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APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	June 28, 2016
From	Theresa M. Michele, MD Director, Division of Nonprescription Drug Products
Subject	Division Director Summary Review
NDA/BLA #/Supplement #	20380 S-10
Applicant	Galderma Laboratories, L.P.
Date of Submission	September 10, 2015
PDUFA Goal Date	July 8, 2016
Proprietary Name / Non-Proprietary Name	Differin/ adapalene
Dosage Form(s) / Strength(s)	Gel, 0.1%
Applicant Proposed Indication(s)/Population(s)	Prescription to OTC switch <ul style="list-style-type: none"> • Treatment of acne in adults and children ages 12 years and older • Clears up acne pimples and acne blemishes
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	Prescription to OTC switch <ul style="list-style-type: none"> • Treatment of acne in adults and children ages 12 years and older

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OLDP = Office of Lifecycle Management
DDDP = Division of Dermatology and Dental Products
DNNDP = Division of Nonprescription Drug Products
DPMH = Division of Pediatrics and Maternal Health
OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OLDP = Office of Lifecycle Drug Products
OPDP=Office of Prescription Drug Promotion
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

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The overall risk-benefit assessment supports approval of Differin Gel 0.1% for the treatment of acne in the OTC setting. This product would be a first in class switch for a topical retinoid product and the first new active ingredient for the treatment of acne available OTC for more than 40 years. To support the full switch of this product, Galderma submitted the results of a maximal use pharmacokinetic trial (MUsT). In addition, 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. A review of safety data was submitted including clinical trial data and post-marketing data from the time of first worldwide marketing approval in 1995 through December of 2014; a more comprehensive review was provided from August 2010 to July 2014.

The efficacy of adapalene gel 0.1% for the treatment of acne has been established in the prescription setting. It is expected that the product would have similar efficacy in the OTC setting, as the acne indication is the same in the prescription and OTC settings and treatment of acne is a well-established OTC indication. Professional guidelines recommend adapalene as first line therapy for acne either alone or in combination with other topical or agents due to the comedolytic and anti-inflammatory effects.

The primary consideration for this application is whether the benefits of OTC availability outweigh any potential risk for teratogenic effects on the developing fetus. Oral retinoids are known to cause birth defects in humans. Isotretinoin is available only through a restricted access pregnancy prevention program. Toxicology data clearly demonstrate a teratogenic signal with oral adapalene, with findings consistent with other drugs in the retinoid class although at a higher dose. Congenital anomalies seen in animal studies include cleft palate, microphthalmia, encephalocele, umbilical hernia, exophthalmos, kidney abnormalities, and skeletal abnormalities. However, using data from the human pharmacokinetic study performed using maximal topical administration according to the product label gives a safety margin of at least 70-fold for these effects. Although the margin could potentially be somewhat lower if consumers were to use the product over more than 10% of the body surface area or apply it multiple times per day, data from the actual use study suggest that consumers are likely to apply the product appropriately.

One additional caveat to the calculation of safety margins, particularly for teratogenic effects such as these, is that the actual threshold for an effect in humans is unknown and may be different than in the species tested. One way to evaluate this caveat is to look at available human data on pregnancy outcomes. Post-marketing safety data from 20 years of prescription use demonstrate few cases of abnormal pregnancy outcomes with no clear-cut cases of retinoid embryopathy. Given the high likelihood of significant underreporting, the absence of reports does not necessarily translate to an absence of events, but nonetheless does provide some information regarding the level of potential risk.

It is apparent from the data provided by the consumer studies 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. Overall, women in the actual use study 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. Further, in the actual use study 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 safety profile of adapalene is well-characterized, including a safety database of 5414 subjects exposed to adapalene gel (0.1% and 0.3%) in clinical trials and 20 years of marketing history in the United States and worldwide. The sponsor estimates that there have been over 40 million patients who have been prescribed use. The prescription label for adapalene states that some 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. The Galderma safety database contained 276 cases of pregnancy, with adverse outcomes in 17 that were either inconsistent with retinoid exposure or did not have sufficient data to draw a conclusion. A similar review of FAERS data included 18 cases of abnormal pregnancy, none of which were deemed consistent with retinoid embryopathy. Likewise, a literature review did not reveal any clear cut cases of retinoid embryopathy related to adapalene.

The majority of FDA reviewers, including the Division of Pediatrics and Maternal Health, recommend approval for adapalene gel 0.1%, and I concur with this recommendation. A minority opinion was provided by reviewers in the Division of Dermatology and Dental Products, who are concerned that use under the supervision of a health care professional is required to prevent wide-spread use by pregnant women leading to birth defects. In addition, the review raises concern that the safety calculation based on the MUsT fails to take into account that consumers could use the product on damaged skin, in combination with other vitamin A-containing dietary supplements, with heavy application, and over a larger body surface area, all of which may increase absorption and decrease the safety margin for teratogenicity. The review notes that with extreme use systemic effects may occur based on a well-documented report of hepatitis due to adapalene. While I acknowledge these concerns, the large safety margin, which was calculated in a conservative fashion using the highest level of exposure under maximal use conditions, coupled with the extensive marketing history and lack of clear adverse pregnancy outcomes with adapalene suggest that the risk is limited. In addition, the actual use trial demonstrated most use was substantially less than in the MUsT, giving additional reassurance that there is likely to be a large margin for teratogenicity, despite the fact that the human sensitivity is unknown. Toxicology data also suggest that while retinoid embryopathy may be seen with large oral doses of adapalene, it is less potent than other retinoids in this regard, possibly due to modified receptor binding.

