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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memorandum

Date	July 6, 2016
From	Julie Beitz, MD
Subject	Office Director Decisional Memo
Supplemental 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 / Strengths	Gel, 0.1%
Proposed Indication	Treatment of acne vulgaris, Over-the-Counter Switch
Recommended Action:	Approval

Materials Reviewed/Consulted OND Action Package, including reviews from:	**Discipline Reviewers**
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DDDP / Pharmacology / Toxicology	Cindy Xinguang Li, PhD / Paul Brown, PhD
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DDDP = Division of Dermatology and Dental Products
DPMH = Division of Pediatrics and Maternal Health
OCP = Office of Clinical Pharmacology
OND = Office of New Drugs
DMEPA = Division of Medication Error Prevention and Analysis
OB = Office of Biostatistics
OLDP = Office of Life Cycle Drug Products
OSE = Office of Surveillance and Epidemiology

1. Benefit-Risk Summary and Assessment

Differin (adapalene) Gel, 0.1%, is a naphthoic acid derivative with retinoid activity that was approved in 1996 for the topical treatment of acne vulgaris in adults and children 12 years of age and older. Information was submitted in this supplemental NDA to support a switch from prescription to over-the-counter (OTC) status. If approved, this would be a first-in-class prescription to OTC switch for a topical retinoid.

Since 1996, a variety of different adapalene formulations have been approved, including a 0.1% solution, 0.1% cream, 0.3% gel, and 0.1% lotion. Adapalene is also available in combination with benzoyl peroxide as a topical gel for the treatment of acne in adults and children 9 years of age and older. The proposed OTC dosing of Differin (adapalene) Gel, 0.1%, is the same as the approved prescription dosing.

I concur with the recommendations of the Division of Dermatology and Dental Products, the Division of Nonprescription Drug Products, the Office of Drug Evaluation IV, and the Nonprescription Drugs Advisory Committee to switch Differin (adapalene) Gel, 0.1%, to OTC status. I acknowledge that some members of the review team recommend against the OTC switch. While they agree that the teratogenic risk to the unborn child is low, they cite factors which may lead to increased exposure in the OTC setting that would be poorly managed in the absence of physician oversight. I acknowledge that there is a risk of increased exposure among some users in the OTC setting, but conclude that the teratogenic risk to the unborn children of such users would still be low.

Acne vulgaris is a common inflammatory disease affecting the pilosebaceous follicles of the skin. Acne affects approximately 50 million people in the U.S. and up to 85% of teenagers. It is generally accepted that acne is a self-diagnosable condition. Early, effective treatment of acne is recommended to prevent complications (e.g., scarring) and psychosocial burden. The availability of acne drug products over-the-counter could improve consumer access to effective treatments.

Although nonprescription acne drug products are commercially available in the U.S., there are no topical retinoids available for OTC use despite their known effectiveness and American Academy of Dermatology guidelines recommending their use as first-line treatment of acne. Current nonprescription topical acne drug products are labeled for use up to 3 times daily. Differin (adapalene) Gel, 0.1%, requires only a once daily application which may promote better patient compliance with treatment.

Data submitted in the original NDA supported the efficacy and safety of Differin (adapalene) Gel, 0.1%. Efficacy was established in randomized controlled clinical trials involving acne patients 12 years of age and older. Erythema, scaling, dryness, pruritus, and burning were commonly reported during the first month of therapy, decreased in frequency and severity thereafter, and were reversible upon discontinuation of

therapy. These adverse reactions are similar to those reported with the use of topical acne drug products containing ingredients that are covered under the OTC Topical Acne Drug Products monograph. Thus, it can be reasonably expected that Differin (adapalene) Gel, 0.1%, if used in accordance with labeling, would be safe for self-use.

Adapalene is a third generation retinoid with different receptor binding properties compared to the first generation retinoids, such as isotretinoin, a drug known to cause birth defects in humans. Low systemic exposures in acne patients were observed in *maximal* use trials of adapalene gel products. Among pregnant users, many factors determine the amount of active retinoid ultimately seen by an unborn child. First, the amount of drug applied under normal use conditions would likely be lower in most users than the amount applied in *maximal* use trials. Mean daily usage in the applicant's Actual Use Study was roughly **a third** of that in the *maximal* use trial submitted with this supplement. Second, the drug product commonly causes local irritation thereby limiting its use over large areas of the body. Local irritation would likely be more common with higher adapalene exposures. Third, once the product is absorbed, other factors may play a role including the extent of maternal retinoid metabolism, the half-life of the retinoid in maternal plasma, the placental transfer rate of the retinoid, and the extent of fetal metabolism.

