CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020380Orig1s010

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 20-380 / S-010**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	Efficacy	9/10/2015		10/27/2015	7/10/2016	4/29/2016
Filing Meeting		10/20/2015				
CMC Filing Review		*N/A*				11/8/2015
Environmental Assessment Consult		11/10/2015		*N/A*		*N/A*
74 Day Filing Letter		11/23/2015				
Amendment: Request for Proprietary Name Review		9/22/2015		10/27/2015		4/29/2016
Amendment: Differin Gel 0.1% and Differin 0.3%		10/13/2015				
Proprietary Name granted		11/24/2015		*N/A*		*N/A*
Amendment: Drug Facts and Labels		12/4/2015		12/4/2015		4/29/2016
Amendment: Drug Facts and Labels		1/21/2016		1/21/2016		
Advisory Committee Meeting		4/15/2016		*N/A*		*N/A*
Communication with Dr. Adah about OTC storage statements		4/24 - 25/2016				
Communication with OND PM		4/25/2016				
CMC Review 1		4/29/2016				4/29/2016
CMC Information Request for revised labels and labeling		4/26/2016				5/15/2016
Amendment: Drug Facts and Labels		5/2/2016		5/2/2016		
Amendment: Drug Facts and Labels		5/4/2016		5/4/2016		

3. **(a) Provides For From Cover Letter:** Rx to OTC switch for Differin® (adapalene) Gel 0.1%

   (b) Additional Change(s) Proposed in the Supplement: The name Differin® (adapalene) Gel 0.1% was proposed.

4. **Review #**: **2**

5. **Clinical Review Division**: DNDP

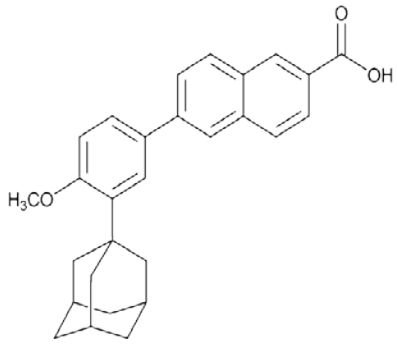
6. Name and Address of Applicant:

Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, Texas 76177

7. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Differin® (Adapalene, USP) Gel	Gel	0.1%	Topical	OTC	No

8. Chemical Name and Structure of Drug Substance:



USAN: Adapalene, USP

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

Molecular Formula: $C_{28}H_{28}O_3$

MW: 412.52

9. Indication: Treatment of acne in patients 12 years of age or older

10. Supporting/Relating Documents: None

11. Consults:

Consults	Recommendation	Date	Reviewer
OPF/Facility	*N/A*		
Microbiology			
Pharm/Tox			
Biopharm			
Statistics			
DMEPA	Proposed name Differin® Gel is acceptable	11/12/2015	Tingting Gao, PharmD
CDRH/ODE	*N/A*		
CDRH/OC			
EA	Claim of categorical exclusion is acceptable.	3/17/2016	Raanan Bloom, Ph.D.

12. Executive Summary:

Galderma Laboratories, L.P. is proposing to have the 0.1% gel drug product be available via over the counter. The proposed name, Differin® (adapalene) Gel 0.1%, was found acceptable by the Agency on November 11, 2015. For Differin® (adapalene) Gel 0.1% there are no changes proposed for the drug substance or the drug product.

At the October 20, 2015 Filing Meeting Dr. Klein informed the review team that inspection of the sites was not necessary and the DNDP Director agreed. In addition, Dr. Klein stated to the review team that the environmental assessment data was not clear and that the drug substance is a teratogen; consequently, an environmental assessment expert review is warranted and the review team agreed.

With respect to the Environmental Assessment Review, Dr. Bloom's Review (3/17/2016) states the following along with the conclusion:

EA Review Statement:

A Nonprescription Drug Advisory Committee (NDAC) meeting is planned. If additional information indicates teratogenic activity at expected environmental concentrations, the EA Team may revisit the issue of drug product retinoids in the environment.