Consistent with the recommendations of the team, I agree that having a pregnancy warning is appropriate, as it is both good medical care for pregnant women to discuss all medications with their physicians as well as helpful for consumers to make informed decisions regarding use of the product during pregnancy for their particular case. Given how poorly the warning tested in the self-selection study, I recommend modifying the warning to give it greater prominence and also to add a statement to “stop use and ask a doctor” if you become pregnant while using the product. In addition, some consumers may be familiar with other retinoids and have concerns whether or not a warning exists. Therefore, it is also important to clarify how this product differs from other retinoids and explain the risk more fully to consumers.

Finally, because of the potential for teratogenicity with this compound, it is of particular importance to do everything possible mitigate overuse.

As such, I recommend strengthening language regarding once daily use, as well as adding other language to the label explaining that increased use will not result in increased benefit. I also recommend limiting packaging size to two 45 g tubes, which was supported by the actual use study, to further mitigate risk of overuse.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Acne vulgaris is a common inflammatory skin disease characterized by open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules. • Acne may have significant physical and psychological morbidity, such as permanent scarring, poor self-image, depression, and anxiety. • Although it may affect any age group, acne occurs most frequently in teenagers, with up to 85% being affected, and may persist into adulthood. • Treatment of acne is a well-established OTC indication. 	<ul style="list-style-type: none"> • The population most likely to use adapalene gel 0.1% includes teens and young-women of child-bearing potential, which makes consideration of use in pregnancy critical. • Because topical acne products have been on the OTC market for many years, consumers are likely to understand how to self-diagnose and use these products. • However, because no other OTC acne products carry a pregnancy warning, labeling will be necessary to explain the risks.
Current Treatment Options	<ul style="list-style-type: none"> • Therapy for acne consists of both topical and oral products. Mild acne is generally treated with topical products, including benzoyl peroxide, topical retinoids, or a variety of different combinations of benzoyl peroxide, topical retinoids, and topical antibiotics. Additional oral agents are added for moderate to severe acne including oral antibiotics, oral contraceptives, spironolactone, or oral isotretinoin. • Professional guidelines recommend topical retinoids as first line therapy for all severities of acne either alone or in combination with other agents. • No new active ingredients have been approved for OTC use in more than 40 years. 	<ul style="list-style-type: none"> • OTC availability of adapalene would give consumers an additional choice for self-treatment and add substantially to the OTC armamentarium of acne therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • Topical acne products currently available OTC are all marketed under the OTC drug monograph. Active ingredients include benzoyl peroxide, resorcinol, salicylic acid, and sulfur. 	
Benefit	<ul style="list-style-type: none"> • The benefit of adapalene gel 0.1% was established for prescription use in controlled clinical trials. • The proposed indication for treatment of acne is the same indication for both prescription and OTC use. 	<ul style="list-style-type: none"> • Adapalene gel 0.1% is expected to have similar efficacy in the OTC setting as with prescription use.
Risk	<ul style="list-style-type: none"> • All retinoids are known to have teratogenic effects in animals, with tazarotene and isotretinoin known to cause birth defects in humans. • Toxicology data demonstrate a teratogenic signal with oral adapalene, with findings consistent with other drugs in the retinoid class. • Based on conservative calculations using the highest systemic blood levels achieved in a maximal use pharmacokinetic study (MUsT) compared to the most sensitive rodent species, the calculated safety margin for adapalene 0.1% gel is at least 70 fold. • Based on data from the actual use study and self-selection study, pregnant women are likely to use adapalene gel 0.1% if it is available OTC. • Post-marketing data over more than 20 years have not demonstrated any defined cases of retinoid embryopathy with adapalene. • Label comprehension and actual use data demonstrate that most consumers use the product correctly. • Other adverse events include erythema, scaling, dryness, pruritus, and burning, which are generally mild. 	<ul style="list-style-type: none"> • Teratogenicity is an important safety concern for this application. • The demonstrated post-marketing safety of adapalene and wide safety margin significantly reduce the potential concern for teratogenicity.
Risk Management	<ul style="list-style-type: none"> • The pregnancy warning tested poorly in the self-selection study. • A limited pregnancy warning might have unintended consequences of causing significant concern (comparable to that of an oral retinoid) if a pregnant woman uses the product. 	<ul style="list-style-type: none"> • In order to provide optimal advice to consumers, I recommend modifying the pregnancy warning to add stop use and ask a doctor if pregnant, as well as to add

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none">The actual use study demonstrated that most consumers used the product appropriately, when use was limited to purchase of two 45 gram tubes at one time.	<p>additional data explaining the differences between adapalene 0.1% gel and topical retinoids.</p> <ul style="list-style-type: none">Because of the potential for teratogenicity with this compound, it is of particular importance to do everything possible mitigate overuse. Therefore, I recommend strengthening the labeling regarding once daily use and limiting packaging size to two 45 gram tubes.

2. Background

2.1. Proposed product and indication

Galderma Laboratories, L.P. (Galderma) submitted this supplemental New Drug Application (sNDA) seeking approval for a full prescription to OTC switch of adapalene gel 0.1% (prescription trade name Differin[®]) for the treatment of acne vulgaris as a once daily topical administration.

Adapalene is approved as a prescription product for the topical treatment of acne vulgaris in adults and children 12 years of age and older in a variety of different formulations, including a 0.1% solution, 0.1% gel, 0.1% cream, 0.3% gel, and 0.1% lotion. It 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 is the same as the approved prescription dosing. If approved, this would be a first-in-class prescription to OTC switch for a topical retinoid.

