CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020380Orig1s010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 20380 SUPPL # 010 HFD # 560

Trade Name Differin Gel, 0.1%

Generic Name adapalene

Applicant Name Galderma Laboratories, L.P.

Approval Date, If Known July 8, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), Rx-to-OTC switch (SE6)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	020748	Differin Cream 0.1%
NDA#	020380	Differin Gel 0.1%
NDA#	021753	Differin Gel 0.3%
NDA#	022502	Differin Lotion 0.1%
NDA#	020338	Differin Solution 0.1%
NDA#	022320	Epiduo Gel 0.1% (adapalene); 2.5% (benzoyl peroxide)
NDA#	0207917	Epiduo Forte 0.3% (adapalene); 2.5% (benzoyl peroxide)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of

new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

N/A

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. Actual Use Trial (Study 100931) to understand use of Differin Gel, 0.1% in an unsupervised OTC environment. This study was an open label, single arm, multicenter, 6-week actual use study.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 Actual Use Trial (Study 100931) YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such

investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	Actual Use Trial (Study 100931)	YES ☐	NO ☒
Investigation #2		YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Actual Use Trial (Study 100931)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Actual Use Trial (Study 100931)		
IND # 116864	YES ☒	! NO ☐ ! Explain:	
Investigation #2 IND #	YES ☐	! NO ☐ ! Explain:	

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
N/A	

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
N/A	

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

N/A

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Name of person completing form: Lara Akinsanya, MS
Title: Senior Regulatory Health Project Manager
Date: June 08, 2016

Name of Office/Division Director signing form: Karen Murry Mahoney, MD, FACE
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
07/08/2016

KAREN M MAHONEY
07/08/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 20380 BLA # N/A	NDA Supplement # 010 BLA Supplement # N/A	If NDA, Efficacy Supplement Type: SE6 *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Differin Gel Established/Proper Name: Adapalene Dosage Form: Topical gel		Applicant: Galderma Laboratories Agent for Applicant (if applicable): N/A
RPM: Lara Akinsanya		Division: Nonprescription Drug Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is July 10, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): N/A
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☒ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Information Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes N/A
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date Approval – 07/08/16
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ N/A
• Original applicant-proposed labeling	☐ N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ N/A
• Original applicant-proposed labeling	☐ N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptability Letter – 11/24/15 11/12/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: 06/09/16 DMPP/PLT (DRISK): ☒ None OPDP: ☒ None SEALD: ☒ None CSS: ☒ None Product Quality 06/16/16 DNDP – 07/07/16; 06/24/16
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM: Filing Review – 11/09/15 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: This is a complete Rx to OTC Switch Product. PREA was not triggered.	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	**2016 IRs** – 07/07; 07/05; 07/01; 06/17; 06/10; 06/02 (2); 05/31; 04/26; 03/17; 03/01; 02/09; 02/05; 02/03 (3); 02/02; 01/26(2); 01/21; 01/14; 01/12(2); 01/08(2); 01/04 **2015**- IR – 12/16; Filing Review Issues- 11/23; IR – 10/22; Acknowledge NDA – 09/23
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	Pre- NDA – 06/10/15
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	Type C (WRO) – 01/06/14 Type B PIND meeting – 03/12/13
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	April 15, 2016
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	ODEIV – 07/07/16 ODEIII – 07/06/16
Division Director Summary Review *(indicate date for each review)*	DNDP - 06/28/16 DDDP - 06/21/16
Cross-Discipline Team Leader Review *(indicate date for each review)*	06/17/16
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	06/11/16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	06/11/16
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	06/15/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	DDDP Clinical Review – 06/01/16 OSE (DEPI Review) – 03/16/16 DPMH (Pediatric) – 04/08/16; 02/19/16 DPMH (Maternal Health) – 03/28/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Inspection Summary – 04/25/16 Inspection Letter – 04/12/16
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review N/A
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review 05/31/16
Statistical Review(s) *(indicate date for each review)*	05/30/16
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review N/A
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review 05/18/16
Clinical Pharmacology review(s) *(indicate date for each review)*	05/18/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review 06/03/16
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	06/03/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None 05/16/16
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	05/16/16; 04/29/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	03/17/16
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☐ Acceptable Re-evaluation date: ☐ Withhold recommendation ☒ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONSURAT O AKINSANYA
07/08/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, July 06, 2016 9:48 AM
To: 'GRIFFIN Sean'
Subject: RE: Additional Labeling Information Request DUE 7/6- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Sean,

Its ok. Thanks for making all the requested changes so far. The following changes also needs to be made:

Immediate containers for all SKUs
Revise the statement [redacted] (b) (4) to "ask a doctor" under Children under 12 years of age

CIL
Add a period after the word :

- "day" in the sentence that starts with "Apply this product…." under How often do I apply the product?
- "hands" in the sentence " Wash hands after use' under How do I apply the product?
- "away" in the sentence "You may want to delay…" under the When is my skin most likely to become irritated? And what do I do?"

Regarding your question on indenting the bullets, I am checking with a few others on that and will get back to you ASAP.

Thanks,
Lara

From: GRIFFIN Sean [mailto:Sean.GRIFFIN@galderma.com]
Sent: Wednesday, July 06, 2016 9:33 AM
To: Akinsanya, Lara
Subject: RE: Additional Labeling Information Request DUE 7/6- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Lara,

We spotted something we missed, on the 45-gram carton the second "I" in Inactive Ingredients should have been lower case. We will correct prior to the official submission and of course anything else you request.

Sorry about that!
Sean

From: Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]
Sent: Tuesday, July 05, 2016 7:39 PM
To: GRIFFIN Sean
Subject: RE: Additional Labeling Information Request DUE 7/6- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Sean,

Thanks for the quick response to our IRs. We will review them and get back to you by tomorrow.

Thanks again,
Lara

From: GRIFFIN Sean [mailto:Sean.GRIFFIN@galderma.com]
Sent: Tuesday, July 05, 2016 6:20 PM
To: Akinsanya, Lara
Subject: RE: Additional Labeling Information Request DUE 7/6- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Lara,

Revised artwork for the cartons to address the comments received today are attached along with the 2 gram sample card, where we made the same changes for consistency. Redlines also provided.

We had one question on aligning all bullets left in the DFL. Should we have left the sub-bullets under "Irritation (redness, itching…) is more likely to occur:" indented? We aligned all left per your e-mail but just wanted to bring that to your attention in case we should have left them indented. We are happy to change back prior to submission if the Agency prefers - we think it is more clear if the sub-bullets are indented.

Please advise if acceptable and we will submit along with the container and leaflet labels provided for review earlier today.

Thank you!
Sean

From: Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]
Sent: Tuesday, July 05, 2016 4:04 PM
To: GRIFFIN Sean
Subject: RE: Additional Labeling Information Request DUE 7/6- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Ok. Please remember to email me first and wait for my confirmation before making the official submission.

Thank you,
Lara

From: GRIFFIN Sean [mailto:Sean.GRIFFIN@galderma.com]
Sent: Tuesday, July 05, 2016 5:02 PM
To: Akinsanya, Lara
Subject: RE: Additional Labeling Information Request DUE 7/6- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Lara,

Received and in process.

Best regards,
Sean

From: Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]
Sent: Tuesday, July 05, 2016 3:38 PM
To: GRIFFIN Sean
Cc: Akinsanya, Lara
Subject: Additional Labeling Information Request DUE 7/6- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Sean,

The modified Drug Facts label format for the 2-gram carton is acceptable.

Please respond to the below additional Labeling Information Request by Noon on **Wednesday, July 06, 2016.** For time, please reply by e-mail in addition to submitting an amendment to the NDA to include revised labeling with tracked changes)

(1) The bullets used in Drug Facts for the 2-, 15-, and 45-g cartons, are rectangular in shape and do not appear to align horizontally or vertically with the text font. The bullets should be revised to square bullets and ensure the text is fully left justified.
(2) For Drug Facts on all outer cartons (e.g., 2-, 15- and 45-g),

a. the following should be in lower case:
ingredient (in "Active ingredient")
treatment (in "Acne treatment")
information (in "Other information"
store (in "store at room temperature…")
protect (in "protect from freezing")
ingredients (in "Inactive ingredients")
all the inactive ingredients listed in the "Inactive ingredients" section should all be in lower case
Under "May contain statement", "hydrochloric acid" should be in lower case
b. Also, remove the "-s" under the section entitled "Uses" so that it should read as "Use".
c. Under "**When using this product**", place a period after the 6th bulleted statement so that it reads as follows:
▪avoid product contact with eyes, lips, and mouth. If contact occurs, immediately flush the area with water.
d. Under the "**Stop use and ask a doctor if**", a comma should be added after the word, eyelids.

Thank you.
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

10903 New Hampshire Ave
Silver Spring, MD 20993
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/s/

MONSURAT O AKINSANYA
07/07/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, July 05, 2016 4:38 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Additional Labeling Information Request DUE 7/6- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Sean,

The modified Drug Facts label format for the 2-gram carton is acceptable.

Please respond to the below additional Labeling Information Request by Noon on **Wednesday, July 06, 2016.** For time, please reply by e-mail in addition to submitting an amendment to the NDA to include revised labeling with tracked changes)

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▪avoid product contact with eyes, lips, and mouth. If contact occurs, immediately flush the area with water.
d. Under the "**Stop use and ask a doctor if**", a comma should be added after the word, eyelids.

Thank you.
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products

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/s/

MONSURAT O AKINSANYA
07/05/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, June 30, 2016 9:19 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Labeling Information Request DUE 7/1- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Sean,

Please respond to the below Labeling Information Request by Noon on **Friday, July 01, 2016.** For time, please reply by e-mail in addition to submitting an amendment to the NDA to include revised labeling with tracked changes)

Consumer Information leaflet

How do I apply the product?

Revise so that the following statement reads:

Apply Differin Gel as a thin layer to the affected areas of the skin "**only <u>one time a day</u>**". Remove underline from "**one time a day**".

Immediate Container Labels for the 2-g, 15-, and 45(tubes) count SKUs

a. **Directions-** Revise from [redacted] (b) (4) to "adults and children 12 years of age and older" to be consistent with the DFL.
    1. Under the Directions for this age group, revise from [redacted] (b) (4) to "clean the skin gently and pat dry before applying the product" to be consistent with the DFL.

b. **Directions-** Revise statement from [redacted] (b) (4) to "children under 12 years of age" to be consistent with the DFL.
c. **If pregnant or breast-feeding-** Revise from "ask a [redacted] (b) (4) before use" to "ask a doctor before use".

Annotated Specifications for Drug Facts Labels

(1) Per the labeling IR sent on June 17th, 2016 (via email), it was requested that you ensure that bullets follow format specifications per 21 CFR 201.66 throughout your proposed label. Also, it was requested that the bullets be revised such that
additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading are vertically aligned with the bulleted statements appearing on the previous line in accordance with 21 CFR 201.66 (d). However, the labeling submitted on June 29, 2016, via email for the 2-g outer carton (card) is not in compliance.

Revise the labeling of the 2-g outer carton (card) to be in compliance these format/font regulations.