EA Conclusion:

The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the anticipated amount of Differin® (adapalene) Gel, 0.1% to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

Via the 5/2/2016 and 5/4/2016 Amendments the Applicant provided the revised labels and labeling as requested via the CMC Information Request.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Donald N. Klein, Ph.D., Acting Quality Assessment Lead, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

Donald N. Klein -S

Digitally signed by Donald N. Klein -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300098862, cn=Donald N. Klein -S
Date: 2016.05.15 13:09:34 -04'00'

16. Secondary Reviewer:

Ramesh Raghavachari, Ph.D., Branch Chief, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

Ramesh Raghavachari -S

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Date: 2016.05.16 12:18:48 -04'00'

CMC Assessment

I. Background Information

Galderma Laboratories, L.P. is proposing to have the 0.1% gel drug product be available via over the counter. The proposed name, Differin® (adapalene) Gel 0.1%, was found acceptable by the Agency on November 11, 2015. For Differin® (adapalene) Gel 0.1% there are no changes proposed for the drug substance or the drug product.

CMC Review 1 (4/29/2016) requested the following:

> *Revise the Drug Facts and the label to include a storage statement. Also, the label and the Drug Facts must have the statement, "Protect from freezing".*

The Applicant provided the revised labels and labeling in the 5/2/16 and 5/4/16 Amendments.

II. Proposed Changes

a. Rx to OTC switch for Differin® (adapalene) Gel 0.1%.

b. The name Differin® (adapalene) Gel 0.1% was proposed.

III. Data Submitted to Support the Proposed Changes

a. Environmental Assessment data to support the request for a categorical exclusion.

b. **Revised** (5/2/16 and 5/4/16 Amendments) Drug Facts and labels.

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety

a. From the CMC point of view there are no risks because there are no changes proposed for the drug substance or the drug product. The Drug Facts and the labels have been revised as requested.

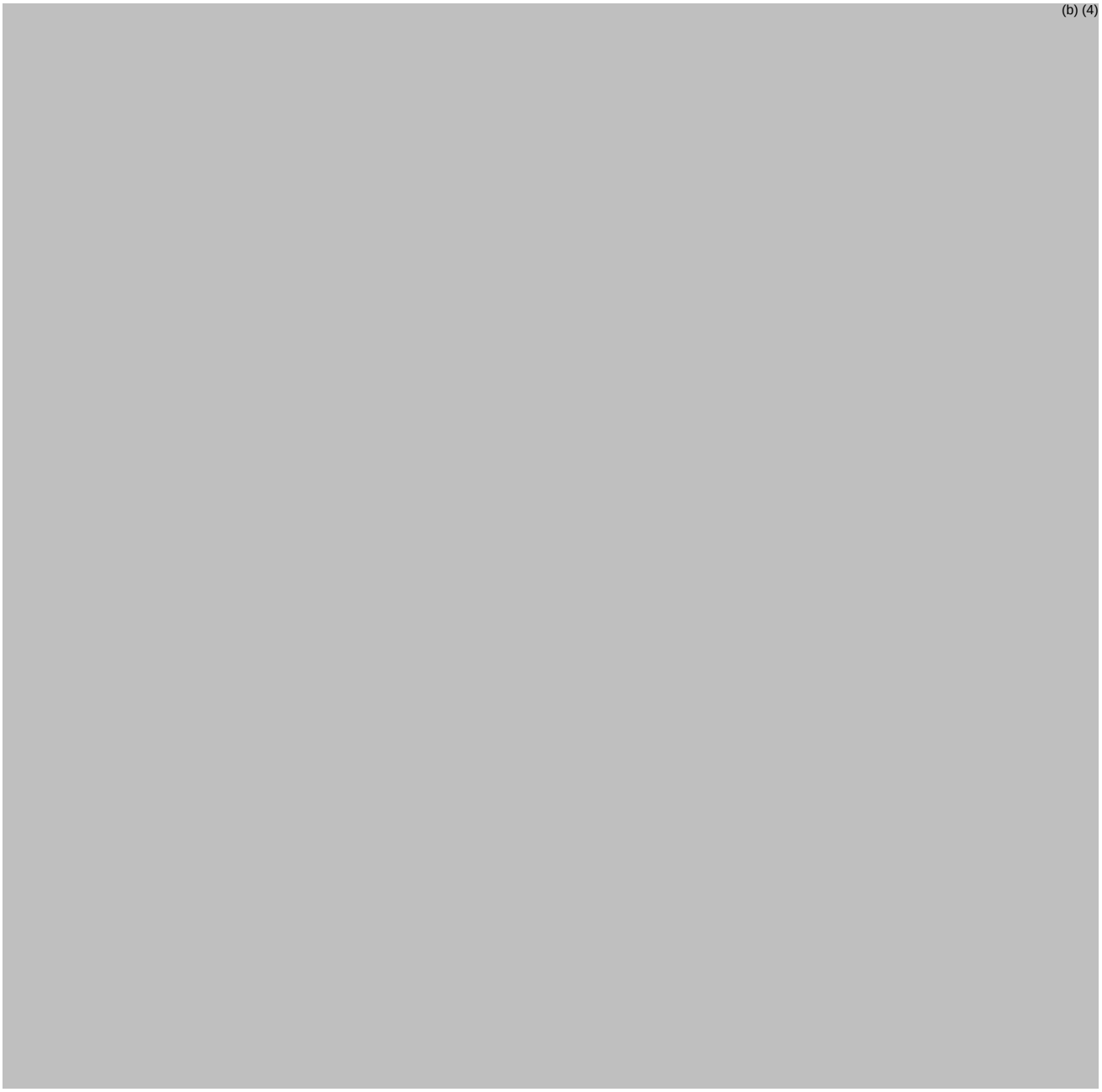
MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.2 PRESCRIBING INFORMATION