Additionally, the available preclinical and clinical pharmacology data suggest that there is a clinically relevant margin of exposure with normal or *maximal* use of adapalene gel 0.1%. A previous assessment of adapalene gel 0.3% led to the conclusion that the teratogenic risk for that product was low. After 20 years of global marketing experience, no discernible pattern of congenital malformations has emerged in children born to adapalene-exposed women. Taken together, these data suggest that systemic exposure of adapalene gel 0.1% when used by pregnant women poses a low teratogenic risk to the unborn child. Given that the postmarketing experience also includes adapalene gel 0.3%, it is likely that the teratogenic risk would still be low even among users of the 0.1% gel who achieve higher than expected exposures (e.g., by using excessive or more frequent applications, dressings that increase absorption, concomitant Vitamin A-containing products, etc.)

In this supplemental NDA, the applicant has demonstrated that a majority of consumers 12 years of age and older who self-report acne can appropriately use adapalene gel for their condition in a simulated "real world" scenario without physician oversight. Since an actual use study cannot completely predict "real world" use, it is likely that some misuse of the product will occur if adapalene is available over-the-counter, e.g., use more frequent than labeled, or use for other conditions such as fine lines or wrinkles. Local irritation would likely limit use over large areas of the body.

Although a majority of pregnant or breast-feeding women in a targeted self-selection study stated they would heed the pregnancy/breast-feeding warning in the Drug Facts Label, it is likely that adapalene gel will be used by pregnant or breast-feeding women who do not consult a physician before use. As noted above, many factors may mitigate the extent of exposure to the unborn child. Thus, while some pregnant or

breast-feeding women may not consult a physician before use, the risk of teratogenicity or other adverse effects to the unborn child is expected to be low. Regarding risks to the breast-fed infant, it is not known whether adapalene is excreted in human milk.

The Drug Facts Label (DFL) for Differin (adapalene) Gel, 0.1%, adequately conveys the key safety and dosing information for consumers. In the applicant's studies, most participants comprehended key messages in labeling and used the product appropriately without physician oversight. Consistent with the recommendation of team members supporting the OTC switch, I concur with the applicant's proposal to include the Warning statement "**If pregnant or breast-feeding**, ask a doctor before use", even though the teratogenic risk to the unborn child is low. I also concur with inclusion of the statement "Stop use and ask a doctor if you become pregnant, or are planning to become pregnant, while using the product". These statements are consistent with advice provided by the CDC for women who are pregnant or thinking about becoming pregnant, namely, that they speak with their healthcare provider about any medications they are taking or thinking about taking, including prescription and over-the-counter medications. While I do not believe that a prescription is necessary to ensure safe use of Differin (adapalene) Gel, 0.1%, I do see a continuing role for an involved healthcare provider in the management of acne patients to ensure that they properly adhere to their acne regimens.

Dimension	Evidence, Uncertainties and Conclusions
Analysis of Condition	Acne vulgaris is a common inflammatory disease affecting the pilosebaceous follicles of the skin. Acne affects approximately 50 million people in the U.S. and up to 85% of teenagers. The prevalence of acne in adult women is about 12% and over 50% of adults at some point in their lives have acne.[1] Acne is a multi-factorial disease, characterized by follicular keratinocyte desquamation, anaerobic *Propionibacterium acnes* (*P. acnes*) proliferation, formation of the microcomedone, inflammatory response, and excess sebum production. It is generally accepted that acne is a self-diagnosable condition. Patients with acne face numerous physical and psychological challenges, such as permanent scarring, poor self-image, depression, and anxiety. Acne focus groups report social avoidance, feelings of anger, sadness, or frustration. Quality of life improves as acne clears with successful treatment.[2]

[1] Zaenglein AL *et al.* Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016; 74:945-973.
[2] Barnes LE, Levender MM, Fleischer AB Jr, Feldman SR. Quality of life measures for acne patients. *Int J Dermatol* 2012; 30(2):293-300.