Thank you.
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
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/s/

MONSURAT O AKINSANYA
07/01/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, June 17, 2016 5:14 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Labeling Information Request DUE 6/22- NDA 20380/Differin (adapalene), 0.1%/Galderma – Full Switch Efficacy supplement

Hi Sean,

Please respond to the below Labeling Information Request regarding the PDP and immediate containers by **Wednesday, June 22, 2016**

Consumer Information Leaflet

a. Remove (b) (4) graphic design wherever it appears as it implies that Differin may be a biologic product, instead of a drug product
b. Revise the order of the proprietary name and SOI to the following: Differin Gel, adapalene gel 0.1% Acne Treatment (see recommendations for PDP).

Principal Display Panel (PDP) for all SKUs

1. **Statement of identity (SOI) (see 21 CFR 201.61)**
   a. For the pharmacological category, identify the product as an "acne treatment" for consistency as you have used under the Purpose section of the Drug Facts label. Use this term consistently throughout your labeling to prevent confusion.
   b. Revise SOI to the following: adapalene gel 0.1% Acne Treatment.
   c. Submit revised labeling so that the SOI is at least 25% to 50% of the most prominent printed matter on the PDP.
   d. Reformat the orientation of the proprietary name Differin Gel and SOI"adapalene gel 0.1% to comply with 21 CFR 201.61 (c). Your current proposed PDP labels has these terms relatively perpendicular (vertical) to the package's base, instead of relatively parallel to the base as required.
2. Remove the (b) (4) If you would like to keep this statement on the PDP, it is suggested that you should place as a statement (b) (4)
3. Remove the statement (b) (4) as this may be confusing to consumers (b) (4)
4. Provide data to support this statement (b) (4) for this proposed OTC Differin Gel 0.1% product or remove it.
5. Revise the statement (b) (4) to "**One Time A Day Acne Treatment**" for clarity and consistency with the Drug Facts label and consumer information leaflet.
6. Remove the (b) (4) statements for 15-g and 45-g products respectivel (b) (4)
7. Remove (b) (4) graphic design from PDP and anywhere else proposed in the labeling (b) (4)

Outer Panels except the PDP, 15- and 45-g outer cartons

1. Revise statement from (b) (4) to:

"First FDA-approved over-the-counter topical retinoid* for acne treatment"

Also, include the following statement:

*** Read carton and enclosed consumer information leaflet before using this product. Keep this carton and consumer information leaflet. They contain important information.**

This may be placed in a flag prominently on the outer carton in close proximity to the "**First FDA approved over-the-counter topical retinoid* for acne treatment**" where it would be the most visible to the consumer at point of purchase.

2. These comments refer to the claims and statements present within the outline of the actual size tube figure.
   a) Refer to the comments made for the statement of identity for the PDP and revise all labels accordingly.
   b) Remove the following claims (b) (4) (b) (4)
   c) Remove the statement (b) (4) as it already appears in other areas of your proposed labeling (e.g., Drug facts label).
   d) Justify or remove the statement "Dermatologist developed (b) (4)" as data are required approval of such a statement for Differin Gel 0.1% marketed OTC.
   e) Remove (b) (4) image here and wherever it appears in labeling.

Annotated Specifications for Drug Facts Labels

As requested in our April 27, 2016, labeling information request, provide the following annotated font specifications:

a. Revise the font specifications so that they meet the font specifications required under 21 CFR 201.66(d)(2). For example, the font type or size of the headings is required to be 8-point type and the subheadings not smaller than 6-point type.
b. Provide the specifications for characters per inch and leading per 21 CFR 201.66(d)(3) (e.g., annotate the specifications directly to the DFL or annotate the specifications in tabular format alongside the label)
c. Revise bullets so that they all are a solid circle or solid square bullet of 5-point type size (21 CFR 201.66 (d)(4)). Also, ensure that bullets follow format specifications per 21 CFR 201.66 throughout your proposed label.
d. The bulleted statements are difficult to read and follow from line to line. Revise the first bulleted statement on each horizontal line of text so that it is either left justified or separated from an appropriate heading or subheading by at least two square "ems" (21 CFR 201.66(d)(4)).
e. Revise such that additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading are vertically aligned with the bulleted statements appearing on the previous line.
f. Submit revised annotated font specifications following the recommendations in this review for DFL and PDP in same tabular format that was submitted in your May 2, 2016, submission.

Immediate Container Labels

a. Revise label so that the proprietary name and SOI are as follows and appears in this order: Differin Gel, adapalene gel 0.1% Acne Treatment
a. Delete the underline and instead bold the word "once".
b. Identify the location of the expiration and lot numbers on the immediate container labels (21 CFR 201.10(i) and 21 CFR 201.17).
c. For the 2-g package size, add the following statement: "**Warnings: For external use only**. Do not use on damaged skin (cuts, abrasions, eczema, sunburn)" for consistency with all labels and this is important safety information be conveyed to the consumer.
d. For the 15-g and 45-g package sizes, add the following statement: "Purpose: Acne Treatment" as you have done so for the 2-g physician sample immediate container. Delete the "-ed" after word "sunburn"
e. Remove (b) (4) graphic design and wherever it appears in the label and labeling.

Lot number and Expiration Date

Identify the location of the lot number and expiration date on the immediate containers (2-, 15- and 45-g tubes) (see recommendations under Immediate Container labels).

Also, we refer to you the Guidance for Industry – Labeling OTC Human Drug Products as a reference: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm150994.pdf

Thank you.
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
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Center for Drug Evaluation and Research
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Silver Spring, MD 20993
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/s/

MONSURAT O AKINSANYA
06/17/2016

From:	Klein, Donald N
To:	Kong, Yoon
Cc:	Raffaelli, Ryan; Akinsanya, Lara; Adah, Steven
Subject:	CMC response for labeling of N20-380, S-010: Fragrance Free and Oil Free claims are acceptable
Date:	Thursday, June 16, 2016 9:49:00 PM
Attachments:	image003.png

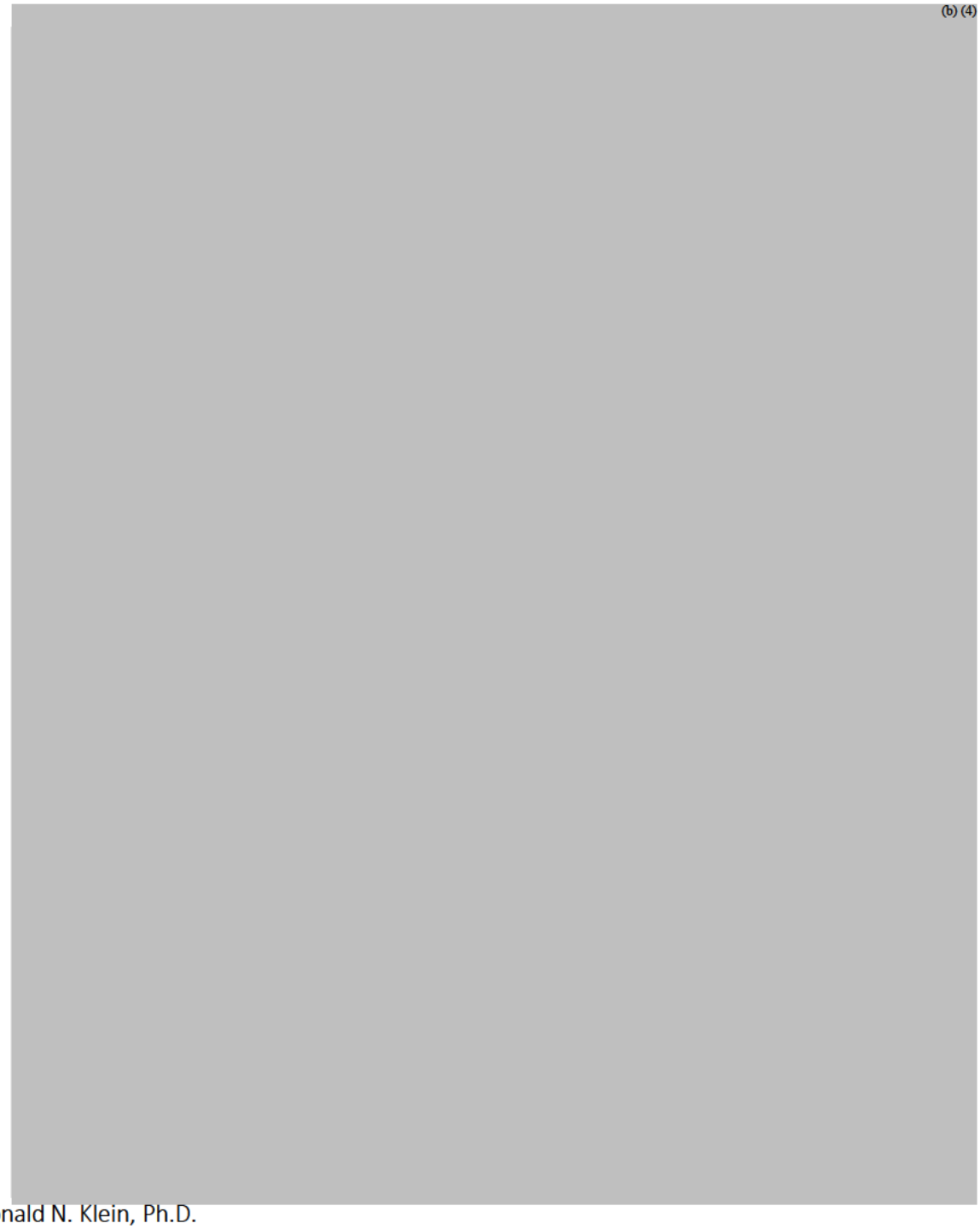
As a result of a labeling meeting Dr. Klein, CMC Reviewer, investigated the claim that the drug product was “Fragrance Free” and “Oil Free”.
Respective CMC IRs were sent and corresponding responses received.

Both of these claims are acceptable.

No fragrances are included in the drug product composition.

The drug product composition dos not contain a component that is an oil.

I’ll pdf this email into DARRTS and PAN in support of approval of N20-380, S-010.



Donald N. Klein, Ph.D.
Quality Assessment Lead (Acting) for DMIP, DPARP, DMEP, and DNDP
Senior Review Chemist
Lead USP Liaison PD EC (2015 - 2020)
Branch I
Division of Post Marketing Activities I
OLDP/OPQ/CDER/FDA
301-796-1689

(Please, always remind me if I forget a needed reply)

Drug Facts Label

Drug Facts

(b) (4)

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

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/s/

MONSURAT O AKINSANYA
06/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116864

MEETING MINUTES

Galderma Laboratories, Inc.
Attention: Sean Griffin
Director, Regulatory Affairs
14501 North Freeway
Fort Worth, Texas 76177

Dear Mr. Griffin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Differin® (0.1% adapalene) Gel, 0.1%, Differin® (0.1% adapalene) Cream, 0.1%, and Differin® (0.1% adapalene) Lotion, 0.1%.

We also refer to the teleconference between representatives of your firm and the FDA on June 10, 2015. The purpose of the meeting was to discuss the content of the supplemental NDA applications for a proposed Rx-to-OTC switch of each of the above referenced products.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, M.D.
Deputy Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sNDA

Meeting Date and Time: June 10, 2015, 9:00 AM – 10:00 AM ET
Meeting Location: Teleconference

Application Number: IND 116864
Products: Differin (adapalene) Gel 0.1% (b) (4)

Indication: Acne vulgaris
Sponsor/Applicant Name: Galderma Laboratories, Inc.