a. CMC Review 1 (4/29/2016) requested the following:

Revise the Drug Facts and the label to include a storage statement. Also, the label and the Drug Facts must have the statement, "Protect from freezing".

(b) (4)



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(b) (4)

EVALUATION: Acceptable.

1. From the CMC perspective the label and carton are acceptable.

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE

a. No changes proposed for Adapalene, USP.

3.2.P DRUG PRODUCT

a. No changes proposed for the Differin 0.1% Gel.

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4. **Review #**: 1

5. **Clinical Review Division**: DNDP

6. **Name and Address of Applicant**:

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   14501 North Freeway
   Fort Worth, Texas 76177

7. Drug Product:

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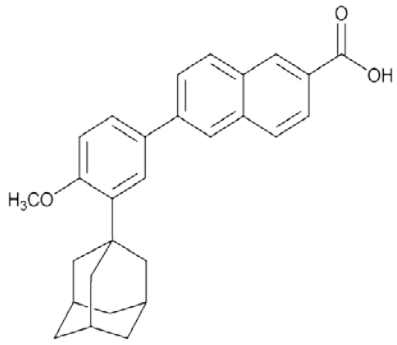

USAN: Adapalene, USP

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MW: 412.52

9. Indication: Treatment of acne in patients 12 years of age or older

10. Supporting/Relating Documents: None

11. Consults:

Consults	Recommendation	Date	Reviewer
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Pharm/Tox			
Biopharm			
Statistics			
DMEPA	Proposed name Differin® Gel is acceptable	11/12/2015	Tingting Gao, PharmD
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EA Conclusion:

The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the anticipated amount of Differin® (adapalene) Gel, 0.1% to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

For the Chemistry point of view the Drug Facts and the labels are not acceptable. The Applicant will be requested to provide new labels and Drug Facts such that the required storage statement is present.

13. Conclusions & Recommendations:

This supplement cannot be approved in its present form.