The indication that the sponsor proposed “for the treatment of acne” is consistent with other OTC products available for treatment of this condition, and also consistent with the prescription indication “for the topical treatment of acne vulgaris”. Galderma initially also proposed “clears up acne pimples and acne blemishes,” which would be a new indication for adapalene in the OTC setting. Because there were no new efficacy data submitted as part of this application, this indication was not supported and was withdrawn from the application.

Galderma’s OTC development program for adapalene relies on the safety and efficacy established for the prescription product, since the acne indication is considered to be similar for both prescription and OTC use. To support the full switch of this product, Galderma submitted the results of a maximal use pharmacokinetic trial (MUsT). In addition, 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. A review of safety data was submitted including clinical trial data and post-marketing data from the time of first worldwide marketing approval in 1995 through December of 2014; a more comprehensive review was provided from August 2010 to July 2014.

This memorandum provides an overview of the original sNDA submission and serves as a summary review for the application.

2.2. Acne

Acne vulgaris is a common inflammatory skin disease characterized by open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules, particularly affecting pilosebaceous follicles of the face, chest, and upper back. Acne may have significant physical and psychological morbidity, such as permanent scarring, poor self-image, depression, and anxiety.¹ Although it may affect any age group,

¹ Zaenglein AL, Pathy AL, Schlosser BJ, et al. American Academy of Dermatology Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* <http://dx.doi.org/10.1016/j.jaad.2015.12.037>.

acne occurs most frequently in teenagers, with up to 85% being affected, and may persist into adulthood.² The prevalence of acne in adult women is about 12%.³

Therapy for acne consists of both topical and oral products. Although there is no standardized grading system for acne, it is generally divided into mild, moderate and severe, with therapy escalated in a step-wise fashion. Mild acne is generally treated with topical products, including benzoyl peroxide, topical retinoids, or a variety of different combinations of benzoyl peroxide, topical retinoids, and topical antibiotics. Additional oral agents are added for moderate to severe acne including oral antibiotics, oral contraceptives, spironolactone, or oral isotretinoin.⁴

Topical retinoids are vitamin A derivatives that include various formulations of tretinoin, adapalene, and tazarotene. Isotretinoin is an oral retinoid. Professional guidelines recommend these agents as first line therapy for all severities of acne either alone or in combination with other topical or oral agents for more severe disease due to their comedolytic and anti-inflammatory effects.⁴ All retinoids are known to have teratogenic effects in animals, with tazarotene and isotretinoin known to cause birth defects in humans. Oral isotretinoin is available only with a Risk Evaluation and Mitigation Strategy (REMS) consisting of a medication guide and a pregnancy prevention program and registry.

In the OTC setting, acne is a well-established indication. Topical acne products are marketed under the final OTC Drug Monograph for Topical Antimicrobial Products 21CFR Part 333.310 for the treatment of acne. Under this monograph, the following ingredients have been found to be Generally Recognized as Safe and Effective (GRASE) for OTC use under the conditions established in the monograph: benzoyl peroxide 2.5-10%, resorcinol 2% when combined with sulfur, resorcinol monoacetate 3% when combined with sulfur, salicylic acid 0.5-2%, sulfur 3-10%, and sulfur 3-8% when combined with resorcinol. Monograph instructions for use for products containing these ingredients state to apply “one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor. If bothersome dryness or peeling occurs, reduce application to once a day or every other day.”

2.3. Relevant regulatory history for adapalene

Adapalene is registered worldwide in more than 80 countries as of July 2014, primarily as a prescription product. The 0.1% gel formulation is the most extensively prescribed, and is available in 28 countries, including the European Union, Canada, Japan, and Australia. Russia is the only country which currently permits OTC marketing of adapalene, where it is available OTC as the 0.1% gel.

Adapalene gel 0.1% was originally approved in the U.S. in 1996 as a prescription product under NDA 20380. For the OTC switch of adapalene, two major milestone meetings were held between Galderma and FDA [Division of Nonprescription Clinical Evaluation (DNCE, now Division of Nonprescription Drug Products (DNDP)) and Division of Dermatology and

² Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol*. 2013; 168:474-85.

³ Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. *J Am Acad Dermatol*. 1999; 41:577-80.

⁴ Zaenglein AL, Pathy AL, Schlosser BJ, et al. American Academy of Dermatology Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* <http://dx.doi.org/10.1016/j.jaad.2015.12.037>.

Dental Products (DDDP)] regarding the development program. These included a pre-IND meeting in March 2013 and a pre-NDA meeting in June 2015. In addition to these, FDA also provided written advice on several occasions regarding consumer study design. Key interactions are summarized below.

March 12, 2013: Pre-IND meeting

- Concerns raised related to potential for teratogenicity and carcinogenicity
- For label comprehension study recommended testing pregnancy warning to ensure that the warning would prevent use in pregnant women, and testing sun exposure warning
- Recommendation for self-selection study to determine if adapalene would be used by pregnant women or women looking to become pregnant
- Recommendation for pharmacokinetic study under conditions of maximal use (MUsT)
- Recommendation to provide information on reproductive counseling practices by health care professionals for the prescription product

January 6, 2014: Type C Written Response Only meeting

- Recommendation for self-selection study to determine if adapalene would be used by pregnant women and if adapalene would be discontinued by women who became pregnant while using the product
- Recommendation for actual use study to evaluate off-label use and amount applied; also recommended evaluating self-selection related to pregnancy as part of the actual use study
- Recommendation for a pharmacokinetic study under conditions of maximal use (MUsT); may not extrapolate data from one adapalene formulation to another
- Discussed design of MUsT; recommendation to include an adequate number of adolescent subjects aged 12 to 17 years