Meeting Chair: Theresa Michele, M.D.
Meeting Recorder: Lara Akinsanya, M.S.

FDA ATTENDEES

Office of Drug Evaluation IV, Immediate Office
Charles Ganley, MD, Director

Division of Nonprescription Drug Products
Theresa Michele, M.D., Director
Frank Becker, M.D., FACP, Lead Medical Officer
Mona Khurana, M.D., Medical Officer
Brenda Gierhart, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacology & Toxicology Reviewer
Barbara Cohen, MPA, Social Science Analyst
Steven Adah, Ph.D., Interdisciplinary Scientist Team Leader
Yoon Kong, Pharm.D., Interdisciplinary Scientist
Dan Brum, Pharm.D., Chief Project Management Staff
Lara Akinsanya, M.S., Senior Regulatory Project Manager

Office of New Drug Quality Assessment (ONDQA); Division of Post-Marketing Activities
Don Klein, Ph.D., Chemist Team Leader

Division of Dermatology and Dental Products
David Kettl, M.D., Medical Team Leader
Amy Woitach, D.O., M.S., Clinical Reviewer

Office of Translational Sciences/Office of Biostatistics/ Division of Biometrics IV (OTS/OB/DBIV)
Karen Higgins, ScD, Mathematical Statistician Team Leader (OTC)
Scott Komo, DrPH, Mathematical Statistician Reviewer (OTC)

Office of Surveillance and Epidemiology
Abiola Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager

SPONSOR ATTENDEES

Sean Griffin, Director Regulatory Affairs
Oliver Watts, Vice President Regulatory Affairs
Kathy Springer, Senior Regulatory Affairs Associate
(b) (4)

1.0 BACKGROUND

According to the sponsor, the following is a timeline of major events in their Rx-to-OTC development program for Differin (adapalene) 1%:

1. On March 12, 2013 Galderma met with the Agency to review the proposed Rx-to-OTC switch of Differin (adapalene) Gel, 0.1% (NDA 20-380). In this meeting, the Agency stated that four primary studies would be required to support the Rx-to-OTC switch of this product – label comprehension, self-selection, actual use and a maximal use PK study.
2. On January 6, 2014 Galderma received feedback from the Agency (Type C Meeting; Written Response Only) based on questions submitted on October 24, 2013 regarding the actual use and maximal use PK studies.
3. On June 30, 2014 Galderma received feedback from the Agency on the draft maximal use PK study protocol submitted on April 1, 2014.
4. On July 10, 2014 Galderma submitted IND 116864 which included the new clinical protocol for Study RD.06.SPR.18254 titled, "*A Pharmacokinetic Study to Determine the Systemic Exposure in Differin 0.1% Topical Gel During Dermal Application Under Maximal Use Conditions for 4 weeks in Adolescent and Adult Subjects with Acne Vulgaris*".
5. On October 22, 2014 Galderma received feedback on the draft actual use study protocol submitted to the Agency on June 13, 2014.
6. On November 18, 2014 Galderma submitted the new clinical protocol for Study 13049 "Actual Use Study for Adapalene Gel, 0.1%".
7. On January 12, 2015 Galderma submitted a Request for Proprietary Name Review.

Per the meeting package, Galderma proposes (b) (4) a switch of prescription Differin (0.1% adapalene) gel, (b) (4) to nonprescription (over-the-counter or OTC). The proposed OTC use is for the topical treatment of acne vulgaris – the same use as currently approved Rx.

The purpose of this Pre-sNDA Meeting is to obtain the Agency's feedback on general administrative aspects and content for the proposed (b) (4) and to enable the preparation and submission (b) (4) that will be sufficient for filing.

Galderma included several questions in the briefing package dated April 27, 2015. FDA sent Preliminary Comments to Galderma's questions on June 8, 2015.

2. DISCUSSION

The sponsor's questions are in **bold**, FDA's introductory comments and preliminary responses are in *italics,* and the meeting discussion is in regular font.

Introductory Comments:

Future (b) (4) will likely be discussed at an advisory committee meeting given that this would entail a first-in-class switch for a topical retinoid, a drug class with known teratogenicity risks. In light of this concern, we are doubtful this product would be appropriate for nonprescription availability.

We continue to have serious concerns that your proposed development program does not address many issues that are critical to the safe use of these products in the OTC setting. Your (b) (4) must include: (1) a thorough evaluation of the impact that OTC availability may have on the reproductive risks to female consumers of childbearing potential; and (2) an evaluation of the potential (b) (4) to be used off-label, especially on large body surface areas. Failure to address such issues (b) (4) may impact the fileability of these applications.

On previous occasions we conveyed that consumer use studies would be needed to support OTC switch (b) (4) (see March 12, 2013 Pre-IND Meeting Minutes; January 6, 2014 FDA Written Response; June 30, 2014 FDA Written Response; and October 22, 2014 FDA Feedback Letter). While the adequacy of the consumer use studies you have chosen to conduct will be a review issue, we strongly urge you to address the following issues before submitting (b) (4):

- *Your proposed eCTD Table of Contents (b) (4) indicates a Targeted Self-Selection Report will be included in Modules 2 and 5. Provide additional details about the content of this report and clarify whether or not the report is based on a completed self-selection study.*
- *If you have chosen not to conduct a self-selection study, provide a strong rationale for why you have not, given the known teratogenic risks associated with this class of drugs (see January 6, 2014 FDA Written Responses).*

- *We previously communicated to you that the pivotal actual use study (AUS) will need to address pregnancy self-selection and patterns of off-label usage as primary objectives (see October 22, 2014 Advice Letter). However, the current design of the AUS does not include these as the primary objectives. Other major deficiencies in the design of the AUS include the following: (1) no pre-specified analysis of women excluded due to pregnancy; (2) no clinical justification for the performance thresholds established for the primary objectives; (3) no provisions in study diaries to document the amount of product applied, the size of the application surface area, and instances of product application onto broken or eczematous skin; (4) no concomitant usage recorded of other topical acne drug products utilized (Rx or OTC); and (5) no provision in the diaries for subjects to record the reason they were using the product. As conveyed previously, this information is necessary for us to make an adequate safety assessment regarding the OTC usability of your proposed product among women of childbearing potential and adolescents (see October 22, 2014 Advice Letter).*

- *The annotated Drug Facts Label (DFL) in Appendix 4 of your Briefing Document continues to lack key safety language which is currently included in prescription labeling. Provide explanations for any discrepancies in safety language between the prescription and OTC labeling as previously requested (see March 12, 2013 Pre-IND Meeting Minutes).*

- *We have strongly recommended that you submit all complete protocols for label comprehension studies (LCS) for our review prior to fielding the studies (see March 12, 2013 Pre-IND Meeting Minutes). Our records do not reflect the Agency having received any revised LCS protocols for review. Clarify whether or not the DFL tested in LCS was the actual DFL used in the AUS.*

- *The annotated DFL includes* (b) (4) *an indication for product use.* (b) (4) *The current evidence would not allow a claim* (b) (4) *for your product. If you wish to pursue such a claim, provide adequate efficacy and safety information to substantiate such a* (b) (4) *claim* (b) (4)

We acknowledge you have completed a maximal use PK study for the 0.1% gel formulation. (b) (4) *Failure to provide these data may impact the fileability of your applications.*

The deficiencies in your consumer use studies may adversely impact the approvability (b) (4) *you plan to submit given that you intend to cross-reference the consumer use data generated under this IND to support full OTC switches.*

Meeting Discussion:

During the slide presentation (attached), Galderma made the following comments:

Galderma Statement:

In the Meeting Preliminary Comments provided June 8, 2015, the Agency stated the following:

"Future (b) (4) will likely be discussed at an advisory committee meeting given that this would entail a first-in-class switch for a topical retinoid, a drug class with known teratogenicity risks. In light of this concern, we are doubtful this product would be appropriate for nonprescription availability."

We are concerned that the above appears to indicate that the Agency has pre-determined the approvability of Galderma's proposed Rx-to-OTC switch prior to reviewing any data from the studies requested by the Agency in communications that have occurred since 2013.

Adapalene gel, 0.1% has been prescribed by physicians to millions of women of child-bearing potential for nearly two decades in the United States and is a Pregnancy Category C drug, much like current OTC acne medications such as benzoyl peroxide and salicylic acid. In addition, we note a number of pregnancy category C drugs that have been approved by the Agency to switch from Rx-to-OTC status including most recently Rhinocort Allergy Spray (budesonide), Nexium 24 HR (esomeprazole magnesium), Flonase Allergy Relief (fluticasone proprionate), Nasacort Allergy 24HR (nasal spray) and Allegra (fexofenadine). It is also notable that all of these Pregnancy Category C products contain the same codified pregnancy warnings in the labeling as proposed for adapalene 0.1% and that all of these products are for conditions that commonly occur in pregnancy.

Given the extensive consumer studies conducted, in additional to the maximal use PK study requested by the FDA, can you clarify the reason for the statement that the Agency is "doubtful that this product would be appropriate for nonprescription availability", prior to the review of data collected in support of the proposed application?

FDA Response and Discussion:

FDA clarified that it had not come to a conclusion regarding the approvability of the application given no application had been submitted for review; however, FDA emphasized that it foresees significant challenges regarding Galderma's argument that this product has no risk to females of childbearing potential and that a learned intermediary is not required for safe OTC use of this product. FDA reiterated that a marketing application would likely be discussed at an Advisory Committee meeting.

Regarding the Pregnancy Category C products mentioned in the Galderma response, FDA inquired if the sponsor's contention was that those products had a similar teratogenicity risks to adapalene and this might support the OTC marketing of adapalene. The sponsor stated that they did not have this information immediately available. The FDA noted that if this was intended to be part of the scientific justification for OTC switch for adapalene gel, adequate information should be included in the application.

Galderma Statement:

Based on the Agency's feedback in the June 8, 2015 Pre-NDA Meeting Preliminary Comments regarding required additional maximal use PK and consumer usage studies (b) (4) we do not believe that we currently have the data requested. Additional dialog will occur between Galderma and the Agency prior to initiation of any studies in support of a potential Rx-to-OTC switch (b) (4) Does the Agency agree with the submission plan proposed?

FDA Response:

FDA responded that it is the sponsor's choice to pursue this plan, but the Agency continues to have concerns about the safe OTC use of this product. FDA stated that the sponsor's proposal is acceptable if the sponsor feels that they have the necessary data available from the actual use studies. FDA re-iterated the Agency's concern regarding the impact that OTC availability of adapalene may have on the reproductive risks to female consumers of childbearing potential. FDA emphasized the importance of demonstrating that pregnant women will not use the product.

Further Discussion:

Galderma presented the attached slides for FDA's information and clarification regarding the consumer behavioral studies. Galderma stated the pivotal label comprehension study (LCS) was submitted to FDA on January 18, 2013, and that the Agency had provided feedback. Galderma stated they did not resubmit the final revised LCS to the Agency but that FDA's comments were incorporated into the revised protocol. FDA noted Galderma's clarifications and stated that the bulleted items would be review issues. FDA inquired what the target threshold had been for the pregnancy self-selection studies and Galderma responded that it was 90% and that the endpoint was related to asking a doctor (as opposed to deselecting the product). Galderma inquired as to what FDA considered an appropriate threshold to be and FDA responded that it was a review issue, but that in any case a very rigorous clinical justification needed to be provided for the threshold that was utilized, especially for the low health literates, in the study.