Dimension	Evidence, Uncertainties and Conclusions
	Comment. Early, effective treatment of acne is recommended to prevent complications and psychosocial burden. The availability of topical acne drug products over-the-counter could improve consumer access to effective treatments.
Current Treatment Options	Nonprescription topical drug products for the treatment of acne have been available in the U.S. for decades and their use is common. There are several active ingredients included in the Topical Antimicrobial Drug Products for Over-the-Counter Human Use monograph, hereafter referred to as the OTC Topical Acne Drug Products monograph.[3] While these ingredients are considered Generally Recognized as Safe and Effective for nonprescription use, only benzoyl peroxide is recommended by the American Academy of Dermatology (AAD) for the first-line treatment of acne due to its antimicrobial properties. Benzoyl peroxide is recommended both as monotherapy for mild acne and in combination with a topic retinoid or systemic antibiotic for moderate to severe acne. Published data on the efficacy of the other named ingredients for the treatment of acne vulgaris are limited. In contrast, retinoids, such as adapalene gel, are the core of topical therapy for acne; they are comedolytic, resolve the microcomedone lesion, and are anti-inflammatory. Retinoids enhance topical acne regimens and allow for maintenance of clearance after discontinuation of oral therapy.[4] Data on prescriptions dispensed at U.S. outpatient retail pharmacies for the period December 2010 – November 2015 estimate that 91% of users of single ingredient adapalene products were 12-45 years of age; 74% of these users were female. The most common diagnoses associated with female users in this age group were "acne – not elsewhere classified" (99.3%) and "rosacea" (0.7%). Similarly, "acne – not elsewhere classified" was the most common diagnosis among male users 12-45 years of age.[5] Medication non-adherence is a common cause of acne treatment failure. Unmet treatment expectations of rapid, visible improvements or poor tolerability (skin dryness, irritation) may impact treatment compliance. Strategies that may improve

[3] *See* 21 CFR Part 333, Subpart D. Acne active ingredients include benzoyl peroxide, resorcinol when combined with sulfur, resorcinol monoacetate when combined with sulfur, salicylic acid, and sulfur.
[4] *Ibid*., Zaenglein *et al.* 2016.
[5] *See* OSE's Pharmacovigilance, Epidemiology and Drug Utilization Review authored by Thambi L, Ding H and Greene P, dated March 14, 2016.

Dimension	Evidence, Uncertainties and Conclusions
	compliance include patient education, individual treatment plans, good physician–patient relationships, and enhanced quality and quantity of office visits.[6] ***Comment.*** Although nonprescription topical acne drug products are commercially available in the U.S., there are no topical retinoids available for over-the-counter use despite their known effectiveness and AAD guidelines recommending their use as first-line treatment of acne. Differin (adapalene) Gel, 0.1%, would be the first topical retinoid that could be legally marketed as a nonprescription acne drug product, if this supplement were approved. Current nonprescription topical acne drug products are labeled for use up to 3 times daily. Adapalene gel's once daily regimen may promote better patient compliance with treatment.
Benefit	In the original submission of NDA 020380 for Differin (adapalene) Gel, 0.1%, results of five randomized controlled trials supported the 1996 approval of adapalene gel as a single agent for the topical treatment of acne vulgaris in adults and children 12 years of age and older. These trials compared adapalene gel with either vehicle gel or a commercially available topical retinoid (tretinoin gel 0.025%). In one of two vehicle-controlled trials, adapalene gel was superior to vehicle gel in reducing both non-inflammatory and inflammatory acne lesion counts from baseline by Week 12 of treatment. For non-inflammatory lesions, the mean percent reduction in lesion count for adapalene gel was 26% vs. 1% for vehicle gel; for inflammatory lesions, the mean percent reduction in lesion count for adapalene gel was 34% vs. 12% for vehicle gel. The second trial showed favorable reductions in lesion counts for adapalene gel, but the difference from vehicle gel was not statistically superior. In four of the five trials designed with a retinoid gel control, reductions in lesion counts were numerically similar for adapalene gel and tretinoin gel, but the studies were not designed to formally test non-inferiority. In 2008, the applicant submitted NDA 022320 for a fixed combination gel product containing adapalene 0.1% and benzoyl peroxide 2.5%. Adapalene gel 0.1% served as a control treatment in two randomized controlled trials in acne patients. For non-inflammatory lesions, the mean percent reduction in lesion count for adapalene gel 0.1% compared to vehicle gel at Week 12 was 30% vs. 28% and 41% vs. 23% in the two trials, respectively. For inflammatory lesions, the mean percent reduction in lesion count for adapalene gel compared to vehicle gel at Week 12 was 40% vs. 32% and 42% vs. 30% in the two trials,

