purchase a maximum of two boxes per visit and three boxes over the entire duration of the trial. Subjects were not provided information on how to use the product or for what conditions it should be used.

A total of 35 subjects appear to have made a potentially clinically-relevant, incorrect selection decision, i.e., they selected to use the product when they had a contraindication, e.g., did not have acne, or should have spoken with a doctor first, e.g., the subject was pregnant.

Pregnancy

At screening, pregnancy or the possibility of pregnancy accounted for a number of subject exclusions. Of the subjects excluded by investigators, 4 subjects were pregnant and 2 were determined to be pregnant upon screening. Subjects excluded by investigator judgment also included a number of cases related to the investigator's suspicion of a potential pregnancy or inability to ensure the subject was not pregnant.

Fourteen subjects chose to use the product while pregnant or breast feeding. Similar to the self-selection study, the stated reasons for this suggest that women perceive a low risk

with topical products, lack of perception of the seriousness of the warning, or not seeing the warning.

The 6 week actual use trial captured 4 pregnancies: one terminated based on personal reasons, and the remaining three are lost to follow up.

Reviewer comment: Four subjects in the actual use trial became pregnant within the 6 week study (median duration 42 days) and a number of other pregnant females would have used the product if not for investigator intervention. Based this trial along with the other consumer studies, if the product should become available OTC, adapalene will be used in pregnancy females. This use will likely occur in various stages of pregnancy. Also, given the reluctance of a number of practitioners to use retinoids in pregnancy, it is possible that a larger number of pregnancy females will be exposed to adapalene if the product moved into the OTC setting.

Exposure
Overall, 89.1% (LCB 87.1%) of subjects used the product once daily. Results in subjects with low literacy and in adolescents were generally comparable. However, in the subjects that were considered to have used the product correctly (i.e. once daily), 61 subjects had reported using the product more than once daily on a single occasion.

The reasons given by subjects that frequently or singly applied product more than once daily were similar. These include reapplying adapalene after showering, using twice daily per routine or in an attempt to obtain greater or faster benefit.

The mean use of the product was 24.3 g with a maximum reported use of 129.5 grams. Thirteen subjects (1.37%; 13/947) used at least 80 g, nearly two tubes (90 g), or more of adapalene over the six week treatment phase. Nine were in the 12-29 year age bracket and five were women of childbearing potential.

Reviewer comment: It is not clear to this reviewer that the conducted actual use study will be predictive of actual over-the-counter use. A number of pregnant subjects would have used the product if not for investigator intervention as discussed above. A number of subjects used the product more than once daily and in some cases it appears to be based on subscribing to the idea that 'more is better'. It is difficult to predict whether the confines of the study (i.e. the knowledge that their behavior being recorded and followed) minimized the amount of product used (mean <1 gram per day compared to< 2 grams per day in the MUsT). It is this reviewer's opinion that when adapalene is used broadly in the OTC setting, pregnant females will use the product without guidance from their physician and because of misuse some will achieve higher levels of exposure than characterized in controlled clinical trials. How these changes in use will affect teratogenic risk is unknown since the adapalene threshold for human teratogenicity is also unknown.

Due to study design, information on potential off-labeled use for conditions known to respond to retinoids (e.g. fine lines, wrinkles, melasma) and potential use on skin conditions that would increase systemic absorption could not be determined.

Advisory Committee Meeting

On April 15, 2016 the Nonprescription Drugs Advisory Committee (NDAC) was convened to provide advice on the regulatory decision making process related to the approval of adapalene gel, 0.1% for over-the-counter marketing in the United States.

The committee found by a vote of 16-0 that the safety profile and the totality of the data for adapalene gel, 0.1% were adequate to allow the product to be sold over-the-counter.

Members of the committee could not agree on labeling as it related to pregnancy. Some members urged removal of a warning for pregnant women to consult their primary care providers; others urged strengthening the warning around pregnancy, and at least one panelist suggested a contraindication.

Reviewer comment: Although the committee was unanimous in its support for OTC marketing, there appeared to be various levels of concern regarding the pregnancy labeling. This reviewer finds the rationale that supports that product is safe to be used OTC, but should be contraindicated in pregnancy in labeling is inconsistent. This reviewer finds that the varied opinion on how to inform patients in the OTC setting about the use of adapalene in pregnancy supports the position of keeping the product available by prescription where these complicated concepts that the panel was trying to convey in labeling, can best be discussed with a learned intermediary.

Labeling

The applicant is seeking to label the OTC indication as follows:

(b) (4)

What is Differin and what is it used for?

- (b) (4)
- (b) (4)

Reviewer comment: As stated above, it is this reviewer's opinion that (b) (4)

DDDP defers to DNDP to determine appropriate labeling for products used in the OTC setting.

Conclusions:

Adapalene is effective for treatment of mild to moderate acne, and with the exception of teratogenicity, the product's safety concerns, primarily local irritation, could be managed appropriately in the OTC setting with labeling
Approval of this application, however, would allow over-the-counter availability of the first product that has a significant toxicology signal for teratogenicity. This reviewer is recommending that the status quo be preserved and maintain adapalene gel, 0.1% available by prescription only, as was recently determined by the German regulatory authorities earlier this year as they reviewed similar data. Adapalene Gel 0.1% would still be available as it has been for two decades to patients, who, in the estimation of their healthcare prescriber, need this therapy.

The risk of teratogenicity, albeit probably small based on exposure measured in clinical trials and post-marketing data analyzed, cannot be accurately predicted with OTC use. Assuming a low enough price point for consumers, actual use, particularly for adolescents, should be substantially greater than that observed in the "actual use" study with consequentially higher systemic exposures in a population of women of child bearing potential.

The human threshold for teratogenicity is unknown. It is known that with increased dose (e.g., concentration, frequency, percent body surface area of application, disease severity, and skin integrity impairment) there is increased systemic absorption. There are also other factors which may contribute to increased exposure (use under occlusion, with other retinoid/ vitamin A products). These factors are not easily controlled in the OTC setting.

The multiples of exposure based on nonclinical data has been widely concluded to be a "safety margin", but this multiple is more appropriately used to determine initial starting doses in product development than as a "safe use margin". Safety and efficacy are determined in clinical trials. While there is no concern regarding historical efficacy, safety in pregnant women and women who may become pregnant has not been adequately demonstrated.

While not specifically germane to this application, another concern is the precedent setting conclusion if OTC marketing is approved for adapalene. Given the discussion at the NDAC Advisory Committee, it seems likely that other retinoid products such as topical tretinoin and the higher approved concentration of adapalene 0.3% would have an equal argument for OTC marketing. Products such as Retin A, and Renova, which have limited clinical and clinical pharmacology information in existing labeling, might follow a similar argument based on multiples of exposure from nonclinical data that is 30 years old. While one might acknowledge that the clinical risk is low, post marketing adverse event reporting would never be sufficient to further characterize the risk, and affected pregnancies would likely never be identified in the absence of "classic" retinoid embryopathy.

It is this reviewer's opinion that the optimal approach for keeping systemic exposure within a range where teratogenic risk is likely to be a low is through interactions with a healthcare prescriber. Volume amounts of dispensed product could be limited, clinical response assessed, and pregnancy/contraception discussions could take place within the prescriber-patient relationship as they have for decades of use. In this reviewer's opinion, the applicant has not provided an acceptable plan to mitigate the potential teratogenic risk without the presence of a learned intermediary.

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/s/

AMY S WOITACH
06/01/2016

DAVID L KETTL
06/01/2016
Concur with primary review recommendation.