FDA Post-meeting Addendum:

In the analysis dataset for the self-selection study, provide verbatim as well as coded responses for each question involved with the self-selection decision. In addition, ensure that the self-selection outcome can be derived based on the responses to the questions involved with self-selection decisions.

2.1. General/Regulatory

Question 1:

(b) (4)

Does the Agency agree with the above proposal (b) (4) **?**

FDA Preliminary Response to Question 1:

We have serious concerns (b) (4) *See Introductory Comments.*

(b) (4)

(b) (4)

Meeting Discussion:

No discussion occurred.

Question 2:

(b) (4)

Does the Agency agree (b) (4)

FDA Preliminary Response to Question 2:

An actual use clinical study conducted by or for an applicant and essential to approval may qualify that applicant to a period of exclusivity. However, the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food Drug and Cosmetic Act, and 21 CFR 314.108, until after approval of a marketing application. As described in 21 CFR 314.50(j), an applicant should include (b) (4) *a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review* (b) (4)

Meeting Discussion:

No discussion occurred.

Question 3:

The proposed format and a draft Table of Contents (b) (4) **for NDA 20-380** (b) (4) **are provided in Appendix 1 of this briefing document.**

Does the Agency agree with the proposed format and content (b) (4) **for NDA 20-380** (b) (4) **?**

FDA Preliminary Response to Question 3:

In general, the format [redacted] *is acceptable. See the Introductory Comments, responses to questions 4 through 7, and the Additional Comments section regarding the content* [redacted]

Meeting Discussion:
No discussion occurred.

2.2. Chemistry, Manufacturing, and Controls (Quality)

Question 4:
In the proposed Rx-to-OTC switch [redacted] **described herein, Galderma will not propose any changes to the Chemistry, Manufacturing and Controls (CMC) aspects currently approved. Consequently, we do not intend to include CTD Section 2.3 and Module 3** [redacted]

Based on the above, does the Agency agree that CTD Section 2.3 and Module 3 are not required to be included [redacted]**?**

FDA Preliminary Response to Question 4:

In Section 2.3, include a description of the approved drug product packaging, the expiry and the storage conditions. This information is in support of the proposed labeling. Also, include in this section a reference statement [redacted].

Meeting Discussion:

No discussion occurred.

2.3. Nonclinical

Question 5:
In the proposed Rx-to-OTC switch [redacted] **described herein, Galderma does not plan to include any new Nonclinical information. Consequently, we intend to cross-reference to the information in the original NDA applications in CTD Sections 2.4 and 2.6** [redacted] **and we do not intend to include Module 4. The draft Table of Contents for** [redacted] **for NDA 20-380** [redacted] **provided in Appendix 1.**

Does the Agency agree with the proposed approach for the Nonclinical information [redacted]**?**

FDA Preliminary Response to Question 5:

Your plan to cross reference previously approved NDAs and not to include any new nonclinical information appears acceptable. In the nonclinical section of Module 2, provide an integrated summary of the pharmacology and toxicology information of your product for FDA review.

Meeting Discussion:

No discussion occurred.

2.4. Clinical

Question 6:

In accordance with the Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009), Galderma proposes to provide the Agency with Sections 2.7.3 Summary of Clinical Efficacy (SCE) and 2.7.4 Summary of Clinical Safety (SCS) that are sufficiently detailed to also serve as the full narrative portions of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), respectively, while remaining within the suggested size limitations for Module 2 (i.e., maximum 400 pages for Section 2.7 Clinical Summaries). The draft Table of Contents (b) (4) for NDA 20-380 (b) (4) provided in Appendix 1 including the intended placement of the reports for the various studies conducted (b) (4)

Does the Agency agree with the proposed structure and content of the Clinical information (b) (4)?

FDA Preliminary Response to Question 6:

No, we do not agree. Inclusion of only a Summary of Clinical Safety will not satisfy the regulatory requirement for inclusion of an Integrated Summary of Safety (ISS) (b) (4) (CFR 314.50(d)(5)(vi). Failure to include an ISS may impact the fileability of your applications. Inclusion of an ISS is particularly important for your proposed product given that it would be a first in class OTC switch for a topical retinoid. In your ISS, include strong justification for why a product with a known teratogenicity signal should be approved for OTC use. See Introductory Comments.

Include study reports for all pilot label comprehension studies. Regarding the eCTD (b) (4) specify where you plan to include the datasets for the consumer behavior studies.

Meeting Discussion:

Galderma noted the following during the meeting discussion as part of the attached presentation slides (appendix):

Galderma Statement:

> As you have suggested, we will submit an ISS including a justification for why we believe it is acceptable for our pregnancy category C drug product to be switched to an OTC marketing status. We also plan to cross-reference all relevant data submitted in section 2.7.4 Summary of Clinical Safety (SCS) to further support the ISS. Is this proposal acceptable? If not, please clarify what additional information should be included and/or cross-referenced in the ISS.

FDA Response and Discussion:

> FDA stated that the sponsor's proposal was acceptable and that inclusion of an ISS would provide the sponsor with the ability to provide more data in support of their program. In response to FDA inquiry, the sponsor stated that the target date for sNDA submission is third quarter 2015.

Post-meeting Addendum:

Given the presentation on the Real World Standard of Care Study, FDA asked Galderma to confirm that a complete study dataset (as opposed to just a study report) would also be submitted as part of the sNDA. Galderma confirmed that it would be:

> "With regard to the Agency's request for our planned eCTD dataset location, we propose including the datasets for the consumer behavior studies in Module 5, Section 5.3.5.2 (for the actual use study) and Module 5, Section 5.3.5.4 (for the other studies) per the May 2015 Guidance for Industry - Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications Guidance for Industry). Although the Label Comprehension Study Report will be provided in Module 1, Section 1.14.1.4, this Guidance states that datasets cannot be included in Module 1, thus we believe Section 5.3.5.4 is most appropriate. Does the Agency agree with this proposal? If not, will the Agency provide the eCTD location where the datasets for the consumer behavior studies should be provided?"

FDA Post-meeting Addendum Response:

The sponsor may submit their ISS information in module 5.3.5.5.

Question 7:
Details of the proposed dataset submission plan are provided in Section 10.4.4.

Does the Agency agree with the proposed dataset submission plan?

FDA Preliminary Response to Question 7:

Submit analysis datasets for all consumer behavior studies. In order to expedite the review, we recommend that you submit sample datasets for the consumer behavior studies prior to

submission [redacted] *so that we can provide feedback on any suggested modifications that would facilitate our review.*

Meeting Discussion:

No discussion occurred.

2.5. FDA Additional Comments

1. *Clarify whether you are planning to make any packaging changes* [redacted]
2. *Given that you are planning to cross reference the actual use study data for sNDA 20380, provide evidence* [redacted]
3. *Table 3 in the Statistical Analysis Plan (SAP) does not explicitly state for what scores on the REALM-Teen test a teenager would be considered to have low literacy. Modify the SAP to explicitly state for what scores a teenager would be considered to have lower literacy.*
4. *Neither the protocol nor the SAP provides clinical justification for the performance threshold used for the primary endpoints in the AUS. Include in the application clinical justification for all of the performance thresholds used in all of the consumer behavior studies.*
5. *We have concerns with your proposed a priori mitigations. For instance, for the secondary endpoint, proportion of pregnant or breastfeeding women who state they would ask a doctor before use, your proposed mitigations would consider a subject to have demonstrated correct use if either they decided to purchase or used the product prior to the subject learning that she was pregnant based on a self-administered pregnancy test. We do not agree with these mitigations because both of these occurrences could pose a safety concern.*

Meeting Discussion:

No discussion occurred.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

A copy of Galderma's slide presentation is attached.

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KAREN M MAHONEY
07/14/2015

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, June 01, 2016 10:53 AM
To: 'Sean.GRIFFIN@galderma.com'
Cc: Akinsanya, Lara
Subject: DUE 06/03 - NDA 20380/S-010/Differin (adapalene), 0.1%- CMC Information Request

Good Morning,

Reference is made to NDA 20380/S-010 for Differin (adapalene), 0.1%. Please respond to the following information request by Noon on **Friday, June 3, 2016** (for time, respond via email and later officially submit your response to the sNDA):

- Provide justification that the drug is "Oil Free" as you have proposed.

Thanks,
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993
(301) 796-9634 (phone)
(301) 796- 9899 (fax)

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/s/

MONSURAT O AKINSANYA
06/02/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, June 02, 2016 4:20 PM
To: 'Sean.GRIFFIN@galderma.com'
Cc: Akinsanya, Lara
Subject: DUE 06/03 - NDA 20380/S-010/Differin (adapalene), 0.1%- CMC Information Request

Good Afternoon,

Please respond to the following information request by COB on **Friday, June 3, 2016** (for time, respond via email and later officially submit your response to the sNDA):

- Provide a list of marketed drugs that claim product is oil free. We assume you are aware of such products, Rx or OTC.

Thanks,
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993
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/s/

MONSURAT O AKINSANYA
06/02/2016

Sensie, Tinya

From: Sensie, Tinya
Sent: Tuesday, May 31, 2016 3:22 PM
To: 'Sean.GRIFFIN@galderma.com'
Cc: Akinsanya, Lara
Subject: NDA 20380/S-010/Differin (adapalene), 0.1%- CMC Information Request

Follow Up Flag: Follow up
Flag Status: Flagged

Good Afternoon,

Reference is made to NDA 20380/S-010 for Differin (adapalene), 0.1%. Please respond to the following information request by **Wednesday, June 1, 2016 at noon** (for time, respond via email and later officially submit your response to the sNDA):

- Refer to 21 CFR 201.100(b)(5). Provide a statement citing this 21 CFR to support your proposed label that claims, "Fragrance Free".

Kindly confirm receipt of this message.

Thanks,

Tinya

Tinya Sensie, M.H.A.
Regulatory Health Project Manager
Division of Nonprescription Drug Products|Office of Drug Evaluation IV
Center for Drug Evaluation and Research|U.S. Food and Drug Administration
10903 New Hampshire Ave., WO22, Rm 5487
Silver Spring, MD 20903

P: 240-402-4230|F: 301-796-9849|e: tinya.sensie@fda.hhs.gov

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/s/

TINYA J SENSIE
05/31/2016

Akinsanya, Lara

From:	Akinsanya, Lara
Sent:	Tuesday, April 26, 2016 10:34 AM
To:	GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc:	Akinsanya, Lara
Subject:	Labeling Information Request DUE 05/02 : NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Labeling Information Request by **Monday, May 2, 2016**:

- 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".
- Please provide proposed package sizes (including outer carton and immediate containers)

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993
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/s/

MONSURAT O AKINSANYA
04/26/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, March 16, 2016 3:07 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Clinical Pharmacology Information Request DUE 03/21: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request by **Monday, March 21 2016**:

- Provide information on the metabolic pathway of adapalene. Also include information on CYP enzymes involved in the metabolism of adapalene.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993
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/s/

MONSURAT O AKINSANYA
03/17/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration Silver Spring MD 20993

PIND 116864

MEETING MINUTES

Galderma Laboratories, L.P.
Attention: Sean Griffin
Associate Director, Regulatory Affairs
14501 North Freeway
Forth Worth, TX 76177

Dear Mr. Griffin:

Please refer to your Pre-Investigational New Drug Application (PIND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Differin® (adapalene) gel, 0.1%.