June 30, 2014: Written feedback provided on MUsT

July 10, 2014: Galderma submitted IND 116,864

October 22, 2014: Advice letter regarding actual use study

- Recommendation to address self-selection during pregnancy, off-label use (misuse), application amount, and duration of use in actual use study

June 10, 2015: Pre-NDA meeting

- Recommendation to address impact of OTC availability on reproductive risks to women of child-bearing potential
- Recommendation to address potential for off-label use
- Recommendation to evaluate self-selection related to use in pregnancy

3. Product Quality

The proposed OTC product is identical to the prescription Differin Gel 0.1% in terms of the drug substance, drug product, and container closure. Galderma is proposing a 2 g, 15 g, and 45 g tube size for OTC marketing. Because there were no changes to the product for the OTC setting, manufacturing site inspections were not required and a categorical exclusion for an environmental assessment was granted.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical data were submitted with this sNDA. A comprehensive non-clinical program for adapalene was conducted in support of the prescription approval. Because of the concern regarding teratogenicity in the OTC setting, these data were extensively reviewed again as part of this prescription to OTC switch application.

4.1. Teratogens and Teratogenic Potential

A teratogen is a drug, chemical, or exposure that has the capacity under certain conditions to produce abnormal development in an embryo or fetus.⁵ Whether a drug is considered a teratogen depends on several factors, including the physical and chemical nature of the drug (e.g., whether the drug crosses the placenta); the fetal exposure resulting from the maternal dose as well as the duration, frequency, and route of administration of that dose; maternal and fetal metabolic integrity; and gestational timing of fetal exposure. A teratogen generally increases the rate of specific malformations above the background rate for that malformation when the embryo or fetus is exposed to the drug at specific times during gestation.⁶ These factors are evaluated along with other available relevant information. The evidence must be biologically plausible when determining whether a drug or exposure is a human teratogen.

The first trimester of pregnancy is considered a sensitive time for the embryo and developing fetus, as it is the time of many key developmental processes of organogenesis. Exposure to a teratogen during the first trimester of pregnancy may result in spontaneous abortion (i.e., miscarriage) or major structural congenital malformation (e.g., orofacial cleft, neural tube defect, heart defect).⁷ Exposure to a teratogen during the late first trimester, second trimester, and/or third trimester may also lead to abnormal organ differentiation, growth and function.

Major congenital malformations are defined as those that are life-threatening, require treatment or major surgery, present significant disability, or have significant cosmetic impact. In the United States, the estimated annual rate of major congenital malformations is approximately 2-4% of live births.^{8,9,10} The etiologies of most congenital malformations are unknown.

⁵ See the guidance for FDA reviewers on *Evaluating the Risks of Drug Exposure in Human Pregnancies*, available at <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071645.pdf>.

⁶ Holmes LB. Human Teratogens: Update 2010. Birth Defects Research (Part A): Clinical and Molecular Teratology, 2011; 91:1-7.

⁷ Bleyl SB, Schoenwolf GC. "What is the Timeline of Important Events During Pregnancy That May Be Disrupted by a Teratogenic Exposure?," Chapter 2. In: Hales B, Scialli A, Tassinari M. (eds.). Teratology Primer. Second Edition. Teratology Primer. 2010.

⁸ CDC. Update on Overall Prevalence of Major Birth Defects – Atlanta, Georgia 1978 -2005. MMWR Weekly, Jan 11 2008; 57 (01):1-5.

However, maternal medical conditions, such as diabetes and hypertension, contribute to the development of some congenital malformations.¹¹

Chemically-induced congenital malformations, including those associated with drug products, probably account for less than 1% of all congenital malformations, but are important because they are potentially preventable.¹² Prenatal exposures to drugs or other chemicals can also lead to damage that impacts the normal development of function. For example, developmental neurotoxic effects may cause changes in brain structure and chemistry (i.e., neurotransmitter signaling) which produce long-lasting effects on the developing brain. Studies in humans and animals have documented impaired intellectual function and various behavioral abnormalities that resulted from prenatal exposure to drugs.¹³ Drugs are evaluated for their teratogenic potential during the drug development process in a series of animal reproductive and developmental toxicity studies. By design, these studies cover all aspects of reproduction.¹⁴ Typically, one of the studies performed is the embryofetal toxicity study that assesses the potential for teratogenicity. This study consists of multiple dose groups that are administered the study drug during the period of organogenesis (implantation through palate closure). The data from these dose groups are compared to data from an internal control group of animals. Usually, three doses are studied and selected to provide exposures that, at the low dose, at or near the exposure of the anticipated human therapeutic range and at the high dose, are an exposure sufficient to elicit some maternal toxicity in the pregnant female animal. This provides a dose response that allows for an evaluation of teratogenic risk (potential) for the drug. Based on an integrated review of data that includes the reproductive and developmental toxicity data, the general toxicity data, and available pharmacokinetic data, a drug may be determined to have teratogenic potential in humans.

For drugs with known teratogenic potential based on animal data, the anticipated level of risk may be quantified using a safety margin calculation. A margin of exposure is a calculation that takes the highest animal no observed adverse effect level and estimates a maximum safe level of exposure for humans. One caveat is that 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 a drug is often unknown, as is the case with adapalene.

⁹ Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. *N Engl J Med.* 1989 Jan 5; 320(1):19-23.