[6] Tan X, Feldman SR, Chang J, Balkrishnan R. Topical drug delivery systems in dermatology: a review of patient adherence issues. *Expert Opin Drug Deliv* 2012; 9(10):1263-1271.

Dimension	Evidence, Uncertainties and Conclusions
	respectively. ***Comment.*** The efficacy of adapalene gel 0.1% has been established in randomized controlled clinical trials involving acne patients 12 years of age and older.
Risk	**Structure / Function Considerations.** Adapalene is a third generation retinoid, a synthetic naphthoic acid derivative structurally different from retinoic acid due to the presence of a phenoxy-adamantyl group. Its structure is believed to result in low percutaneous flux and limited systemic exposure. Typical retinoids exert their pharmacological activities by binding to specific retinoic acid nuclear receptors (RARα, ß, γ) and cellular retinoid binding proteins I and II (CRAB I and II). In contrast, adapalene has a much lower binding affinity for RARα and does not bind to CRAB II. **Common Adverse Reactions.** In clinical trials submitted in the original NDA, erythema, scaling, dryness, pruritus, and burning were reported in 10-40% of acne patients. Pruritus or burning immediately after application was reported in approximately 20% of patients. These reactions were most commonly seen during the first month of therapy and decreased in frequency and severity thereafter. All adverse reactions associated with use of adapalene gel 0.1% during clinical trials were reversible upon discontinuation of therapy. Since global marketing introduction in 1995, approximately 41 million patients have been exposed to topical adapalene-containing products (in strengths of 0.1 and 0.3%); clinical trials have been conducted involving approximately 6000 patients.[7] The adverse reactions commonly associated with the use of topical adapalene gel 0.1% in the postmarketing setting were similar to those described in clinical trials. Local irritation is more common with higher adapalene exposures.[8] ***Comment.*** The adverse reactions commonly reported with the use of adapalene gel 0.1% are dermatologic in nature, localized and generally mild. These adverse reactions are also similar to those reported with the use of topical acne drug products

[7] *See* Briefing Document on Differin (adapalene) Gel, 0.1%, prepared by Galderma for the April 15, 2016 FDA Nonprescription Drugs Advisory Committee meeting.

[8] As stated in Dr. David Kettl's March 27, 2007 review of NDA 021753 for adapalene gel 0.3%, "In the pivotal Phase 3 study (RD.06.SRE.18081) study, erythema, scaliness, and dryness, were more common for adapalene gel, 0.3%, than for the 0.1% formulation, and least for the vehicle, symptoms being generally mild, developed early in the treatment and decreased with continued treatment."