We also refer to the meeting between representatives of your firm and the FDA on March 12, 2013. The purpose of the meeting was to discuss your proposed Rx to OTC switch and the studies you propose to support this activity.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Celia Peacock, Regulatory Project Manager at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-IND
Meeting Date and Time:	March 12, 2013 10:00 AM – 11:00 AM
Meeting Location:	Teleconference
Application Number:	PIND 116864
Product Name:	Differin® (adapalene) gel, 0.1%
Indication:	Treatment of acne
Sponsor/Applicant Name:	Galderma
Meeting Chair:	Joel Schiffenbauer, M.D.
Meeting Recorder:	Celia Peacock, M.P.H., R.D.

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation
Shaw Chen, M.D., Acting Director
Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Medical Team Leader
Linda Hu, M.D., Medical Officer
Steve Osborn, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacologist Toxicologist Reviewer
Barbara Cohen, M.P.A., Social Scientist
Dan Brum, Pharm.D., M.B.A., B.C.P.S., R.A.C., Acting Chief Project Manager Staff
Celia Peacock, M.P.H., R.D., Regulatory Project Manager

Office of Drug Evaluation III
Julie Beitz, M.D. Director
Victoria Kusiak, M.D., Deputy Director

Division of Nonprescription Regulation Development
Lydia Velazquez, Pharm.D., Interdisciplinary Scientist Team Leader
Reynold Tan, Ph.D., Interdisciplinary Scientist Reviewer

Division of New Drug Quality Assessment III
Swapan De, Ph.D., Team Leader
Muthukumar Ramaswamy, Ph.D., Chemistry Reviewer

Division of Clinical Pharmacology-III
Doanh Tran, Ph.D., Team Leader

Division of Dermatology and Dental Products
David Kettl, M.D., Clinical Team Leader
Amy Woitach, M.D., Medical Officer

SPONSOR ATTENDEES

Galderma
Sean Griffin, Associate Director, Regulatory Affairs
(b) (4) Consultant, Dermatologist
Patricia Meuse, Ph.D., Associate Director, Clinical Operations
(b) (4) Consultant, (b) (4)
(b) (4) Consultant, (b) (4)
Oliver Watts, Ph.D., Vice President, Regulatory and Technical Affairs
Bertrand Rousse, Regulatory Affairs

1.0 BACKGROUND

Galderma submitted a request to the FDA on November 5, 2012 for a Type B meeting to discuss their proposed Rx to OTC switch and the studies proposed to support this activity. The Agency's preliminary responses to the questions contained in Galderma's January 18, 2013 meeting background package were provided to Galderma via e-mail on March 11, 2013. These preliminary responses appear in italics below. After review of the Agency's preliminary responses, Galderma stated that they wanted to further discuss questions 2, 3, and 4.

For questions where no additional discussion is indicated, neither Galderma nor the FDA raised any additional issues pertaining to these questions.

2.0 DISCUSSION

Question 1

Does the Agency agree that an Rx-to-OTC switch of NDA 20-380 for Differin (adapalene) Gel, 0.1% may be pursued and that the currently approved higher strength formulation, adapalene gel, 0.3%, may be retained as a prescription-only medication, pending a more complete review of the proposed NDA-S by the Agency?

FDA Preliminary Response:

Yes, this is possible given adequate justification based on the safety and efficacy of the products.

However, we have some concerns that you will need to adequately address for a prescription to OTC switch for Differin 0.1%:

- *the potential for teratogenicity as we consider adapalene to be a retinoid.*
- *the potential for carcinogenicity as there are carcinogenicity signals in the animal studies which raise concerns. Animal studies have also shown an increased tumor risk with the use of pharmacologically similar drugs (retinoids) when exposed to UV irradiation or sunlight.*

You will also need to address any differences in safety between the 0.1% and 0.3% formulations regarding, for example, the labeling for teratogenicity.

Finally, we are also interested in data on use in the prescription setting with regards to current prescribing practice and how clinicians counsel patients who may potentially become pregnant or who are pregnant (see also response to question 6).

Question 2

Does the Agency have any comments about the proposed OTC Drug Facts Label (DFL) for adapalene gel, 0.1% provided as Appendix 3?

FDA Preliminary Response:

Your final label may change depending on data gathered during your Rx-to-OTC development program. These are our preliminary comments on the proposed labeling:

- *The keep out of reach of children warnings should appear as follows:*
  ***"Keep out of reach of children.** If swallowed, get medical help or contact a Poison Control Center right away"*
- *The "**If pregnant or breast-feeding**, ask a* (b) (4) *before use" warning will also need further evaluation. Although this language can be found on other labels, in the context of this product, adherence to this warning is of particular importance. Unless you can adequately address the issue of teratogenicity, we would need to understand that the warning would prevent the use of this product in pregnant women and women of childbearing potential (see also response to question 4). Given potential teratogenicity concerns, your pregnancy warning may need to be enhanced for the OTC market. We strongly recommend that you incorporate the most restrictive scenario warning in your consumer testing program so as not to delay your development timeline in the event that this is the warning that is eventually determined necessary to be on the label.*

*These warnings must appear in their own section directly before the "**Directions**" section.*

- *The statement* [redacted] *or a similar statement must be supported by data. We note that the prescription label states that moisturizers containing alpha hydroxy or glycolic acids should be avoided. Please clarify the disparity between your prescription label warning on moisturizers such as alpha hydroxyl or glycolic acids and the general statement you are making about moisturizers.*
- *You should revise the statement* [redacted] *" to "**Do not use** on damaged skin (cuts, abrasions; eczematous or sunburned skin)." This revised statement must appear in a "**Do not use**" section which is consistent with the "**Do not use** on broken skin" labeling statement we require for OTC topical acne drug products that contain sulfur (21 CFR 333.350(c)(2)).*

We note that the Differin Rx label has some elements that are not included in your proposed OTC label. Please provide insights as to why they do not appear.

- *Use of protective clothing over treated areas when sun exposure cannot be avoided.*
- *Exposure to sunlamps, should be minimized.*
- *Weather extremes such as wind or cold may also be irritating to patients under treatment.*
- *Avoid contact with the lips, angles of the nose and mucous membranes.*
- *Particular caution should be exercised in using preparations containing sulfur, resorcinol or salicylic acid in combination with Differin. 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.*
- *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.*
- *Use of waxing as a depilatory method should be avoided on skin treated with Differin lotion.*

Although avoiding sunlight is not an element unique to this label, if this product is indicated for younger children, and/or if the sunlight exposure effects are more significant for this product than for other products, you may need to strengthen your proposed OTC warning. In any case, the sunlight exposure warning should be tested in label comprehension with users as well as parents and caregivers.

Additionally, you need to ensure that consumers understand that they should not be using other acne medications concomitantly, especially given the possibility that their acne may flare up early in the therapy and therefore they may be more tempted to treat with a second product containing salicylic acid.

Please describe for us the anticipated dosing mechanism for this OTC product (e.g., tube, pump). The directions for usage on the 0.1% lotion Rx label state "apply a thin film of Differin lotion to the entire face and other affected areas of the skin once daily….dispense a nickel size amount of Differin lotion (3-4 actuations of the pump) to cover the entire face." The Rx concept of a nickel size amount from 3-4 actuations gives consumers a clear sense of how much product should be applied. Within the context of your planned dosage delivery mechanism, please provide feedback on whether you think this or any other concept is feasible to be translated to the OTC label.

Meeting Discussion

The Sponsor asked for additional clarification on the Agency's comments regarding the pregnancy use warnings and why these were seen as necessary to include in labeling. The Sponsor stated that this product is functionally a retinoid, but differs from other retinoid products structurally and in its affinity to bind receptors including those involved in the development of teratogenicity.

The Agency stated that the concern with pregnancy has to do with the potential teratogenicity of the proposed product as the Agency considers adapalene to be a retinoid and retinoids are well-known teratogens. The Agency asked if Galderma could provide information as to how the 0.1% product is used in the general community. For example, the Agency inquired as to whether physicians give warnings to the general community or specifically to pregnant women or women of child-bearing age when it is prescribed.

The Sponsor stated, that in actual practice, practitioners do not have the same level of concern for teratogenicity with use of the 0.1% product as compared with "true" retinoids. Practitioners do err on the side of caution, and decide if the benefit is worth the risk, e.g., if a patient on adapalene becomes pregnant and has severe acne, they would not discontinue the treatment.

The Agency reiterated that this product would likely go to an Advisory Committee for further discussion.

The Sponsor stated that adapalene is a pregnancy Category C drug and will propose to use the standard OTC pregnancy warning. The Sponsor also will further address the teratogenicity issue in the proposed NDA.

FDA stated that the meeting package mentioned a 9% rate of malformations found in pharmacovigilance reports available for evaluation of women who were exposed to adapalene during pregnancy and asked the Sponsor to elaborate on this. The Sponsor will send in additional information regarding this.

Question 3

Does the Agency have any comments about the proposed Label Comprehension Study, including protocol, questionnaire and screeners, provided as Appendices 4 through 6?

FDA Preliminary Response:

Some of the primary and secondary objectives that you have proposed to test are not necessary to assess as they are of lesser clinical importance or do not represent unique OTC label elements. The most important objectives that you have already proposed are your primary objective warning #1 (pregnancy/breastfeeding) and secondary communications objective warning #2 (sun exposure), for the reasons discussed in our response to Question 2. (Please note that the sun exposure should be a primary communication objective)

The other items discussed in our response to Question 2 represent potentially unique warnings/directions and/or elements that are necessary for safe use of this particular product and therefore need to be assessed in a label comprehension study. For those primary communications objectives involving medically important outcomes with the potential for risk to the consumer (including but not limited to the pregnancy/breastfeeding warning), please define your success thresholds based on a clinical rationale prior to fielding the research.

Please note that the label comprehension study should be conducted with all-comers, not just acne sufferers. We strongly recommend that you resubmit all complete protocols for our review prior to fielding the study.

Also note that all items on the Drug Facts label need to be in consumer friendly language. It may be beneficial to test various wording options in qualitative research with consumers prior to fielding the pivotal study.

Question 4

Does the Agency agree that no additional studies, other than the proposed Label Comprehension Study, are required to support filing of an NDA-S for the proposed Rx-to-OTC Switch of adapalene gel, 0.1%?

FDA Preliminary Response:

No, we do not agree.

A self-selection and actual use study will be needed to support an NDA filing for the proposed switch, in order to see how consumers will use the product and for what indications. The following should be examined in these studies:

- *Self-selection to use or not to use the product by women of childbearing age, women who are pregnant, looking to become pregnant etc.*
- *What indications will the product be used for (e.g., for wrinkles, skin roughness, chloasma, hyperpigmentation or skin mottling…)? How much will be used, how often and for how long?*
- *Will consumers use a sunscreen prior to sun or UV exposure?*

Submit full protocols for our review and comment before you initiate these studies.

We recommend that you determine the pharmacokinetics (PK) of your product under maximal use conditions as consumers may apply the product to extensive areas of the body. Provided below is some information to help you design a maximal use PK trial.