14. Comments/Deficiencies to be Conveyed to Applicant:

a. Revise the Drug Facts and the label to include a storage statement. Also the label and the Drug Facts must have the statement, "Protect from freezing".

15. Primary Reviewer:
Donald N. Klein, Ph.D., Acting Quality Assessment Lead, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

Donald N. Klein -S
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Date: 2016.04.25 15:32:08 -04'00'

16. Secondary Reviewer:
Ramesh Raghavachari, Ph.D., Branch Chief, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

Ramesh Raghavachari -S
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Date: 2016.04.29 10:00:32 -04'00'

CMC Assessment

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a. Rx to OTC switch for Differin® (adapalene) Gel 0.1%.

b. The name Differin® (adapalene) Gel 0.1% was proposed.

III. Data Submitted to Support the Proposed Changes

a. Environmental Assessment data to support the request for a categorical exclusion.

b. Drug Facts and labels

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety

a. From the CMC point of view there are no risks because there are no changes proposed for the drug substance or the drug product. However, the Drug Facts and the labels need to be revised to include a storage statement and the statement, “Protect from freezing”.

MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

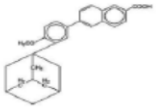
1.2 PRESCRIBING INFORMATION

a. Amendment (1/21/2016) presented a summary and the draft labels. The Applicant has intentionally omitted a storage statement. Inserted is the email discussion with Dr. Adah, DNDP, and the OND PM about the storage statement requirement.

Comparison Approach for Rx to OTC

Galderma Laboratories, L.P.
Differin (adapalene) Gel 0.1% - NDA 020380 Seq 0017

Comparison of Current Prescription Label and Proposed OTC Drug Facts Labeling for Differin Gel (adapalene 0.1%)

Current Prescription Drug Label	Located in Proposed OTC Drug Facts Label (DFL) and, if yes, location	Comment
DESCRIPTION: DIFFERIN Gel, containing adapalene, is used for the topical treatment of acne vulgaris.	Yes. **Active Ingredient/Purpose**	
Each gram of DIFFERIN Gel contains adapalene 0.1% (1 mg) in a vehicle consisting of carbomer 940, edetate disodium, methylparaben, poloxamer 182, propylene glycol, purified water and sodium hydroxide. May contain hydrochloric acid to adjust pH.	Yes. **Inactive Ingredients**	
The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula: 	No	This information is not included in OTC drug labeling.
CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological	No	This information is not included in OTC drug labeling.
profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris.		
Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. 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.	No	This information is not included in OTC drug labeling.
Pharmacokinetics: Absorption of adapalene through human skin is low. Only trace amounts (<0.25 ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.	No	This information is not included in OTC drug labeling.
INDICATIONS AND USAGE: DIFFERIN Gel is indicated for treatment of acne vulgaris.	Yes. **Active Ingredient/Purpose**	
CONTRAINDICATIONS: DIFFERIN Gel should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle gel.	No	This information is not included in OTC drug labeling. More recently approved prescription drug labels for adapalene-containing acne products have not included this statement.

WARNINGS: Use of DIFFERIN Gel should be discontinued if hypersensitivity to any of the ingredients is noted.	No. Consumers are not expected to understand hypersensitivity signs without a physician, however, consumers are directed to "**Stop use and ask a doctor if** irritation becomes severe" which would address potential hypersensitivity.	Also from current acne monograph labeling (21 CFR 333.350)
Patients with sunburn should be advised not to use the product until fully recovered.	Yes. "**Do not use** on damaged skin (cuts, abrasions, eczema, sunburned)."	Adapted from 333.350 based on FDA comments on the draft DFL at the Pre-IND Meeting on March 12, 2013
PRECAUTIONS: **General:** If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued.	Yes. "**Stop use and ask a doctor if** irritation becomes severe".	Also from current acne monograph labeling (21 CFR 333.350)
Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.	Yes. "**When using this product** • (b) (4) sun exposure, including tanning beds, and use sunscreen when going outdoors."	
	No	Galderma is not aware of data to support including this statement

Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.		and it does not appear in the current OTC acne monograph.
Avoid contact with the eyes, lips, angles of the nose, and mucous membranes.	Yes. "**When using this product** • avoid contact with eyes, lips and mouth. If contact occurs, immediately flush with water.	
The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.	Yes. "**Do not use** on damaged skin (cuts, abrasions, eczema, sunburned)."	
Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication.	Yes. "**When using this product** • irritation (redness, itching, dryness, burning) is more likely to occur: ○ in the first few weeks of use ○ if using more than one topical acne medication at a time.	
Depending upon the severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.	Yes. "**Stop use and ask a doctor if** irritation becomes severe".	
Drug Interactions: As DIFFERIN Gel has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high	Yes. "**When using this product** • irritation (redness, itching, dryness, burning) is more likely to occur: ○ in the first few weeks of use	The noted general precaution regarding use of more than one topical acne medications is included, however, a precaution about avoidance of other potentially irritating topical

concentrations of alcohol, astringents, spices, or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN Gel. If these preparations have been used, it is advisable not to start therapy with DIFFERIN Gel until the effects of such preparations in the skin have subsided.	○ if using more than one topical acne medication at a time.	products is not included as this is not found in the current OTC acne monograph and Galderma is not aware of any data that indicates that adapalene use with the specific product types listed (alcohol, astringents, spices or lime) is of greater concern than the existing OTC acne treatments.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4-75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats. No photocarcinogenicity studies were conducted. Animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.	No	This information is not included in OTC drug labeling.
In a series of in vivo and in vitro studies, adapalene did not exhibit mutagenic or genotoxic activities.		
Pregnancy: Teratogenic Effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5.0 mg/kg/day, up to 120 times the maximal daily human topical dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	No • **If pregnant or breast-feeding,** ask a (b) (4) before use.	This information is not included in OTC drug labeling. Galderma has proposed the existing codified warning from 21 CFR 201.63 (a). Although this warning is only required for systemically absorbed OTC drug products, Galderma is proposing to include this warning in the DFL as an added precaution even though the product is not for systemic use.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Gel is administered to a nursing woman.	• **If pregnant or breast-feeding,** ask a (b) (4) before use.	

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.	The directions for use state that the product is for 12 years and older and under 12 years of age should consult a physician.	
ADVERSE REACTIONS: 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 following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN Gel during clinical trials were reversible upon discontinuation of therapy.	Yes, with modification. **"When using this product** • irritation (redness, itching, dryness, burning) is more likely to occur: o in the first few weeks of use o if using more than one topical acne medication at a time.	Rates of adverse events are not included in proposed OTC labeling.
OVERDOSAGE: DIFFERIN Gel is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. The acute oral toxicity of DIFFERIN Gel in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.	No	
DOSAGE AND ADMINISTRATION: DIFFERIN Gel should be applied once a day to affected areas after washing in the evening before retiring. A thin film of the gel should be	**Yes, Directions.** Use <u>once</u> daily • Clean the skin (b) (4) before applying the product.	

applied, avoiding eyes, lips, and mucous membranes. During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.	Cover the entire affected area with a thin layer. And • irritation (redness, itching, dryness, burning) is more likely to occur: o in the first few weeks of use o if using more than one topical acne medication at a time. No	
HOW SUPPLIED: DIFFERIN (adapalene gel) Gel, 0.1% is supplied in the following size: 45 g laminate tube - NDC 0299-5910-45	Principle display panel includes required information	
Storage: Store at controlled room temperature 68° - 77°F (20° - 25°C), excursions permitted between 59° and 86°F (15° - 30°C). Protect from freezing.	Not applicable, no special storage requirements.	

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

BEST AVAILABLE COPY

Internal Discussion with Dr. Adah, DNDP

From: Adah, Steven
To: Klein, Donald N
Subject: RE: OTC Labeling that does not require a storage statement?
Date: Monday, April 25, 2016 6:51:55 AM
Attachments: image001.png

I agree both that it needs a storage statement and about the freezing comment.