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	containing ingredients that are covered under the OTC Topical Acne Drug Products monograph. Thus, it can be reasonably expected that adapalene gel 0.1%, if used in accordance with labeling, would be safe for self-use. **Specific Concerns.** This supplement raised several specific concerns that are discussed below: 1. **The implications of systemic exposure from topical use.** Concerns have been raised that systemic exposure from topical use of adapalene gel 0.1% during pregnancy could lead to the development of retinoid embryopathy in the unborn child, especially if the exposure occurs during the period of active organogenesis. ***Adapalene gel 0.1%.*** This adapalene gel 0.1% supplement submitted in support of the OTC switch contained the results of a newly conducted *maximal* use clinical pharmacokinetic trial in 6 adults and 18 adolescents with moderate to severe acne. Drug was applied over the face, shoulders, upper back and upper chest over a 4 week period. The mean daily amount applied was 1.95 g, and the mean percent treated body surface area was 9%. All patients had quantifiable (LOQ = 0.02 ng/mL) plasma concentrations at the end of the treatment period (Day 29); steady state was achieved by Day 15. The mean C_{max} and $AUC_{0\text{-}24h}$ on Day 29 were 0.05 $\pm$ 0.03 ng/mL and 0.83 $\pm$ 0.49 ng.h/mL, respectively. No significant gender or age differences were detected. The highest $AUC_{0\text{-}24h}$ was 2.9 ng.h/mL observed on Day 29 in a 16 year old male administered 1.89 g/day. There was no evidence for drug accumulation over the treatment period. Additional information regarding systemic exposures with the use of adapalene gel 0.1% are available from: • NDA 022320 (for the combination topical gel containing adapalene 0.1% and benzoyl peroxide 2.5%) contains additional, albeit limited, information on systemic exposures from *maximal* use of adapalene gel 0.1%. Twenty-four acne subjects were treated once daily for 30 days with 2 g of either adapalene/benzoyl gel or adapalene gel 0.1 % applied to the face, upper chest, and upper back. Three subjects treated with adapalene gel 0.1% had quantifiable (LOQ = 0.1 ng/mL) adapalene plasma concentrations, ranging between 0.11 ng/mL to 0.16 ng/mL. The $AUC_{0\text{-}24h}$ was reported for only one of these subjects as 2.7 ng.h/mL on Day 10 and 1.3 ng.h/mL on Day 21. • NDA 021753 (for adapalene gel 0.3%) contains exposure data for adapalene gel 0.1% from a 30-day *maximal* use trial in 51 acne patients directly comparing adapalene gel 0.1% with adapalene gel 0.3%. The LOQ for the assay

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	method was 0.1 ng/mL. For adapalene gel 0.1%, the highest mean C_{max} was 0.04 ng/mL, and the highest mean AUC_{0-24h} was 0.50 ng.h/mL, both noted on Day 15. One subject achieved an AUC_{0-24h} of 3.4 and 3.5 ng.h/mL on Day 15 and Day 30, respectively. ***Adapalene gel 0.3%.*** The original submission of NDA 021753 contained results of a clinical pharmacokinetic trial in 16 acne subjects treated once daily for 10 days with 2 g of adapalene gel 0.3% applied to the face, chest and back (5-6% body surface area). Fifteen subjects had quantifiable (LOQ = 0.1 ng/mL) adapalene levels with a mean C_{max} of 0.55 ± 0.47 ng/mL and a mean AUC_{0-24hr} of 8.4 ± 8.5 ng.h/mL on Day 10. To assess the teratogenic risk of higher systemic exposures with use of the 0.3% gel, a review of the global postmarketing experience with adapalene gel 0.1% was conducted. As of March 2006, 19 million patients had been exposed; there were 156 reports of pregnancy but no discernible pattern of congenital malformations in children born to pregnant women using the 0.1% gel product. In consultation with the Pediatric and Maternal Health Staff and staff in the Office of Surveillance and Epidemiology, DDDP determined that the teratogenic risk associated with use of adapalene 0.3% gel was low. When approved in 2007, the 0.3% gel product was classified as the 0.1% gel product had been – as Pregnancy Category C. Following the approval of adapalene gel 0.3%, the applicant conducted a 30-day *maximal* use trial (described above) directly comparing systemic exposures for the 0.3% and 0.1% gel products (LOQ = 0.1 ng/mL). For adapalene gel 0.3%, the highest mean C_{max} was 0.18 ng/mL, and the highest mean AUC_{0-24h} was 2.8 ± 1.8 ng.h/mL, both noted on Day 15. These exposures appear to exceed those for adapalene gel 0.1% in this head-to-head direct comparison. ***Comment.*** Low systemic exposures in acne patients were observed in *maximal* use trials of adapalene gel products. Among pregnant users, many factors determine the amount of active retinoid ultimately seen by the unborn child. First, the amount of drug applied under normal use conditions would likely be lower. Mean daily usage in the applicant's Actual Use Study was roughly **a third** of that in the *maximal* use trial submitted with this supplement. Second, the drug product commonly causes local irritation thereby limiting its use over large areas of the body. Local irritation would likely be more common with higher adapalene exposures. Third, once the product is absorbed, the extent of maternal