A maximal use PK trial is conducted by obtaining adequate number of PK samples following administration of your to-be-marketed formulation. This trial should be conducted in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- *Frequency of dosing*
- *Duration of dosing*
- *Use of highest proposed strength*
- *Total involved surface area to be treated at one time*
- *Amount applied per square centimeter*
- *Method of application/site preparation*
- *Sensitive and validated analytical method*

You should take steps to ensure that the target patient population (age, gender, race etc.) is properly represented in your maximal use PK trial. For the acne indication, the drug product should be applied to the entire area of the face, shoulders, upper chest and upper back. The amount applied should be sufficient to leave at least a thin film on the entire area.

Meeting Discussion

In regards to the self selection and actual use studies, the Sponsor asked why self selection studies are necessary if acne treatment is an existing indication for OTC use.

The Agency expressed interest in seeing the results of an actual use study because, for example, there is a potential for off-label use of retinoid products on larger body surface areas. For example, FDA would want to know location of application, and the size of the

surface area to which this product is applied. FDA would want to know how consumers will use this product.

Furthermore, the Agency's concerns regarding self selection and use pertain to the potential teratogenic risk. However, additional consumer studies may not be needed if concerns about teratogenic risk are adequately addressed by the Sponsor. (See discussion of Question 1.)

In addition, the Agency reiterated its recommendation that the Sponsor conduct studies to determine the pharmacokinetics of their gel product under maximal use conditions as consumers may apply the product to extensive areas of the body. Also emphasized was the need to include a larger body surface area, and to include adolescents in their studies. This information is needed to address a complete safety assessment of the product. The Agency advised that 15% of the total body surface area (i.e., the entire area of the face, shoulders, upper chest and upper back) is the optimal application area to study in subjects with acne, as those studies previously performed only covered 5-6 % of body surface area.

Question 5

Galderma believes that an NDA Supplement to NDA 20-380 is the appropriate submission pathway for the proposed switch of NDA 20-380 for Differin (adapalene) Gel, 0.1%. Does the Agency agree?

FDA Preliminary Response:

Yes, we agree.

Question 6

Is there any general information not listed in Section 10.4 of this briefing document that the Agency believes is required to support filing of the proposed NDA-S for the Rx-to-OTC switch of Differin (adapalene) Gel, 0.1%?

FDA Preliminary Response:

In addition to what you have proposed, provide the following:

- *data on use in the prescription setting with regard to current prescribing practice and how clinicians counsel patients who may potentially become pregnant or who are pregnant with respect to use of these products; for example, do they co-prescribe oral contraceptives or advise patients to stop using the product if they become pregnant? Do they prescribe this product to pregnant patients?*
- *a copy and translation of all foreign nonprescription labels*
- *listing of countries where product is marketed, marketing status (whether prescription or OTC or behind the counter), dosage strength, when approved, for what age ranges*

- *drug distribution and usage by country*
- *an analysis of FAERS and WHO databases in addition to your adverse event database and literature with respect to clinical safety of adapalene, addressing teratogenicity, fetotoxicity, and carcinogenicity.*

Data should be summarized and analyzed by marketing status (Rx vs. OTC or behind the counter), dosage strength, duration of use, when approved, year of reporting, and age of patients. The time period for the review of the safety databases should begin with the initiation of marketing after original approval of adapalene. Narrative summaries of deaths, teratogenic and cancer cases should be provided.

The review of medical literature should include a table listing the references with the type of study, objectives, population and principal results.

Additional Comment
We anticipate that your application will be discussed at an Advisory Committee meeting.

Additional Administrative Comments:
Comments shared with you today are based upon the contents of the January 18, 2013 meeting package, which is considered to be an informational aid to facilitate the meeting discussion. The comments are not meant to be viewed as commitments from the Agency.

We strongly encourage you to send your submissions electronically. We recommend eCTD submissions using CDISC standards for study data and MedDRA coding for adverse events. General guidance and contact information is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

We encourage you to submit your requests for FDA review of your proposed proprietary name as early as possible. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, "Contents of a Complete Submission for the Evaluation of Proprietary Names" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

We encourage you to request and attend, at a minimum, a pre-NDA meeting prior to submitting your application to discuss the content and format requirements of the Agency.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

- The sponsor stated they will move forward using the current standard OTC pregnancy warning in their proposed labeling but understands that they need to further address the teratogenicity issue in the NDA supplement.
- The sponsor agreed to conduct a new PK trial using a larger surface area and include adolescents.
- The sponsor will submit a summary of malformations reported following exposure to adapalene during pregnancy.

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/s/

JOEL SCHIFFENBAUER
03/29/2013

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, February 29, 2016 12:32 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Social Science Information Request DUE 03/01: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request by COB Tomorrow, **Tuesday, March 1 2016**:

In the physician standard of care (SOC) study,

1. How were the enrollment targets by specialty determined? Were they based on proportion of adapalene prescribed by specialty? If so, what was the data source from which this information was obtained?
2. Was sampling stratified by physician specialty? If so, how was the sampling fraction determined for each stratum?
3. How were the key demographic and practice type target enrollments determined, both nationally and by region/subgroup? Provide the data source from which this information was obtained.
4. Provide explanation as to how the methodology ensured that it included marketing research-resisting physicians and/or heavily burdened or otherwise hard to reach physicians.

In the patient standard of care (SOC) study,

1. Confirm that total number of adapalene only female users of childbearing age was 52.
2. Was a skip pattern programmed into the questionnaire, e.g. did a patient only see Q6 if they responded "Yes" to Q5. If yes, then provide details on the skip pattern used.
3. Confirm that the total number of subjects who used adapalene in Q20_B1, and Q21_B1 was based on QF rather than Q10.
4. Explain why the questions about physician concerns (such as Q20, Q 21) only explicitly asked about Differin and not Epiduo, since many more patients used Epiduo?

In the label comprehension study report, point us to where the clinical justification for the threshold was discussed, or provide this justification.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
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/s/

MONSURAT O AKINSANYA
03/01/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, February 09, 2016 9:57 AM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara; Pham, Jade
Subject: Social Science Information Request DUE 02/10: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request by **Wednesday, February 10, 2016**:

The panel utilized for the Standard of Care Study was from (b) (4) *managed the panels for* (b) (4) *related to both the physician and patient surveys in the Standard of Care study. Information about the company can be viewed on their website* (b) (4)

We refer to the above excerpt in your response to your IR dated Feb 8th.

You already provided us with the information above in a previous response. We are not interested in learning more about the company; we need to learn more about the panel. The company's website has no information about this panel of 3 million active participants; we cannot even locate a mention of this panel on the company's website. An assessment on our part of this survey cannot take place without understanding, in detail, the panel methodology and recruitment.

Therefore, provide direct responses the following questions:

1) Is this panel managed and operated by (b) (4)? You stated in your response that the panel was "from" (b) (4) – but that is not the same as being directly managed by them. Provide this requested clarification.
2) If it is not managed and operated by (b) (4) who does manage and operate the panel, and where is there publicly available information about the panel?
3) You stated that an "active" participant is defined as any participant that has attempted to participate in a survey in the previous 90 days. We are not clear as to what "attempted to participate in a survey" means. Is this referring to people who tried to opt in from (b) (4) website? Is this referring to people who attempted to participate in surveys run by dozens of companies, which may or may not have been affiliated with the said panel? Or is this referring to people who were contacted (b) (4) to possibly participate in one of their panels if they qualified?

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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/s/

MONSURAT O AKINSANYA
02/09/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, February 04, 2016 2:32 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Social Science Information Request DUE 02/05: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request by **Friday, February 05, 2016**:

1. Regarding Q 10 of the self-selection study (result of the urine pregnancy test), why did 11/109 of pregnant women have a missing value in the dataset?

2. For the Patient Standard of Care Study:

   - Were the patients who were currently on adapalene (Differin and/or Epiduo) asked what other Rx products they were already on or being simultaneously started on(including but not limited to Accutane*)* *at the time that they were started* on the adapalene prescription? If so, point to the relevant question.

   - Were the patients who had been on adapalene (Differin and/or Epiduo) sometime in the previous twelve months asked what other Rx products they were already on or being simultaneously started on (including but not limited to Accutane) *at the time that they were started* on the adapalene prescription? If so, point to the relevant question.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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/s/

MONSURAT O AKINSANYA
02/05/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, February 03, 2016 3:58 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Pediatric and Maternal Health Information Request DUE 02/09: NDA 20380 _S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request by **Tuesday, February 09, 2016**:

- Provide us with any available clinical trial and post-marketing safety data you have in pediatric patients 9 years to less than 12 years of age exposed to approved adapalene-containing single-ingredient (Differin 0.1% Gel , 0.1% Lotion, 0.1% Solution, 0.1% Cream, 0.3% Gel) or combination (Epiduo gel and Epiduo gel Forte) drug products. Present post-marketing safety data from your global pharmacovigilance database for all reports (serious non-fatal reports and serious fatal reports) with the reported MedDRA SOC and Preferred Terms in decreasing order of frequency. Using the same format, provide tabular summaries of all serious reports stratified by sex and formulation. Provide the full narratives for all serious reports. Separate U.S. from ex-U.S. cases.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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MONSURAT O AKINSANYA
02/03/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, February 03, 2016 1:50 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Social Science Information Request DUE 02/08: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request by **Monday, February 08, 2016**:

1) For both the physician and patient standard of care studies, provide an annotated version of the survey instrument (or screen shots) that shows, for each question, whether response options were closed end or open end.
2) For the patient standard of care study, provide details on how many of the 3 million panelists are active panelists, and provide the definition of "active".
3) For the 166 female respondents in the patient standard of care banner set most recently provided in response to our IR, provide data on how many other online surveys each respondent had completed within the past year, prior to completing the patient standard of care survey.
4) Provide an explanation as to how to interpret the column in the dataset entitled INT_LEN and LENGTH. We are unclear as to the units of time that these columns refer to.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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MONSURAT O AKINSANYA
02/03/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, February 03, 2016 4:32 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Additional Social Science Information Request DUE 02/08: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request by **Monday, February 08, 2016**:

- What is the name of the panel that was utilized in the Patient Standard of Care Study? Who manages the panel ((b) (4) or another organization?) Where can publicly available information about the panel be obtained? Regarding the adolescents (ages 13-18 on the panel, but especially ages 13-16), how are they recruited? Is parental permission required for participation on the panel or in any studies, particularly those in which they are asked to discuss what medicines they take? How exactly are they paid the $25 – checks cut and mailed to their home address, money deposited to Paypal, etc.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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MONSURAT O AKINSANYA
02/03/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, January 29, 2016 11:32 AM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Clinical Information Request DUE 02/05: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Clinical Information Request by **Friday, February 05, 2016**:

1) Submit a table similar to Table 16 on p. 28 of Final report of study 100931 with data on total dosage used during the actual use period compared by gender and with an age category including those female subjects of childbearing potential. Provide an analysis of any overall differences in total dosage used, or outliers, if evident, based on gender.
2) Provide follow up information (Section 10.6.3, protocol #13049 – Procedure for Reporting Pregnancy) on the clinical course and pregnancy outcomes for the three female subjects (05-008, 10-016 and 15-007) who became pregnant and were in the use population (study 100931). Information provided in the final report is inadequate to determine the outcomes of these subjects' pregnancies.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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MONSURAT O AKINSANYA
02/02/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, January 25, 2016 9:23 AM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Social Science Information Request DUE 01/27: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request regarding the patient standard of care study - by **Wednesday, January 27, 2016**:

1. For the Patient Standard of Care study, rerun the entire set of banners with columns for age only. Include ***only*** female respondents under the age of 50. Add the following age columns 25-29; 30-34, 35-39, 40-49. Do **not** include male respondents or female respondents over the age of 49.
2. The study population was currently being treated with various combinations of drugs. For Q 13, 16, 17, provide a chart (in the format of a banner) listing the different responses to each question; however, instead of the current banner columns, provide six other columns: 1) respondents currently on Differin alone and/or Epiduo but no other drugs, 3) respondents currently on Differin/Epiduo and other retinoids, 4) respondents currently on Differin/Epiduo and non retinoids and 5) respondents not on Differin/Epiduo but on other retinoids and 6) all others. This chart should include ***only*** the female respondents under the age of 50 (and not male) respondents.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
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MONSURAT O AKINSANYA
01/26/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, January 26, 2016 2:30 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Social Science Information Request DUE 01/29: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Information Request - by **Friday, January 29, 2016**:

1) Label Comprehension: Provide more detail on the databases used for recruitment for the label comprehension study.
   a. Where are they sourced from?
   b. If subjects have ever previously participated in a label comprehension study with the sites, what information is stored in the site database about their participation in/responses for that study?
   c. For the pivotal label comprehension study, were the parents/guardians in the room when the survey was administered to them? If so, what was their role?

