

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-502

OTHER REVIEW(S)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: A in vivo pharmacokinetic study following the treatment with Differin (adapalene) Lotion, 0.1% in adolescents aged 12 years to 17 years with acne vulgaris

PMR/PMC Schedule Milestones:

Protocol Submission Date:	06/15/2010
Study Initiation Date:	02/15/2011
Study Completion Date:	08/15/2011
Final Study Report Submission Date:	02/15/2012
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Differin (adapalene) Lotion, 0.1%, is being developed to treat the patients with acne vulgaris in ages of 12 years and older. While two phase 3 trials were conducted in accordance to the target age group, the subject enrollment criteria in the pharmacokinetic study evaluating the potential for systemic exposure did not fully reflect the target patient population and only patient 18 years and older were studied. A possibility exists that there may be differences in skin penetration potential between adult and adolescent (12-17 years) group. Given the low exposure level of this drug in adult and the observed safety data across age groups in phase 3 trials, a PMC was chosen, as it balances the informational need with safety.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

While the drug under review is targeting patients 12 years and older, the bioavailability study evaluating the potential for systemic exposure to the drug was conducted only patients 18 years and older. Evaluation of systemic levels of topical drug products is one of the safety measures. Since there may be differences in skin penetration potential between adult and adolescent patients, the sponsor is requested to conduct a pharmacokinetic study in adolescents aged 12 years to 17 to cover all intended target age population.

5. What type of study or clinical trial is required or agreed upon (describe)?

It will be a pharmacokinetic study in patients with acne vulgaris aged 12 years to 17 years following treatment with Differin (adapalene) Lotion, 0.1%, under maximal use conditions consistent to those used in clinical trials. Following measurements of plasma drug concentrations at adequate number of sampling time points, PK parameters such as total exposure, peak plasma concentrations and time to peak concentrations will be evaluated.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

KELISHA C TURNER
03/17/2010

DAVID L KETTL
03/17/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 3, 2010

To: Susan Walker, MD, Director
Division of Dermatology and Dental Products

Through: Kristina Arnwine, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Lori Cantin, RPh, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Differin (Adapalene) Lotion, 0.1%

Application Type/Number: NDA 022502

Applicant/sponsor: Galderma

OSE RCM #: 2009-1820

1 INTRODUCTION

This review was written in response to a request from the Division of Dermatology and Dental Products to evaluate the container labels, carton and package insert labeling for the product Differin (Adapalene) Lotion 0.1%, for areas that could lead to medication errors.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Since Differin has been marketed as a 0.1% Gel (since 1996), a 0.1% Cream (since 2000), and a 0.3% Gel (since 2007), DMEPA conducted a search of the Adverse Event Reporting System (AERS) database to determine if there are any medication errors associated with the currently marketed Differin products which may be indicative of potential confusion with Differin 0.1% Lotion.

The MedDRA Higher Level Group Term (HLGT) Medication Error, the Preferred Term (PT) Product Quality Issues, the active ingredient “Adapalene”, the verbatim substance name “Adap%”, and the tradename “Differin” were used as search criteria.

The cases were manually reviewed to determine if medication errors occurred involving the labels or labeling for the Differin product line. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify contributing factors.

2.2 LABELS AND LABELING

DMEPA used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the Differin Lotion 0.1% container labels and carton labeling submitted on October 22 and December 1, 2009 (see Appendix A), and the insert labeling (no image) submitted on June 12, 2009.

3 RESULTS

3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE

A search of the AERS database was performed on November 9, 2009. We retrieved a total of 4 reports (including 1 duplicate report), for a total of three (3) cases. These cases were not evaluated further because they were deemed not related to labels and labeling for the Differin products. One case was of an accidental ingestion, the second case was an adverse event, and the third case described exposure during pregnancy. None of the cases reviewed could be attributed to the labels, labeling, or packaging configuration of the Differin products.

4 RECOMMENDATIONS

Our evaluation of the proposed container labels, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1 *Comments to the Division* for discussion during the review team’s label and labeling meetings. Section 4.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Janet Anderson, at 301-796-0675.