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	retinoid metabolism, the half-life of the retinoid in maternal plasma, the placental transfer rate of the retinoid, and the extent of fetal metabolism may play a role in the amount of active retinoid seen by the unborn child.[9,10] 2. **Margin of Exposure.** In humans, administration of retinoids has been associated with embryopathy characterized by developmental abnormalities to the CNS (hydrocephalus, hypoplastic or malformed cerebellar or cerebral cortices), craniofacial region (cleft palate, external ear defects), heart, thymus and limbs. Retinoids, however, vary in teratogenic potency, and their effects are dose-dependent. To assess the magnitude of teratogenic risk to the unborn child associated with human use of adapalene gel 0.1%, a margin of exposure was calculated as the ratio of the lowest AUC in the most sensitive animal species (the rat) at the NOAEL for teratogenicity to the highest human AUC observed in a *maximal* use trial. ***Nonclinical Reproductive Toxicity Studies.*** In rats, no teratogenic effects were noted with *oral* doses of 0.15 to 5.0 mg adapalene/kg/day, equivalent to up to 25 times the estimated human dose of 2 g of topical adapalene gel 0.1%. In rats and rabbits, no teratogenic effects were noted with *topical* doses of 0.6 to 6.0 mg adapalene/kg/day, equivalent to 25 to 59 times the estimated human dose. Teratogenic effects were observed in rats and rabbits treated with *oral* doses of ≥ 25 mg adapalene/kg/day representing 123 and 246 time the estimated human dose. Using the available nonclinical and clinical pharmacology data, a margin of exposure was calculated to be 70.[11] The margin of exposure is expected to be higher under normal human use conditions. ***Reports of Pregnancy Exposures.*** Forty-one million patients have been exposed to adapalene-containing products, in strengths of 0.1% and 0.3%, since the product's international birthdate in 1995. A total of 336 pregnancy exposures have

[9] Soprano DR and Soprano KJ. Retinoids as Teratogens. *Annu Rev Nutr* 1995; 15:111-132.

[10] In pregnant rats, placental/fetal transfer was studied after adapalene administration. After repeated oral administration at 0.1 or 1 mg/kg between gestation Days 6 and 13, fetal AUC values were less than 60% of the maternal plasma values.

[11] This is calculated as the ratio of the $AUC_{0\text{-}24h}$ of 204 ng.h/mL in rats dosed at 6 mg/kg/day (the lowest AUC in the most sensitive animal species at the NOAEL for teratogenicity) to the highest human $AUC_{0\text{-}24h}$ observed in the *maximal* use trial submitted in this supplement, i.e., 2.9 ng.h/mL. The margin of exposure would be calculated to be 58 if one were to use the highest human $AUC_{0\text{-}24h}$ observed in a patient receiving adapalene gel 0.1% in the post-approval *maximal* use trial submitted under NDA 021753, i.e., 3.5 ng.h/mL.

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	been reported (276 from postmarketing surveillance and 60 from clinical trials). Outcomes are known for 170 of these pregnancies, namely, 109 healthy infants, 19 elective abortions, 23 miscarriages, and 19 other abnormal outcomes.[12] The rates of miscarriage and congenital malformations were consistent with rates in the U.S. Among pregnancies reporting a first trimester exposure and a congenital malformation there was no discernible pattern to the malformations observed. ***Comment.*** The available preclinical and clinical pharmacology data suggest that there is a clinically relevant margin of exposure with normal or *maximal* use of adapalene gel. After 20 years of global marketing experience, no discernible pattern of congenital malformations has emerged in children born to adapalene-exposed women. Taken together, these data suggest that systemic exposure of adapalene gel 0.1% when used by pregnant women poses a low teratogenic risk to the unborn child. Given that the postmarketing experience also includes adapalene gel 0.3%, it is likely that the teratogenic risk would still be low even among users of the 0.1% gel who achieve higher than expected exposures (e.g., by using excessive or more frequent applications, dressings that increase absorption, concomitant Vitamin A-containing products, etc.) 3. **Assess Appropriate Use in the Absence of Physician Oversight.** The applicant conducted consumer behavior studies to assess comprehension of key communication messages in the proposed Drug Facts Label and assess the extent to which off-label use of adapalene gel might occur without physician oversight. These studies are briefly summarized as follows: ***Labeling Comprehension Study.*** This study was conducted in 586 subjects, ages 12-70 years; there were 33 subjects ages 18-24 years. There were 515 subjects in the General Population cohort and 130 in the Low Literacy cohort. The primary messages tested were: "Do not use on damaged skin (cuts, abrasions, eczema, sunburned)" and "Use once daily". Both populations demonstrated comprehension of these messages, exceeding the pre-specified 85% lower bound threshold. Of note, comprehension of "Use Once Daily" was only 75% among low literacy adolescents ages 12-14 years. ***Actual Use Study.*** A 6-week actual use study was conducted in 947 subjects who self-reported acne who were 12 years of age and older. Subjects relied on the Drug Facts Label for directions of use and were permitted to purchase up to 3 boxes during the study period (each containing a 45 g tube). Sixty-eight percent of participants were female and 21%