2) Patient Standard of Care: Provide more detail on the patient database used for recruitment for the Patient Standard of Care study. In your response to our previous IR, you stated that patients were recruited through an online database generated from inbound physician referrals or outbound contact with various support groups for different medical conditions, and that patients may also have been included in the database if they were recruited for a specific study and wished to participate in future studies. Explain the recruiting source for this particular study – was it through the patients' physicians who may have participated in the physician standard of care survey? Were random visitors to the medical marketing research firm's website able to opt into the study, since the website contains this option? Additionally:
   a. What is the overall panel size from which these patients were recruited?
   b. What was the response rate for this survey and how was it calculated?

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
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MONSURAT O AKINSANYA
01/26/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, January 20, 2016 3:28 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Clinical Information Request DUE 01/25: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Clinical Information Request by **Monday, January 25, 2016**:

1) Submit the CRFs for the four subjects who became pregnant during the JUNO trial – 05008, 10016, 15007 and 28002.
2) Submit the CRF for subject 30006.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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MONSURAT O AKINSANYA
01/21/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, January 14, 2016 4:35 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Clinical Information Request DUE 01/21: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Clinical Information Request by **Thursday, January 21, 2016**:

1) Provide a table that includes all of the "subject verbatim reason codes" that were applied to determine whether behaviors met mitigation criteria (a priori or post-hoc criteria) or were incorrect in the primary and secondary endpoint assessments. Include a table/spreadsheet that maps a sample of the subjects' verbatim responses and the "reason codes" applied to those responses in the listings used to determine the endpoints. Provide the algorithm for how reason codes were matched to responses.

2) Was the "Blank Diary Questionnaire" utilized? Explain why there are no data (Listing 16.2.6.1) stemming from those questions.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
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MONSURAT O AKINSANYA
01/14/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, January 11, 2016 1:21 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Clinical Information Request DUE 01/15: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Clinical Information Request by **Friday, January 15, 2016**:

- We have reviewed your 12/18/15 response to our 12/14/15 information request regarding the targeted self-selection study and find that there are still significant differences in the age group distribution between the study report (Table 9-1 and Banner 1, Table M1) and the data in the SUPPDM dataset submitted on 12/18/15. Please submit a revised analysis dataset with the corrected age categories using the same data structure as the analysis.xpt dataset submitted on 10/27/15.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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MONSURAT O AKINSANYA
01/12/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, January 11, 2016 5:01 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Labeling Information Request DUE 01/22: NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Labeling Information Request by **Friday, January 22, 2016**:

- **Provide annotated font and format Drug Facts label specifications for all proposed draft labeling per 21 CFR 201.66. Also, provide font specifications for all the statements on the PDP.**

- **Submit a complete, unannotated patient leaflet.**

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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MONSURAT O AKINSANYA
01/12/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, January 08, 2016 12:31 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Labeling Information Request DUE 01/21 : NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Labeling Information Request by **Thursday, January 21, 2016**:

- Please submit revised container labels and carton labeling to reflect the recently granted proprietary name, "Differin Gel." The original submission for this Supplement 10 contains container labels and carton labeling with the proprietary name, "Differin."

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
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MONSURAT O AKINSANYA
01/08/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, January 08, 2016 4:20 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Social Science Information Request DUE 01/15 : NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Social Science Information Request by **Friday, January 15, 2016**:

- For the physician Standard of Care study, describe in detail the sampling methodology, including information on how specifically the respondents were recruited to participate in the study (if through an established web-based panel, provide a link to information about the panel). Provide details as to compensation for participation in the survey, as well as whether the respondents had ever previously received payments for services on behalf of the sponsor.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993
(301) 796-9634 (phone)
(301) 796- 9899 (fax)

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/s/

MONSURAT O AKINSANYA
01/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 116864

**MEETING REQUEST-
WRITTEN RESPONSES**

Galderma Laboratories, L.P.
Attention: Sean Griffin
Associate Director, Regulatory Affairs
14501 North Freeway
Forth Worth, TX 76177

Dear Mr. Griffin:

Please refer to your Pre-Investigational New Drug Application (PIND) for Differin® (adapalene) gel, 0.1%.

We also refer to your submission dated October 24, 2013, containing a Type C meeting request. The purpose of the requested meeting is for Galderma to discuss aspects of FDA's recommended studies as discussed in the meeting minutes from the meeting held March 12, 2013. Specifically Galderma wants to discuss the Agency's recommendation that the sponsor conduct self selection and maximal use PK studies.

Further reference is made to our Meeting Granted letter dated October 30, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 24, 2013 background package.

If you have any questions, call Celia Peacock, Regulatory Project Manager at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance
Application Number: PIND 116864
Product Name: Differin (adapalene) gel, 0.1%
Sponsor: Galderma
Indication: Treatment of acne

1.0 BACKGROUND

On March 12, 2013 Galderma met with the Agency to discuss the proposed Rx-to-OTC switch development program for Differin (adapalene) Gel, 0.1%. In that meeting, the Agency stated that four studies would be required to support the Rx-to-OTC switch of this product – label comprehension, self-selection, actual use and maximal use PK. The purpose of this Type C meeting is to request that the Agency reconsider two of the studies, self-selection and maximal use PK. In support of this position, Galderma provided additional studies in their background package.

2. QUESTIONS AND RESPONSES

In this section, the Sponsor's questions are **bolded**; the Agency's responses are in *italics.*

Question 1

Does the Agency agree that, based on the well-established OTC acne category, intended population, and proposed precaution labeling that is identical to that found in the CFR, that a self-selection study is not required to support the proposed Rx-to-OTC switch of Differin (adapalene) Gel, 0.1%? If the Agency still believes that a self-selection study is required, what rationale does the Agency believe exists for conducting this study for a well-established OTC category and proposed precaution labeling identical to that found in the CFR?

FDA Response

We agree that a self-selection study to evaluate consumers' ability to diagnose acne is unnecessary. However, we strongly recommend a self-selection study to assess the likelihood of pregnancy exposures. Refer to the March 12, 2013, meeting minutes in which we expressed our concerns regarding correct self-selection by pregnant women and discontinuation by women who become pregnant due to the potential risk of teratogenicity. You do not need to conduct a separate stand alone, self-selection study, but may evaluate self-selection as part of your actual use study. If you decide not to evaluate self-selection to assess the likelihood of pregnancy exposures, you will need to provide a strong rationale in your NDA submission explaining why the risk of teratogenicity does not warrant such concerns.

Your actual use study should evaluate who will use the product, for what indications (acne and off-label uses), body areas to which the product is applied, amount applied, and length of use.

Specify specific indications for off-label use (e.g. wrinkles, rough skin, and hyperpigmentation). Enroll adequate numbers of women of reproductive age and those who are pregnant so that assessments can be made regarding correct self-selection. Include female adolescents since teenagers are a major acne population. Note that pregnant subjects should be allowed to select whether or not they wish to use or purchase the product. However, if pregnant, drug should not be dispensed for their use.

Adapalene is a retinoid-like compound and has the potential for retinoid teratogenicity. In an NDA submission, you will need to thoroughly evaluate the teratogenicity risk in the OTC setting, without the advice of a healthcare provider. Include in your evaluation experience with prescription use (to help us understand how it is used with the advice of a healthcare provider), nonprescription use in other countries, literature, post-marketing experience, and results of your consumer studies. As noted at the meeting in March 2013, current prescribing practice in the prescription setting and how clinicians counsel patients who may become pregnant or who are pregnant or breastfeeding may be helpful. Data from pregnancy registries, if available, may also be helpful. Include a targeted evaluation for evidence of fetal retinoid syndrome in your evaluation of postmarketing data.

As noted at the meeting on March 12, 2013, the Rx-to-OTC application would likely be presented at an Advisory Committee meeting. We anticipate the Advisory Committee would discuss reproductive risk.

Question 2

Does the Agency agree that, based on the data collected in the nine (9) previously conducted maximal use PK studies on adapalene, an additional maximal use PK study is not required to support filing of an NDA-S for the proposed Rx-to-OTC switch of Differin (adapalene) Gel, 0.1%? If the Agency does not agree, and instead believes that an additional maximal use PK study is required, what specific data and outcomes will the Agency be looking for when evaluating this data to determine if this drug is appropriate for OTC use, that has not been obtained in the 9 studies previously conducted?

FDA Response

Our main concern is to ensure that there are data available to evaluate the potential systemic safety of Differin gel 0.1% in adolescents as subjects may apply the gel to a large surface area without monitoring or direction from a healthcare provider. As there are no PK trials with Differin gel 0.1% in adolescents or application to areas larger than 1000 cm^2, you have proposed an indirect approach to support your conclusion that the systemic exposure of adapalene following application of Differin gel 0.1% to adolescent subjects will be low. Whether or not an indirect approach will be sufficient to determine the maximal exposure will be a review issue. Alternatively, you may choose to conduct a maximal use PK study.

We have the following concerns with the indirect approach you propose:

1. *Your approach includes an observation that there were similar systemic exposures following application of adapalene lotion 0.1% to adolescents and adults. We note that this was a cross trial comparison which concerns us. In addition, your conclusions were*

based on the lotion formulation and applicability to the gel formulation would need to be addressed in your rationale.