From: Klein, Donald N
Sent: Sunday, April 24, 2016 2:31 PM
To: Adah, Steven
Subject: OTC Labeling that does not require a storage statement?

I'm reviewing N20-380, S-010, RX to OTC switch, for Differin Gel 0.1% and the Applicant intentionally omitted a storage statement from the label and carton.
As far as I know all drugs, Rx and OTC, require a storage statement. Also, this one has protect from freezing which is critical.
Correct me if I'm in error.

Galderma Laboratories, L.P.
Differin (adapalene) Gel 0.1% - NDA 020380 Seq 0017

applied, avoiding eyes, lips, and mucous membranes. During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.	Cover the entire affected area with a thin layer. And • irritation (redness, itching, dryness, burning) is more likely to occur: o in the first few weeks of use o if using more than one topical acne medication at a time. No	
HOW SUPPLIED: DIFFERIN (adapalene gel) Gel, 0.1% is supplied in the following size: 45 g laminate tube - NDC 0299-5910-45	Principle display panel includes required information	
Storage: Store at controlled room temperature 68° - 77°F (20° - 25°C), excursions permitted between 59° and 86°F (15° - 30°C). Protect from freezing.	Not applicable, no special storage requirements.	

Donald N. Klein, Ph.D.
Quality Assessment Lead (Acting)
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Branch I
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OLDP/OPQ/CDER/FDA
301-796-1689

Internal Discussion with OND Project Manager

From: Akinsanya, Lara
To: Klein, Donald N
Cc: Adah, Steven; Bloom, Raanan; Kong, Yoon
Subject: RE: N20-380, S-010: Current Draft Labels and Carton and Leaflet?
Date: Monday, April 25, 2016 2:32:26 PM

Hi Don,

You are correct regarding the inconsistency with the submitted labeling. Galderma is planning to revise their proposed labeling based on the discussion at the AC- they plan to submit by May 2, 2016.

It might not be a bad idea to send in your IR so they can make your changes as well in the May 2, 2016 submission.

Thanks,

Lara

From: Klein, Donald N
Sent: Monday, April 25, 2016 10:53 AM
To: Akinsanya, Lara
Cc: Adah, Steven; Bloom, Raanan
Subject: N20-380, S-010: Current Draft Labels and Carton and Leaflet?
Importance: High

Hi Lara,

I had completed my CMC review and found that the Draft Label for the 4/15 Advisory Committee Meeting is different from the 1/21/16 Amendment.

Specifically, the 1/21 Labels, Leaflet, and Carton are fine except for the storage statement and the Protect from Freezing statement.

I just checked EDR and is the 1/21/16 Amendment the current proposed labeling?

Perhaps Galderma doesn't realize the inconsistency?

I can finalize my CMC and we can send an IR for updated labels, etc.

Once received I'll write a second Review.

Let me know how to proceed that is best for U/OND.

The EA review is done.

Donald N. Klein, Ph.D.

Quality Assessment Lead (Acting)

EVALUATION: Not Acceptable.

1. From the CMC perspective the label and carton are acceptable except a storage statement is required. As shown in the review the storage statement requirement was discussed with Dr. Adah, DNDP, and the OND PM.

DEFICIENCY:

1. Revise the Drug Facts and the label to include a storage statement. Also, the label and the Drug Facts must have the statement, "Protect from freezing".

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE

a. No changes proposed for Adapalene, USP.

3.2.P DRUG PRODUCT

a. No changes proposed for the Differin 0.1% Gel.

NDA 020380 S-010

Established/Proper Name: Differin® (adapalene) Gel, 0.1%
Applicant: Galderma Laboratories LP

Environmental Analysis: Review of Claim of Categorical Exclusion

Conclusion:

The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the anticipated amount of Differin® (adapalene) Gel, 0.1% to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

Review:

Galderma has proposed an RX-to-OTC switch of adapalene gel 0.1% (Differin). The drug product is used for the topical treatment of acne vulgaris. All drug products are currently by prescription only.