[12] *Ibid.,* Galderma's Advisory Committee Briefing Document on Differin (adapalene) Gel, 0.1%, April 2016

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	were adolescents. Mean usage was estimated at 0.6 g/day (or 24 g during the course of the study). Key findings from this study include: *Evaluation of once daily use.* Both normal and low literacy subjects correctly used the product no more than once daily in the same location (89% in both cohorts). Results were similar across age groups. Reasons given by subjects who used the product more than once daily included re-applying the product after showering, and using the product twice daily to obtain a better or faster result. *Evaluation of use exclusively in acne.* Both normal and low literacy subjects correctly used the study product only to treat acne (99% in both cohorts). Results were similar across age groups. Since recruitment targeted acne sufferers, these results do not directly address the potential for off-label use in a "real world" setting. *Evaluation of use on correct body area.* Both normal and low literacy subjects correctly used the study product on the correct body area (97% in both cohorts). Results were similar across age groups. *Evaluation of the Pregnancy and Breast-feeding Warning.* In accordance with 21 CFR 201.63, the labeling for an OTC drug product that is intended for systemic absorption should carry the warning "**if pregnant or breast-feeding**, ask a health professional before use." Although Differin (adapalene) Gel, 0.1%, is not intended for systemic absorption, the applicant has proposed to include this warning in its proposed Drug Facts Label. Six pregnant women and 10 breast-feeding women presented for the initial study visit. One of the pregnant women and 4 of the breast-feeding women correctly stated that they should ask a healthcare provider before using the product. ***Targeted Self-Selection Study.*** Given that women who are pregnant or breast-feeding may choose to use nonprescription adapalene gel, the applicant conducted a targeted self-selection study in 293 female subjects 13-54 years of age who were pregnant or breast-feeding and self-reported acne. There were 242 subjects in the General Population cohort (including 80 subjects who were pregnant only, 151 who were breast-feeding only, and 11 who were both pregnant and breast-feeding) and 51 in an augmented Low Literacy cohort. In the General Population cohort, 74% of subjects correctly stated that they should ask a healthcare provider before using the product; the lower bound of the two-sided 95% CI was 68%. In the low literacy cohort, 80% of subjects answered correctly. Thus, the target of 90%

Dimension	Evidence, Uncertainties and Conclusions
	correct was not met for either cohort. A common reason given for not consulting a healthcare provider was the belief that over-the-counter skin care products are safe to use in pregnancy. Some participants missed seeing the warning. ***Comment.*** The applicant has demonstrated that a majority of consumers 12 years of age and older who self-report acne can appropriately use adapalene gel for their condition in a simulated "real world" scenario without physician oversight. Since an actual use study cannot completely predict "real world" use, it is likely that some misuse of the product will occur if adapalene is available over-the-counter, e.g., use more frequent than labeled, or use for other conditions such as fine lines or wrinkles. Local irritation would likely limit use over large areas of the body. Although a majority of pregnant or breast-feeding women stated they would heed the pregnancy/breast-feeding warning, it is likely that adapalene gel will be used by pregnant or breast-feeding women who do not consult a physician before use. As noted above, many factors may mitigate the extent of exposure to the unborn child. Thus, while female users of childbearing potential may not heed the directions to consult a physician before use, the risk of teratogenicity to the unborn child with the use of adapalene gel is expected to be low. Regarding risks to the breast-fed infant, it is not known whether adapalene is excreted in human milk.
Risk Management	**Labeling.** Comparisons to nonprescription acne medications suggest that the overall safety profile of adapalene gel is similar to that of other commercially available topical acne drug products. The applicant has proposed, and I concur, that the Drug Facts Label for Differin (adapalene) Gel, 0.1%, contain similar language regarding ***Warnings*** and ***Directions*** as other topical acne drug products in accordance with the OTC Topical Acne Drug Products monograph. To address concerns regarding overuse of the product, the Drug Facts label will direct consumers to apply the gel in a thin layer "once daily". The DFL will also state "Applying more than directed will not provide faster or better results, but may worsen skin irritation." In the Consumer Information Leaflet, administration frequency will be further clarified as "use only one time a day" to address the finding among low literacy adolescents of lower comprehension of "Use once daily", and the possibility that Hispanics who are of limited English proficiency might confuse "once" with its Spanish translation, "eleven". The DFL will recommend to avoid use on damaged skin, contact with the eyes, lips and mouth, and sun exposure.