2. *With regard to the surface area of application, we recommend application to the entire area of the face, shoulder, upper chest and upper back (i.e., about 15% BSA) to represent maximal use conditions because these are the locations acne lesions typically occur. You have indicated that you disagree with the size of the area, noting that in trial RD.06.SPR.18108 you accurately measured the treated surface area and it totaled 950 cm^2 for treatment on upper back, upper chest and face (not including shoulders). We note that based on the submitted protocol, trial RD.06.SPR.18108 did not appear to measure the entire areas of the upper back, upper chest, or face (excluding shoulders), but may have measured only the areas where the 2 gram pre-specified dose was applied. The 950 cm^2 application area was consistent with the pre-specified application area of 1000 cm^2 but does not necessarily capture the entire area of the face, shoulder, upper chest and upper back.*

3. *You noted that in trial 18229, subjects were allowed to apply a sufficient amount to cover the area with acne, and the preliminary results showed a mean application amount of 2.3 ± 0.4 g. It is unclear if whether subjects were instructed to apply to only acne lesions or to the entire areas of face, shoulder, upper chest and upper back.*

We acknowledge that applications of 2 grams of Differin gel 0.1% to areas of approximately 1000 cm^2 in adults have resulted in low systemic exposure. In the NDA provide a detailed rationale regarding systemic exposure when applied to a large surface area in adolescents. Your rationale should address our concerns and points raised above. In addition, include an analysis that estimates the systemic exposure (Cmax and AUC) following application to the entire area of face, shoulder, upper chest, and upper back based on factors such as ratio of this surface area compared to the area of 1000 cm^2 used in previous PK trials.

Additional Administrative Comments:

We strongly encourage you to send your submissions electronically. We recommend eCTD submissions using CDISC standards for study data and MedDRA coding for adverse events. General guidance and contact information is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

We encourage you to submit your requests for FDA review of your proposed proprietary name as early as possible. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, "Contents of a Complete Submission for the Evaluation of Proprietary Names" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

We encourage you to request and attend, at a minimum, a pre-NDA meeting prior to submitting your application to discuss the content and format requirements of the Agency.

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/s/

THERESA M MICHELE
01/06/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, January 04, 2016 2:52 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Clinical Information Request DUE 01/11 : NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Clinical Information Request by **Monday, January 11, 2016**:

For the Juno trial (Pivotal Actual Use Study for Adapalene 0.1% Gel – 13049), address the following:

1) Provide information, or the location of data, that specifically describes how the screening process was conducted which resulted in the following subjects being excluded based on criterion 5 – "In the judgment of the investigator or designee, the subject will be likely to be harmed by participating in the study or the subject is unlikely to follow study procedures." We cannot locate data to explain why most of these subjects were excluded.

USUBJID

JUNO-13049 -02027
-02046
-03016
-04004
-05040
-06003
-11071
-11072
-11073
-13007
-13035
-13037
-13058
-14025
-15006
-15013
-17068
-18038
-22039
-22070
-22078
-23020
-24032
-24034
-28016
-28081
-28084
-31022

-31037

2) The Study Flow (Table 4; p. 14 of Abbreviated Clinical Study Report (final report); Module 5.3.5.2) notes that excluded subjects were to have undergone a clarification probe, by a professional from the Central Medical Operations Group (CMOG), as part of the screening. That appears to have been conducted for only four of the above subjects (11072, 17068, 22078 and 31037).
    a. Also, subject 31037 had a positive pregnancy test and wanted to purchase and use the product. Her selection decision appears to have been coded as "correct" (see Listing 16.2.6.11). Explain.

3) Four subjects (04004, 14025, 28016 and 31022) stated that they would not be interested in purchasing the product. Two subjects (14025 and 17068) appear to have been excluded due to pregnancy or breastfeeding. Comment on all reasons why the subjects listed above (under 1)) were excluded from participation in the trial and provide verbatim responses, or identify their location, to any questions/answers (Qs/As) in any discussion between the screener and the subject.

4) In addition, provide information on all reasons why subjects (N=104) were considered "Actual Use Screen Failures" (see Table 5 – Subject Disposition; p. 16 of final report).

5) Finally, explain why the final report for this trial is titled as "abbreviated." Clarify whether the report was submitted in its entirety, and if not what material is missing or included elsewhere in the application.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993
(301) 796-9634 (phone)
(301) 796- 9899 (fax)

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/s/

MONSURAT O AKINSANYA
01/04/2016

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, December 14, 2015 3:40 PM
To: GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc: Akinsanya, Lara
Subject: Clinical Information Request DUE 12/18 : NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Clinical Information Request by **Friday, December 18, 2015**:

- For the targeted self-selection study, the age group distribution significantly differs between the study report (Table 9-1 and Banner 1, Table M1) and the analysis dataset submitted on 10/27/15. Please clarify this discrepancy and, if relevant, submit either the revised study report and/or the revised dataset.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993
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MONSURAT O AKINSANYA
12/16/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 20380/S-010

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Sean Griffin
Director, Regulatory Affairs

Dear Mr. Griffin:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adapalene Gel, 0.1 %

We also refer to your correspondence, dated and received September 22, 2015, requesting review of your proposed proprietary name, Differin Gel.

We have completed our review of the proposed proprietary name, Differin Gel and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your September 22, 2015, submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola M. Olagundoye-Alawode, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Lara (Monsurat) Akinsanya, M.S., Regulatory Project Manager in the Office of New Drugs, at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
11/24/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20380/S-010

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Galderma Laboratories,L.P.
Attention: Sean Griffin
Director, Regulatory Affairs
14501 North Freeway
Fort Worth, TX 76177

Dear Mr. Griffin:

Please refer to your supplemental New Drug Application (sNDA) dated September 10, 2015, received September 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Differin (adapalene) Gel, 0.1%.

We also refer to your amendment dated October 27, 2015.

We completed our filing review and determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 10, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling by June 12, 2016.

We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified potential review issues. We request that you submit the following information as soon as possible, and no later than December 18, 2015. The review issues are as follows:

1. In the self-selection study, 184 subjects were breastfeeding, 96 subjects were pregnant, and 13 were both:

   a. Provide more detail about the criteria by which subjects were intercepted in the malls for participation in this study. Was every female of child bearing age stopped for screening, or did recruiters focus on approaching women with infants (i.e., high likelihood of breastfeeding) and women who were visibly pregnant?

   b. If women who were visibly pregnant were the ones targeted for the pregnancy category, did this skew the study subjects to those in their second and third trimesters as opposed to their first trimesters? Did you collect any data on what trimester of pregnancy the subjects were in?

   c. Was the interception methodology conducted in the same way across all of the study sites?

   d. Provide references as to whether the proportions of breastfeeding to pregnant subjects in the study reflect the actual proportions of breastfeeding to pregnant subjects in the true population.

2. Provide a detailed clinical rationale for the 90% a priori threshold in your self-selection study.

3. In the Physician Standard of Care Survey, there were many questions for which multiple responses were accepted. In the instances in which multiple responses were provided, indicate how we can ascertain which response was offered first by each subject.

4. Submit CRFs for the following nine (N=9) subjects who were excluded or discontinued from the Actual Use Trial (AUT) 13049 (Pivotal Actual Use Study for Adapalene 0.1% Gel) due to reported adverse events:
   - 17047, 20054, 24012, 25008, 25012, 26043, 26047, 27045, 30020.

5. Identify the location of or submit the clinical justification for your performance threshold for Trial 13049 (AUT) co-primary endpoints.

6. Submit the following safety analyses as per our request at the meeting held on March 12, 2013. We requested an analysis of data from postmarketing databases to address the clinical safety of adapalene. We acknowledge submission of your analysis of carcinogenicity, teratogenicity and fetotoxicity; however, adapalene has other clinical concerns that require analysis for us to consider whether the product is appropriate for OTC marketing:
   - Submit a summary and analysis of the dermal safety of your product, including sensitivity and irritation, particularly following sun exposure.
   - Submit an analysis of adverse events possibly associated with interactions with products containing sulfur, resorcinol, or salicylic acid.

- Submit a summary and analysis of the literature you included in your NDA. Include in the analysis a table listing the references with the type of study reported, objectives, population and principal results.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

In addition, we have the following information requests. Provide the information below within 10 days of receipt of this letter:

- Clearly identify which version of the Drug Facts Label was tested in AUT 13049.
- Provide a certified English translation of foreign labels (Russian Federation) where the product is marketed nonprescription.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Lara Akinsanya, Senior Regulatory Project Manager at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

THERESA M MICHELE
11/23/2015

Akinsanya, Lara

From:	Akinsanya, Lara
Sent:	Thursday, October 22, 2015 11:45 AM
To:	GRIFFIN Sean (Sean.GRIFFIN@galderma.com)
Cc:	Akinsanya, Lara
Subject:	Clinical Information Request DUE 10/27 : NDA 20380_S010/Differin (adapalene), 0.1%/Galderma – Efficacy supplement

Dear Sean Griffin,

Please respond to the below Clinical Information Request by **Tuesday, October 27, 2015**:

- Submit tabulation and analysis datasets for the actual use study.
- For the actual use study, submit a line listing that contains both the verbatim name and the coded preferred term for each adverse event.
- For the label comprehension study, provide an analysis dataset, which has one (1) record per subject, and a data dictionary. Include the following columns in the dataset:
    - Subject ID
    - Site ID
    - Cohort
    - Subgroup, i.e. adult or adolescent
    - Age
    - Age category (DMAGECAT)
    - Sex
    - Race
    - Ethnicity
    - Education level
    - Income
    - REALM score
    - Literacy subgroup
    - For each comprehension question, i.e. Q1a, Q1b, Q2a,…, columns for the
        - coded response
        - Q1A verbatim text
        - Verbatim text for "other"
    - After each pair of questions, e.g. Q1a and Q1b, a column for the question net comprehension, e.g. Q1 net comprehension and a column for the rationale for the net comprehension determination.
    - Q 13, Q 13 "other"
    - All of the responses for Q14.

- For the self-selection study, provide an analysis dataset, which has one (1) record per subject, and a data dictionary. Include the following columns in the dataset:
    - Subject ID
    - Site ID
    - Cohort
    - Subgroup, i.e. adult or adolescent
    - Age category (DMAGECAT)

- Race
- Ethnicity
- Education level
- Income
- REALM score
- Literacy subgroup
- All Q2 responses, i.e. QS2A to QS2F
- Q8A coded response
- Q8A verbatim text
- Q8 MITNET
- Rationale for Q8 MITNET
- Q8B coded response
- Q8B verbatim text
- Q8FINALSSNET
- Rationale for Q8FINALSSNET
- For Q9, Q11, Q11b and Q11c, the blank CRF says “not submitted”. Explain.
- Q10
- Q11
- Q11b
- Q11c
- Q12, Q12 verbatim

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Senior Regulatory Health Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
10903 New Hampshire Ave
Silver Spring, MD 20993
(301) 796-9634 (phone)
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/s/

MONSURAT O AKINSANYA
10/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 20380/S-010

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Galderma Laboratories, L.P.
Attention: Sean Griffin
Director, Regulatory Affairs
14501 North Freeway
Fort Worth, TX 76177

Dear Mr. Griffin:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 20380

SUPPLEMENT NUMBER: 010

PRODUCT NAME: DIFFERIN (ADAPALENE) GEL, 0.1%

DATE OF SUBMISSION: SEPTEMBER 10, 2015

DATE OF RECEIPT: SEPTEMBER 10, 2015

This supplemental application proposes the following change(s) for Differin (adapalene) Gel, 0.1%: to fully switch marketing status from prescription to over-the counter.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 9, 2015 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Monsurat Lara Akinsanya, MS
Senior Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MONSURAT O AKINSANYA
09/23/2015