4.1 COMMENTS TO THE DIVISION

4.1.1 Package Insert Labeling

1. Revise the package insert to ensure that there is adequate space between a numerical drug dose and a unit of measure in all cases. Lack of placement of adequate space was noted in Section 13 (NONCLINICAL TOXICOLOGY) of the Full Prescribing Information, i.e., ‘20mg adapalene/kg/day’ should be stated as ‘20 mg adapalene/kg/day’. When the numerical drug dose and unit of measure run together it is considered to be an error-prone dose designation. As such, this is included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations². As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error-prone designations in the approved labeling of products.
2. Revise the Dosage and Administration section in the HIGHLIGHTS OF PRESCRIBING INFORMATION to mirror the presentation of the information provided in the Dosage and Administration section in the FULL PRESCRIBING INFORMATION (i.e., remove the phrase “Apply a thin film of Differin Lotion to the entire face” and revise to “Dispense a nickel size amount and apply a thin film of Differin Lotion to the entire face and other affected areas...” etc.
3. We believe that the word (b) (4) in the last bullet of section 17 PATIENT COUNSELING INFORMATION was intended to be (b) (4). Please revise accordingly.

4.1.2 Carton Labels and Container Labeling

We note that the letter “D” in the name “Differin” on the container labels and carton labeling is white with a blue-colored, D-shaped background, whereas all the other letters of the name are displayed in blue. We find that this presentation of the letter “D” detracts from the overall readability of the name Differin. However, we acknowledge that the container labels and carton labeling for the Differin Gel 0.3% product (approved June 2007) also contains this same presentation of the letter “D” in Differin, and this has not lead to any known cases of medication error. Therefore, we will not be providing a comment to the Applicant regarding this issue.

4.2 COMMENTS TO THE APPLICANT

Container Labels and Carton Labeling

1. Ensure the presentation of the established name is displayed per CFR 201.10(g)(2), which requires that the established name shall be printed in letters that are at least half as large and with a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.
2. Revise the carton and container labels to include the route of administration statement on the principal display panel. The route of administration statement “For external use only” is currently displayed in bold font on the back panel of the container labels and on the side panel of the carton labeling, but does not appear on the principal display panel. In its current location, the statement is not displayed with adequate prominence and can be easily overlooked.

3. Increase the prominence of the statement “SAMPLE-NOT FOR SALE” on the 15 mL sample container label.

5 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

LORI G CANTIN
02/03/2010

KRISTINA C ARNWINE
02/03/2010

DENISE P TOYER
02/03/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 24, 2009

To: Susan Walker, M.D., F.A.A.D., Director,
Division of Dermatology and Dental Products (DDDP),
Office of New Drugs (OND)

Through: Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader
Division of Pharmacovigilance I (DPV I)

From: Tracy Salaam, Pharm.D., Safety Evaluator,
Division of Pharmacovigilance I (DPV I)

Subject: Phototoxicity

Drug Name(s): Adapalene (Differin®)

Application Type/Number: NDA 020338, 020380, 021753

Applicant/sponsor: Galderma Laboratories, L.P.

OSE RCM #: 2009-1326

1 INTRODUCTION

The Division of Dermatology and Dental Products (DDDP) requested that the Division of Pharmacovigilance I (DPV I) search the Adverse Event Reporting System (AERS) database for post-marketing reports of adapalene in association with phototoxicity when used concomitantly with tetracycline or doxycycline. DDDP is currently reviewing NDA 22-502 for adapalene lotion 0.1% that if approved, would be indicated for the treatment of acne vulgaris. The purpose of the AERS search was to determine if there was a possibility of phototoxicity associated with adapalene and concomitant tetracycline or doxycycline use.

2 METHODS AND MATERIAL

We searched the AERS database for reports of phototoxicity related terms associated with adapalene products, and then reviewed each report for concomitant tetracycline or doxycycline use.

2.1 DATA SOURCES AND SEARCH CRITERIA

- Search date: July 20, 2009
- Drug names: adapalene and all associated trade, generic, and verbatim terms
- MedDRA search term:
 - **PT Photosensitivity reaction**- including the following Lower Level Terms (LLT): Acute dermatitis due to solar radiation, Dermatitis of exposed site, Dermatitis photosensitive, Eruption of exposed site, Exogenous photosensitive eruption, Heliosensitive rash, Photocontact dermatitis, Photosensitive dermatitis, Photosensitive rash, Photosensitive reaction, Photosensitivity, Photosensitivity reaction, Photosensitivity reaction NOS, Photosensitivity toxic reaction, Photosensitized, Phototoxicity, Phytphotodermatitis, Rash photosensitivity, Solar sensitiveness, Sun blister, and Sun sensitivity.