Dimension	Evidence, Uncertainties and Conclusions
	Differin (adapalene) Gel, 0.1%, has had a Pregnancy Category C classification like many OTC drug products, including monograph-allowed topical acne drug products containing benzoyl peroxide or salicylic acid. The Warning statement "**If pregnant or breast-feeding,** ask a doctor before use" will appear in the Drug Facts Label for Differin (adapalene) Gel, 0.1%, even though this statement is required only for nonprescription drugs intended for systemic absorption, which would not include adapalene gel. The statement "Stop use and ask a doctor if you become pregnant, or are planning to become pregnant, while using this product" will also appear in the Drug Facts Label. In accordance with advice obtained at the April 2016 Nonprescription Drugs Advisory Committee meeting, the Consumer Information Leaflet will contain information on how the teratogenic risk of Differin (adapalene) Gel, 0.1%, differs from other retinoids. To address the likelihood that breast-feeding women will use this product, the statement "Wash hands after use" will be included in the Drug Facts Label and the Consumer Information Leaflet. ***Comment.*** The Drug Facts Label for Differin (adapalene) Gel, 0.1%, adequately conveys the key safety and dosing information for consumers. In the applicant's studies, most participants comprehended key messages in labeling and used the product appropriately without physician oversight. I concur with inclusion of statements directed to pregnant and breast-feeding women, even though the teratogenic risk to the unborn child is low. These statements are consistent with advice provided by the Centers for Disease Control and Prevention (CDC) for women who are pregnant or thinking about becoming pregnant, namely that they speak with their healthcare provider about any medications they are taking or thinking about taking, including use of prescription and over-the-counter medications.[13] While I do not believe that a prescription is necessary to ensure safe use of Differin (adapalene) Gel, 0.1%, I do see a continuing role for an involved healthcare provider in the management of acne patients to ensure that they properly adhere to their acne regimens.

[13] See, for example, https://www.cdc.gov/pregnancy/meds/ or http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118567.htm accessed on June 8, 2016.

2. Additional Comments

2.1 FDA Advisory Committee Meeting

On April 15, 2016, a meeting of the Nonprescription Drugs Advisory Committee was held to discuss the merits of switching Differin (adapalene) Gel, 0.1%, to over-the-counter status. The Committee voted unanimously, 16-0, in favor of nonprescription use of the product for the treatment of acne in adults and children 12 years of age and older.

Views regarding the inclusion of the Warning statement for pregnant and breast-feeding women in the Drug Facts Label were mixed. Some members proposed not to include the Warning statement, "**If pregnant or breast-feeding,** ask a doctor before use" because of concerns that it would be misunderstood and providers may unnecessarily advise against use of the drug when the teratogenic risk was, in fact, low. Others proposed that the statement remain and that the Consumer Information Leaflet contain information on how the teratogenic risk of Differin (adapalene) Gel, 0.1%, differs from other retinoids. Several members also proposed uncoupling the warning to breast-feeding women from the Warning statement for pregnancy and breast-feeding, and removing it, since they could identify no safety issues with use of the product while breast-feeding.

***Comment*.** While I believe the teratogenic risk to the unborn child to be low, and acknowledge that there are no data suggesting that adapalene is excreted in human breast milk, I agree with the Advisory Committee members who preferred to retain the Warning statement for pregnant and breast-feeding women in the Drug Facts Label. This statement is consistent with CDC's advice that women who are pregnant or thinking about becoming pregnant speak with their healthcare provider about any medications they are taking or thinking about taking.

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/s/

JULIE G BEITZ
07/06/2016