¹⁰ Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, Strickland MJ, Duke CW, O'Leary LA, Riehle-Colarusso T, Siffel C, Gambrell D, Thompson D, Atkinson M, Chitra J. Reporting birth defects surveillance data 1968-2003. *Birth Defects Res A Clin Mol Teratol.* 2007 Feb; 79(2):65-186.

¹¹ Cragan JD, Friedman JM, Holmes LB, et al. Ensuring the Safe and Effective Use of Medications During Pregnancy: Planning and Prevention Through Preconception Care. *Matern Child Health J* 2006; 10:S129-S135.

¹² Uhl K, Trontell A, Kennedy D. Risk minimization practices for pregnancy prevention: understanding risk, selecting tools. *Pharmacoepidemiol Drug Saf* 2007 Mar; 16(3):337-48.

¹³ Voorhees CV. "Effects on Brain and Behavior," Chapter 5. In: Hales B, Scialli A, Tassinari M. (eds.). *Teratology Primer*. Second Edition. Teratology Primer. 2010.

¹⁴ See ICH S5 for a complete discussion of the reproductive and developmental studies.

4.2. Developmental and reproductive toxicity data

Reproductive and developmental toxicity studies were conducted in rats and rabbits via both the oral and topical route. 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 umbilical hernia, exophthalmos, and kidney and skeletal abnormalities. No teratogenic effect was seen in rats and rabbits at an oral dose of 5.0 mg/kg/day of adapalene. When given topically, adapalene did not induce malformations, but there were increases in supernumerary ribs in both species and delayed ossification in rabbits. A dermal No-Adverse-Effect-Level (NOAEL) of 36 and 72mg/m²/day was established in rat and rabbit embryo-toxicity studies, respectively.

These findings are generally consistent with the known adverse reproductive effects of retinoids, although adapalene is generally believed to be a less potent teratogen than other drugs in this class due to a lower binding capacity for some retinoid receptors. Using the highest observed dermal absorption from the human MUsT conducted for this OTC switch application, the margin of safety for teratogenic effects of adapalene is estimated to be approximately 70 times for rats and 357 times for rabbits. Because this value was calculated using the highest blood levels observed under maximal use conditions rather than average values, the safety margin represents a conservative estimate. Using maximum AUC values from other PK studies with adapalene gel 0.1%, gives safety margins of 59 and 140 based on the dermal rat teratogenicity study.

4.3. Other pertinent non-clinical data

Adapalene did not demonstrate genotoxicity or clastogenic effects from in vitro or in vivo testing. The carcinogenicity of adapalene was tested in a rat oral study and a mouse dermal study. The rat oral study demonstrated an increased incidence of benign and malignant pheochromocytomas, with an exposure margin of approximately 7.5 times the human dose based on a body surface area comparison, assuming 100% systemic absorption as a conservative estimate. This finding is also observed with other retinoids in rodent studies. However, given the differences between rat and human adrenal glands, the findings are not considered to represent a risk in humans. The mouse dermal carcinogenicity study demonstrated no drug-related neoplastic tumors.

5. Clinical Pharmacology

Adapalene is a retinoid-like compound that modulates cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne. 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. Excretion is primarily by the biliary route.

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. Although PK data were provided as part of the original application, pharmacokinetics for adapalene 0.1% gel were assessed over a limited body surface area and were not assessed in adolescents. Given the wide exposure expected with OTC availability and the need to establish a clear safety margin for potential teratogenic effects observed in

animal studies in order to guide the benefit-risk determination for adapalene, FDA recommended a MUSt consistent with current guidance for acne products.^{15,16} A MUSt is designed to capture the effect of maximal use on absorption into the blood with standard pharmacokinetic assessments (e.g., C_{max} , T_{max} , area under the curve, half-life, clearance, and volume of distribution).

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 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. Adapalene plasma concentrations were determined by HPLC coupled with tandem mass-spectrometry, providing a limit of quantification (LOQ) of the assay of 0.02 ng/mL.

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_{0-24h} by one subject (a 16-year-old male) at Day 24, with a mean value of 0.83 ng·h/mL. 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.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

No new efficacy data were submitted for this sNDA. The efficacy of adapalene for the treatment of acne has been previously established in the prescription setting. Since the acne indication is similar between OTC and prescription use, efficacy will be summarized only briefly here.

A total of five controlled clinical trials were conducted with adapalene gel 0.1% in subjects with mild to moderate acne vulgaris, two of which were vehicle-controlled. The remaining three trials included Retin-A (topical tretinoin) as an active control. One of the vehicle-controlled trials also included an active control arm with Retin-A. Primary assessments were at 12 weeks, and included an assessment of non-inflammatory lesions, inflammatory lesions, and/or a global grade. One placebo-controlled trial demonstrated a statistically significant

¹⁵ See the draft guidance for industry *Acne Vulgaris: Developing Drugs for Treatment*. When final, this guidance will represent the FDA's current thinking on this topic.

¹⁶ Bashaw ED, Tran DC, Shukla CG, et al. Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products. *Therapeutic Innovation & Regulatory Science*. 2015; 49(1), 108-115.

benefit over vehicle for both inflammatory and non-inflammatory lesions, while the other placebo-controlled trial demonstrated a numerical improvement over vehicle. The three active-controlled trials were also generally supportive of a favorable benefit-risk ratio, with the totality of the data supporting approval.

8. Safety

The safety profile of adapalene is well-characterized, including a safety database of 5414 subjects exposed to adapalene gel (0.1% and 0.3%) in clinical trials and 20 years of marketing history in the United States and worldwide. The prescription label for adapalene states that some 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. Adapalene is contraindicated in individuals who are hypersensitive to adapalene. There is also a warning not to use on sunburned skin, cuts, abrasions, or eczematous skin and to minimize sun exposure while using the product.