3 DATA, DISCUSSION AND CONCLUSION

Our search of the AERS database for all reports of phototoxicity reaction related terms associated with adapalene and concomitant tetracycline or doxycycline use retrieved one case. The case was reported by three lawyers and involved “a 16-year old male patient who developed inflammatory bowel disease, ulcerative colitis, intestinal obstruction, appendicitis, anxiety, depression, emotional distress, irritable bowel syndrome, anemia, dry lips, dry hands, rash, fatigue, headache, bleeding, weight loss, interstitial lung disease, pancolitis, bronchitis, enlarged mesenteric lymph nodes and sigmoid diverticulosis as a result of ingesting isotretinoin” to treat acne from October 1999 to May 2000. “Sun sensitivity” was reported as an adverse event occurring in April 2000 while the patient was taking isotretinoin. Concomitant medications reported include prednisone, erythromycin, doxycycline, triamcinolone, azithromycin, Benzamycin® gel (benzoyl peroxide and erythromycin), Sumycin® (tetracycline), Retin-A® (tretinoin), and Differin® gel (adapalene). Adapalene was used March 1999 prior to taking isotretinoin, but the case is unclear regarding whether adapalene and tetracycline were used at the same time or if these treatments were still being used at the time sun sensitivity was reported. Doxycycline was reported to be used November 1999 while the patient was taking isotretinoin. The case is unclear regarding whether adapalene and doxycycline were used at the same time or if these treatments were still being used at the time sun sensitivity was reported. The case is also confounded by the use of other medications that are also labeled for an association with photosensitivity (isotretinoin, doxycycline, tetracycline, and tretinoin).

We are mindful of the fact that the absence of reporting does not necessarily mean the absence of a signal and that AERS data has limitations. A limitation to AERS data includes under-reporting to

the AERS database. The FDA does not receive all adverse event reports that may potentially occur with a product. Many factors can influence the reporting of an event, including the length of time a product has been marketed, and publicity surrounding an event. However, considering these factors, and based on the presence of one confounded and unclear report for photosensitivity with adapalene and concomitant tetracycline and doxycycline use, there does not appear to be an association between phototoxicity and adapalene when used with concomitant tetracycline or doxycycline at this time.

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/s/

TRACY M SALAAM
08/04/2009

IDA-LINA DIAK
08/04/2009

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-502 Supplement # 000 Efficacy Supplement Type SE-

Proprietary Name: Differin Lotion
Established Name: adapalene
Strengths: 0.1%

Applicant: Galderma R&D

Date of Application: February 27, 2009

Date of Receipt: March 2, 2009

Date of Filing Meeting: April 14, 2009

Filing Date: April 17, 2009

Action Goal Date (optional): December 2, 2009

User Fee Goal Date: January 2, 2010

Indication(s) requested: Acne vulgaris

Type of Original NDA: (b)(1) (b)(2)

AND (if applicable)

Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P

Resubmission after withdrawal? Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)

Waived (e.g., small business, public health)

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO

If yes, explain:

- 1). NDA 21-753 Differin (adapalene) gel, 0.3% - Exclusivity expires on June 19, 2010; New Product.
- 2). NDA 22-320 Epiduo (adapalene, 0.1%; benzoyl peroxide, 2.5%) gel – Exclusivity expires on December 8, 2011; New Combination.

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? N/A YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, 3 Years NO

- Correctly worded Debarment Certification included with authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND# 76,057
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) August 7, 2007 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
Note: Meeting was cancelled due to successful results from their Phase 3 clinical studies.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO

Note: Per DDMAC, consult is preferred after Mid-Cycle meeting.

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? N/A YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO
N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? N/A YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 14, 2009

NDA #: 22-502

DRUG NAMES: Differin (adapalene) Lotion, 0.1%

APPLICANT: Galderma R&D

BACKGROUND: NDA 22-502, Adapalene (Differin) Lotion, 0.1%, submitted February 27, 2009 is indicated for the treatment of acne vulgaris. This application was submitted as a 505(b)(1).

Galderma manufacturers other dosage forms of Differin (adapalene). These dosage forms include Differin Cream, 0.1% (NDA 20-748), Differin Gel, 0.1% (NDA 20-380), and Differin Gel, 0.3% (NDA 21-753).