The applicant has submitted a claim of categorical exclusion under 21CFR25.31(b) based on use calculations (see below). Included is a statement that no extraordinary circumstances exist.

The review of the claim for exclusion pertains to the specific NDA for adapalene gel, 0.1%. The applicant provides information indicating that over the first 5 years post-approval, the maximum amount of adapalene (kg) projected for use in any one year in the US, **for all marketed dosage forms containing adapalene**, will be (b) (4) kg. This (b) (4) kg calculation is based on the total adapalene utilization for all marketed drugs (branded and generic), both prescription and OTC for adapalene gel, 0.1% if the proposed Rx-to-OTC switch is approved (see Table 1, below). The OTC increase for this application for adapalene gel 0.1% accounts for approximately (b) (4) KG for a total of (b) (4) kg by 2020. Present prescription level of all adapalene products is (b) (4) kg/yr (IMS, 2014), with Galderma Labs accounting for (b) (4) kg. These values are lower than levels provided in the table.

The estimated introductory concentration (aquatic) for all adalapene containing products is calculated at (b) (4) ug/L (ppb). The estimated worst-case environmental concentration (EEC aquatic) is calculated at (b) (4) ug/L or approx. (b) (4) ng/L. These estimates assume no metabolism, degradation in WWTP or proportion of drug that enter septic tank systems.

Using IMS data, the estimated amount of adalapene manufactured by Galderma Labs accounts for 2014 is (b) (4) kg or an EEC of (b) (4) ng/L.

The estimated additional amount of adalapene added to total adalapene by 2020 by the Rx-OTC application is (b) (4) kg annually. For the purposes of this review, we assume that all adapalene Gel 0.1% is produced by Galderma for a production value of (b) (4) kg or EEC of (b) (4) ng/L.

Table 1: Projected amount of Adapalene (kg) over the next 5 years (adopted from submission**)**

Product	2016 Adapalene (kg)	2017 Adapalene (kg)	2018 Adapalene (kg)	2019 Adapalene (kg)	2020 Adapalene (kg)
Adapalene Gel 0.1% (Rx; branded and Generic)	(b) (4)				
Adapalene Gel 0.1% (OTC)*					
Adapalene Lotion 0.1% (Branded and Generic)					
Adapalene Cream 0.1% (Branded and Generic)					
Adapalene Gel 0.3% (Branded and Generic)					
Epiduo Gel (BPO/ Adapalene) 2.5%/0.1%					
Epiduo Forte Gel (BPO/Adapalene)					
Total					

Numbers in parenthesis are estimated usage if Adapalene Gel, 0.1% remained prescription use only.

Adapalene is practically insoluble in water, sparingly soluble in tetrahydrofuran and practically insoluble in ethanol (96%). The calculated partition coefficient (LogP) between n-octanol /water = 8.11. Solubility and partitioning coefficients indicates that adapalene would be expected to partition to biosolids in waste water treatment plants and lesser amounts would be discharged into the aquatic environment, below the calculated EEC of (b) (4) ng/L. The low production volumes and low absorption and potential WWTP degradation[1], indicate extremely low aquatic exposure levels.

At these levels, ecotox impacts of pharmaceutical residues in the environment have not been observed.

A search of the literature did not locate any information about the toxicity of adapalene to environmental organisms.

MOA: Adapalene is a chemically stable, retinoid-like compound. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. 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. No apparent estrogen, androgen, or thyroid activity is noted.

The claim of categorical exclusion is acceptable. No extraordinary circumstances are noted for this application.

Additional discussion:

Retinoic acids (RA) are metabolites derived from retinoid (vitamin A) precursors in humans and animals which have 3 isomers (all-*trans*-RA, 9-*cis*-RA, and 13-*cis*-RA). Vitamin A is required for growth and development. Retinoic acid is required in chordate animals, which includes all higher animals from fish to humans. RAs are metabolized by the liver and excreted in bile and urine.