8.1. Safety in clinical trials

Adverse events seen in the MUsT and the 6-week actual use trial performed for this application were consistent with the product label for adapalene. There were no serious AEs in either trial. In the MUsT, 33% of subjects reported one or more AEs; the most frequently reported events were skin irritation, pruritis, and headache. In the actual use trial, 50% of patients reported one or more AEs; the most frequently reported events were headache, dry skin, and erythema. There were 4 pregnancies during the trial, one of which resulted in a healthy newborn, one was terminated for personal reasons, and two were lost to follow up. Of note, none of these women spoke to their doctors about adapalene use as instructed on the product label.

8.2. Consumer studies

Galderma 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.

Label comprehension study

A label comprehension study in adults and adolescents ages 12 to 70 years (Study 100544) was conducted in 586 respondents divided into a general population cohort and an augmented low literacy cohort. Overall, 515 were of normal literacy and 130 (22%) were low literacy. Adolescents aged 12 to 17 years were well represented, with 282 adolescents and 304 adults, although there was limited enrollment of adults in the 18-24 year old age group [N=33 (5.6%)]. The primary objective was to test the instruction "Use once daily," and the secondary objective was to test "Do not use on damaged skin." Unfortunately, warnings regarding use in pregnancy and sun avoidance (other than tanning bed use) were not tested, which substantially limits the utility of the study.

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. In general, the adolescent population had a comparable level of understanding of these objectives as adults.

Self-selection study

Study 103439 was a single visit, targeted self-selection study in 293 pregnant and breastfeeding women ages 13 to 54. In the general population cohort of 242 women, against which the a priori target threshold was measured, 91 (37%) were pregnant, the remainder were breastfeeding. An additional low literacy cohort was recruited, with 51 (17%) subjects. The vast majority of subjects were adults, with only 2 adolescent subjects. The primary objective of the 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). Women were recruited for the study at 25 different malls across the country based on the appearance of being visibly pregnant or accompanied by an infant under 18 months of age. Trimester of pregnancy was not recorded; however, given the method of recruitment it is likely that most were in later stages of pregnancy. The majority of women were breastfeeding; there were only 80 subjects (27%) who were pregnant and not breastfeeding, with an additional 11 subjects who were both pregnant and breastfeeding.

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.

Actual use study

Study 13049 (JUNO) 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. Enrollment included 203 (21.4%) adolescents aged 12 to 17 years, and approximately two thirds of the subjects were female. The population included 125 (13.2%) subjects of low literacy.

Of subjects who chose to purchase the product based on reading the product label but were excluded from participation after screening, 7 subjects were younger than 12 years of age. Of these, 5 were within 12 months of their 12th birthday. Nine subjects reported they did not have acne; most of these wanted to prevent acne or unclog pores. None wished to use the product for non-acne skin conditions. 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 primary objectives of the trial were to evaluate the frequency of use and to determine off-label use for non-acne conditions. Because subjects were excluded at screening if they did not self-report acne, off-label use was based on reported use for another skin condition in addition

to acne. A secondary objective was to evaluate whether subjects used the product inappropriately near eyes, mouth, or lips, or used it on damaged skin.

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. Most subjects using the product more than once daily reported reapplying after showering or washing, or used the product twice daily per routine or in an attempt to obtain greater or faster benefit. Almost all subjects in the trial [99.3%, (LCB 98.5%)] used the product for acne and not for other skin conditions. Subjects also did very well using the product on the correct body area [97.5% (LCB 96.2%)].

8.3. Post-marketing data

As part of this application, post-marketing safety data related to carcinogenic and teratogenic potential in humans for adapalene were submitted and reviewed from the following sources: the sponsor's pharmacovigilance database, FDA's Adverse Event Reporting System (FAERS), the World Health Organization (WHO Vigibase), and the published literature. All of these sources are subject to a number of limitations, primarily due to issues inherent in spontaneous reporting. In addition to data submitted by the sponsor, FDA conducted separate reviews of the FAERS data, post-marketing drug use, and epidemiology data available in the literature, with a focus on pregnancy outcomes. Key issues are reviewed here; additional primary discipline reviews are provided in the background package.

Galderma pharmacovigilance database

The sponsor's pharmacovigilance database includes data from first worldwide market introduction in 1992 through August 2013. During this time period, the sponsor estimates that over 40 million patients have been prescribed adapalene gel (0.1% and 0.3%) and there were 4,176 adverse events. Of these, only 21 cases (0.5%) included serious adverse events (SAEs). Over 70% of the adverse events were skin-related, with the most commonly reported events being dry skin and erythema. There were also 15 cases of local hypersensitivity confirmed by patch testing.

A specific review investigating pregnancy cases with all adapalene formulations (including the combination adapalene/benzoyl peroxide products) revealed 276 cases as of September 2014. Of these, adverse outcomes were reported in 17, with varied outcomes that the applicant concluded did not describe patterns consistent with retinoid exposure or there were insufficient data to draw conclusions.

FDA Adverse Event Database (FAERS)

FDA review of the FAERS database from time of approval (May 1996) through November 2015 revealed 127 serious, unduplicated cases associated with adapalene gel (65 cases with 0.1% and 23 with 0.3%). No approved strength was reported for the remaining cases. With one exception, all of the adverse events reported in these cases were consistent with those listed in the label for prescription adapalene. The one exception involves a cases of hepatitis associated with off-label use of adapalene over a large body surface area for Darier disease. Hepatitis is a known adverse event with oral retinoids.