ATTENDEES:

Susan J. Walker, M.D., F.A.A.D., Director
David Kettl, M.D., Clinical Team Leader
Amy Woitach, M.D., Clinical Reviewer
Barbara Hill, Ph.D., Pharmacology Supervisor
Kumar Mainigi, Ph.D., Pharmacology Reviewer
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead
Rajiv Agarwal, Ph.D., Product Quality Reviewer
Mohamed Alesh, Ph.D., Statistical Team Leader
Carin Kim, Ph.D., Statistical Reviewer
Dennis Bashaw, Pharm.D., Director, Biopharmaceutics
Seongeun (Julia) Cho, Ph.D., Biopharmaceutics Reviewer
Barbara Gould, M.B.A.H.C.M., Chief Project Management Staff
Catherine Carr, M.S., Regulatory Health Project Manager
Sue Kang, B.S., Regulatory Health Project Manager
Nichelle Rashid, B.S., Regulatory Health Project Manager
Kelisha Turner, B.S., Regulatory Health Project Manager
Dawn Williams, R.N., B.S.N., U.S.P.H.S., Regulatory Health Project Manager
Roy Blay, Director, Regulatory, Good Clinical Practices Branch

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Chemistry:
Biopharmaceutical:
DSI:
Regulatory Project Management:

Reviewer

Amy Woitach
David Kettl
Carin Kim
Kumar Mainigi
Rajiv Agarwal
Julie Cho
Roy Blay
Catherine Carr

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO

If no, explain: Identified sites recently inspected and found to be acceptable (NAI) by DSI.

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

• GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

• Establishment(s) ready for inspection? YES NO

• Sterile product? YES NO

If yes, was microbiology consulted for validation of sterilization?
N/A YES NO

ELECTRONIC SUBMISSION:
Any comments: None.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
Note: The Pediatric Page will be completed near the time of regulatory action.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Catherine Carr, MSc.
Regulatory Project Manager

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this page is the manifestation of the electronic signature.**

/s/

Catherine Carr
7/9/2009 03:25:46 PM
CSO

Barbara Gould
7/17/2009 09:01:57 PM
CSO

Division of Dermatology and Dental Products

**REGULATORY PROJECT MANAGER REVIEW
(PHYSICIAN LABELING RULE)**

Application Number: NDA 22-502

Name of Drug: Adapalene (Differin) Lotion, 0.1%

Applicant: Galderma Research and Development, Inc.

Material Reviewed:

Submission Date: February 27, 2009

Receipt Date: March 2, 2009

PDUFA Due Date: January 2, 2010

Submission Date of Structured Product Labeling (SPL): February 27, 2009

Type of Labeling Reviewed: PLR Labeling

Background and Summary

NDA 22-502, Adapalene (Differin) Lotion, 0.1%, submitted February 27, 2009 is indicated for the treatment of acne vulgaris. This application was submitted as a 505(b)(1).

Galderma R&D manufacturers other dosage forms of Differin (adapalene). These dosage forms include Differin Cream, 0.1% (NDA 20-748), Differin Gel, 0.1% (NDA 20-380), and Differin Gel, 0.3% (NDA 21-753).

Review

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant in the 74-day letter. These comments are based on 21 CFR 201.1 and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider the comment as a recommendation only.

The following issues/deficiencies have been identified in the proposed labeling:

Highlights Section:

1. The revision date should be the month/year that the application is approved.

Full Prescribing Information (FPI) Section:

2. According to 21 CFR 201.1, manufacturing information should be located at the end of the label, after the Patient Counseling Information section. The manufacturing information should be included for this product according to regulations.

Conclusion and Recommendation

The labeling deficiencies/issues identified above should be addressed by the applicant. A revised label should be submitted by June 15, 2009.

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/s/

Catherine Carr
4/15/2009 08:13:54 AM
CSO

Barbara Gould
4/21/2009 06:01:05 PM
CSO

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-502
APPLICANT	GALDERMA
DRUG NAME	DIFFERIN (Adapalene)
SUBMISSION DATE	March 3, 2009
SEALD REVIEW DATE	November 16, 2009
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

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(CCI/TS)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22502

ORIG-1

GALDERMA
RESEARCH AND
DEVELOPMENT
INC

DIFFERIN LOTION

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/s/

JEANNE M DELASKO
11/16/2009

LAURIE B BURKE
11/17/2009