Environmental levels of RA are primarily due to dietary sources (vegetable and animal) of retinoids. Under normal physiological conditions, RAs are present in human bile urine [2]. In addition, RA is an endogenous compound of human blood [3]. Vitamin A (retinyl palmitate) supplementation significantly increases circulating RA concentrations of all-trans-, 9-cis-, and 13-cis-RA[4]. Other studies have demonstrated that cyanobacteria blooms produce retinoic acids[5].

RAs and their metabolites can enter into the aquatic environments through discharge of domestic sewage. Concentrations of RAs and their bioactive metabolites 4-oxo-RAs in treated wastewater have generally been found to be less than 1.0 ng/L[6].

An Australian study found that even where WWTP discharges represent all of the environmental flow in the warmer months, the observed RAR (as all-*trans*-retinoic acid (RA)) was still significantly lower than the concentrations of RAs known to cause developmental malformations in fish larvae after short-term exposure to these chemicals [7].

According to the Rx label , no teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5.0 mg/kg/day, up to 120 times the maximal daily human topical dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats.

Due to concerns about teratogenicity risk and abnormal pregnancy outcomes with retinoid drug products, The Division of Nonprescription Drug Products (DNDP) has requested that the Divisions of Pharmacovigilance (DPV II) and Epidemiology (DEPI I) review abnormal pregnancy outcomes, (with a focus on congenital anomalies) associated with adapalene (Differin) and other topical retinoids. The Feb 6, 2016, Pharmacovigilance, Epidemiology and Drug Utilization Review indicates that "Based on a lack of a clear pattern of congenital anomalies consistent with retinoid embryopathy, and a lack of compelling medical literature in FAERS cases and epidemiological data, there does not appear to be a signal for adapalene-associated congenital anomalies at this time."

A Nonprescription Drug Advisory Committee (NDAC) meeting is planned. If additional information indicates teratogenic activity at expected environmental concentrations, the EA Team may revisit the issue of drug product retinoids in the environment.

References:

[1] Sawada, K., Inoue, D., Wada, Y., Sei, K., Nakanishi, T. and Ike, M. (2012), Detection of retinoic acid receptor agonistic activity and identification of causative compounds in municipal wastewater treatment plants in Japan. Environmental Toxicology and Chemistry, 31: 307–315. doi:10.1002/etc.741.

[2] Lambert WE, De Leenheer AP. Demonstration of retinoic acid isomers in human urine under physiological conditions. Experientia. 1985;41:359–360.

[3] De Ruyter MG, Lambert WE, De Leenheer AP. Unequivocal demonstration of endogenous retinoic acid in normal physiological conditions. Anal Biochem. 1979 Oct 1;98(2):402-9.

[4] Sedjo RL, Ranger-Moore J, Foote J, Craft NE, Alberts DS, Xu MJ, Giuliano AR. Circulating endogenous retinoic acid concentrations among participants enrolled in a randomized placebo-controlled clinical trial of retinyl palmitate. Cancer Epidemiol Biomarkers Prev. 2004 Nov;13(11 Pt 1):1687-92.

[5] Wu X, Jiang J, Wan Y, Giesy JP, Hu J. Cyanobacteria blooms produce teratogenic retinoic acids. *Proceedings of the National Academy of Sciences of the United States of America*. 2012;109(24):9477-9482).

[6] Zhen HJ, et al. Identification of retinoic acid receptor agonists in sewage treatment plants. Environ Sci Technol. 2009;43:6611–6616.

[7] M. Allinson, F. Shiraishi, S. A. Salzman In Vitro Assessment of Retinoic Acid and Aryl Hydrocarbon Receptor Activity of Treated Effluent From 39 Wastewater-Treatment Plants in Victoria, Australia. Archives of Environmental Contamination and Toxicology, 2011, Volume 61, Number 4, Page 539.

Raanan A. Bloom -S

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