FDA review of the FAERS database from April 2006 through November 2015 identified a total of 18 cases of abnormal pregnancy outcomes in women who used adapalene. These cases included reports of miscarriage (9), congenital anomalies (5), abortion (2), preterm birth (1),

and hemorrhage (1). The five cases of congenital anomalies included two isolated limb malformations, one VACTERL Syndrome (vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal and/or radial anomalies, and limb defects), one 2q37 deletion, and one case of Dandy Walker Syndrome (brain malformation). Of these, only Dandy Walker Syndrome has any known association with retinoids, but the overall range of malformations of the fetus were inconsistent with retinoid exposure. Given the background rate of birth defects (~4%) in the general population, it is typically not possible to establish causality for an isolated birth defect (e.g., heart defect) from a drug exposure based on spontaneous adverse event reports alone. FDA also identified one additional case from the literature that described adapalene-associated anophthalmia and agenesis of the optic chiasma in the fetus of a mother using adapalene 0.3% gel from the month before pregnancy until 13 weeks gestational age. The authors did not report whether the mother was using concomitant medications. The five cases of congenital anomaly associated with adapalene in FAERS appear to be isolated malformations and do not support a causal association between adapalene and these events.

Literature review

FDA performed a literature review for epidemiological studies related to adverse events from topical retinoids. Fifteen publications were reviewed in detail, including five related to pregnancy outcomes, two with other serious adverse events, and eight on local skin reactions. The most common adverse effects of topical retinoids including adapalene reported in the literature are related to local skin irritation, including erythema, dryness, scaling, pruritus, burning, and post inflammatory hyperpigmentation. The majority of these adverse events are generally transient and mild to moderate in severity. The studies related to pregnancy outcomes did not assess adapalene-related risk specifically.

Drug use data

FDA analysis of United States outpatient retail prescription data for single-ingredient adapalene products demonstrated that the overall number of prescriptions has decreased by 16% from 1.2 million prescriptions dispensed in the 12-month period ending in November 2011 to approximately 974,000 prescriptions in the 12-month period ending in November 2015. Of these, patients 12-45 years old accounted for 91% of patients, followed by patients aged 46 years and older at 5-6% of total patients; patients 0-11 years old accounted for 3% of the total patients¹⁷. Among females 12-45 years of age, 99% of the use was for a diagnosis of acne according to office-based physician surveys¹⁸.

9. Advisory Committee Meeting

As this product would be a first in class switch, the application was presented to a meeting of the Nonprescription Drugs Advisory Committee (NDAC) on April 15, 2016. At this meeting, FDA sought opinions related to the overall benefit to risk ratio of adapalene for the treatment of acne in the OTC setting. Factors noted for consideration in these discussions included the

¹⁷ IMS, Vector One®: Total Patient Tracker. Extracted December 2015.

¹⁸ Encuity Research, LLC., TreatmentAnswers™ with Pain Panel. Extracted December 2015.

potential for teratogenic effects including the safety margin, human absorption data, potential for use by pregnant women, post-marketing safety data related to pregnancy, and implications for the pediatric population. In addition to standing members of the NDAC, the committee also included members with expertise in dermatology, teratogenicity, and maternal-fetal medicine.

The committee unanimously agreed that the totality of the data supported the OTC use of adapalene gel 0.1% (16 yes, 0 no, 0 abstain). Members were also comfortable with use in adolescents down to age 12 in the OTC setting. However, the committee was split on the issue of whether the label should include a pregnancy warning and if so, what that warning should be. Members who recommended removing the pregnancy warning altogether were concerned that the warning may have unintended consequences because it may be difficult for consumers and even health care professionals to learn additional information about teratogenicity with adapalene. Data on oral retinoids, which have been shown to cause birth defects in humans, may raise undue concern for women who become pregnant while using the drug, possibly leading to unnecessary pregnancy terminations. Other members felt it was important for pregnant women to discuss all medications with their physicians and potential risk of use during pregnancy. The committee also recommended removing Galderma's proposed labeling regarding "clears up blemishes" because "blemishes" could be confused with other dermatologic conditions.

10. Pediatrics

The sponsor requested approval of adapalene gel 0.1% in the OTC setting for adults and children 12 years of age and older, which is the same population for which it is approved in the prescription setting. Other single ingredient adapalene formulations are also approved down to age 12 years, although the combination with benzoyl peroxide is approved in adults and children 9 years of age and older. Since there is no change in formulation, indication, dosing regimen, or route of administration, this application does not trigger the Pediatric Research Equity Act (PREA).

Given that acne is a disease that occurs predominantly in adolescents, Galderma included a representative sample of adolescent subjects in the majority of studies conducted for this OTC switch. As part of this application, the sponsor performed a pharmacokinetic study in 24 subjects, 18 of whom were adolescents aged 12 to 17 years. The subject with the highest exposure in this study, which was used to calculate the safety margin for teratogenic effects, was a 16 year old male, although age did not appear to influence systemic absorption. In addition, the label comprehension study included 18 (75%) adolescent subjects aged 13 to 17, and the actual use study included 203 (21.4%) adolescent subjects aged 12 to 17. Because the self-selection study focused on pregnant and breastfeeding women, only 2 of 293 subjects were adolescents.

Overall, these results support the proposal for use in adolescents ages 12 years and older. DNDP also consulted with the Division of Pediatrics and Maternal Health to evaluate use in pediatrics and in pregnant and breastfeeding women. The reviewers in these disciplines support approval, with some consideration of use down to age 9 given that acne may occur in younger children who are beginning puberty and Epiduo (combination adapalene/benzoyl peroxide) is approved in this age range. However, since all of the supporting data for the

switch is in the population 12 and older, which is also the population approved in the prescription setting, I recommend OTC approval down to age 12 years.

10. Other Relevant Regulatory Issues

10.1. Office of Scientific Investigations (OSI) audits

The FDA Office of Scientific Investigations conducted a clinical inspection of the Contract Research Organization (CRO) conducting the pivotal actual use study (JUNO), with a specific review of records from the two study-pharmacy sites with the highest enrollment, plus two additional study-pharmacy sites. The inspection report noted that there were no regulatory violations found during the inspection of the CRO and no major deficiencies during the audit of records from the four pharmacy sites. The inspection was classified as no action indicated (NAI).

10.2. Financial disclosure

The sponsor reported that there were no significant financial disclosures for any investigators participating in the actual use study (JUNO).

10.3. Environmental assessment

This application was granted a categorical exemption.

11. Labeling

11.1. Proprietary name

The proposed proprietary name, Differin Gel, was deemed acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). Because there is more than one strength of adapalene gel as well as more than one dosage form available in the prescription setting, I recommend ensuring that the strength of 0.1% is prominently displayed on the principal display panel (PDP) by including it within the statement of identity (SOI) to immediately follow the dosage form “gel” also within the SOI in order to avoid consumer confusion. The SOI would read in bolded text as “adapalene gel 0.1% Acne Treatment.”

11.2. Consumer labeling

Galderma submitted a Drug Facts Label (DFL), outer carton labels, immediate container labels, and a consumer information leaflet (CIL) intended to go inside the box. Significant team discussion occurred regarding these labels, particularly related to the pregnancy warning. As noted previously, the NDAC members were divided on this issue, with some members recommending including a warning and others recommending removing it entirely out of concern that the warning may have unintended consequences by influencing women to terminate pregnancies when there is limited risk. Consistent with the recommendations of the team, I agree that having a warning is appropriate, as it is both good medical care for pregnant women to discuss all medications with their physicians as well as helpful for consumers to make informed decisions regarding use of the product during pregnancy for their particular case. Given how poorly the warning tested in the self-selection study, the warning will be modified to give it greater prominence and also to add a statement to “stop use and ask a

doctor” if you become pregnant while using the product. In addition, some consumers may be familiar with other retinoids and have concerns whether or not a warning exists. Therefore, it is also important to clarify how this product differs from other retinoids and explain the risk more fully to consumers. As such, consumers will be directed to the CIL for further clarification.

Another related issue is the concern for overuse. In general, consumers used the product appropriately in the actual use study (89% used the product once daily). In the label comprehension study, 96% of normal literacy subjects, but only 87% of low literacy subjects (lower bound of the confidence interval 80%) understood to use once daily. While this comprehension is generally good, there is still some room for improvement. Because using the product more frequently could lead to higher blood levels, which, in turn, would decrease the safety margin, it is of particular importance to do everything possible mitigate overuse. As such, the label will be modified slightly to emphasize use only one time per day, with language added explaining that a greater benefit will not be seen with more frequent use.

11.3. Package size

For OTC use Galderma proposed a 2 g, 15 g, and 45 g package size. The sponsor proposes that the 15 g size is intended as a 30-day supply and the 45 g tube is intended as a 3-month supply. In the actual use trial, subjects were permitted to purchase up to three 45 g tubes over a 6 week period and could purchase a maximum of 2 tubes per visit. The majority of subjects (86%) used less than 40 g and only 13 subjects used more than 80 g, with maximum use of 129.5 g.

Research has shown that increased package sizing of products leads to increased usage among consumers^{19,20}. Conversely, limiting pack sizes of medication has been shown to reduce episodes of overconsumption by limiting the immediate availability of the drug to the consumer^{21,22}. The Division has also noted an increasing trend by drug manufacturers to package in larger and larger count sizes of OTC drugs for consumer use, which may be driven by warehouse clubs. In order to mitigate overuse and the resultant potential safety consequences, the DNDP clinical team recommended limiting package size for this product. I concur with this recommendation. Another factor to consider is that the explanation for the pregnancy warning is in the CIL, a separate paper that comes in the box rather than on the actual tube. Since consumers are likely to discard the excess packaging after purchase, repurchasing the product with a new CIL will be important since a consumer’s conditions such as pregnancy may change over time. The actual use study for the product supports packaging of up to two 45 g tubes, which represents a 6-month supply. Additional data would be necessary to support a larger package size. This package size restriction is not expected to

¹⁹ Wansink, B. (1996). Can package size accelerate usage volume? *Journal of Marketing*, 60(3), 1-14.

²⁰ Chandon, P., & Wansink, B. (2002). When are stockpiled products consumed faster? A convenience–salience framework of postpurchase consumption incidence and quantity. *Journal of Marketing Research*, 39(3), 321-335.

²¹ Hawton, K., Bergen, H., 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.

²² Weiss, S. (2009). Compliance packaging for over-the-counter drug products. *Journal of Public Health*, 17(2), 155-164.

limit consumer access to the product in the OTC setting since consumers may repurchase the product or purchase more than one package of the product at their discretion.

12. Postmarketing

12.1. Postmarketing Risk Evaluation and Mitigation Strategies

None.

12.2. Other postmarketing requirements and commitments

None.

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/s/

THERESA M MICHELE
06/28/2016