

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202833Orig1s000**

**OTHER REVIEW(S)**

## SEALD Director Sign-Off Memo and Labeling Review

<b>Product Trade Name (Non-Propriety Name)</b>	<b>PICATO (ingenol mebutate) gel, 0.015% or 0.05%, for topical use</b>
Application Number/Supplement Number	NDA 20-2833
Type of Application	Original Submission
Indication	For the topical treatment of actinic keratosis
Applicant	Leo Pharma AS
Office/Division	ODE III/DDDP
Division Project Manager	Paul Phillips, MS
Submission Date	March 25, 2011
PDUFA Goal Date	January 25, 2012
SEALD Review Date	January 11, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko, RN, MS
SEALD Director	Laurie Burke, RPh, MPH

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

# SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

# SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**
  - For Pregnancy Category X drugs, list pregnancy as a contraindication.
  
- **Adverse Reactions**
  - Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
  - For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
  - For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”
  
- **Use in Specific Populations**
  - Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for “peds only” indications) are required and cannot be omitted.
  
- **Patient Counseling Information**
  - This section is required and cannot be omitted.
  - Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ... (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
    - “See FDA-approved patient labeling (Medication Guide)”
    - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
    - “See FDA-approved patient labeling (Patient Information)”
    - “See FDA-approved patient labeling (Instructions for Use)”
    - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/  
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JEANNE M DELASKO  
01/11/2012

LAURIE B BURKE  
01/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Dr. Nina Ni, CMC Reviewer  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: Nina.Ni@fda.hhs.gov  
Phone: (301)-796-5296  
Fax: (301)-796-9749

**FROM:** FDA  
Division of Pharmaceutical Analysis  
James Allgire, Team Leader  
Suite 1002  
1114 Market Street  
St. Louis, MO 63101  
Phone: (314) 539-3813

**Through:** Benjamin J. Westenberger, Deputy Director  
Phone: (314) 539-3869

**SUBJECT:** Methods Validation Report Summary

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Application Number: NDA 202-833

Name of Product: Picato (ingenol mebutate) gel, 0.015% and 0.05%

Applicant: Leo Pharma A/S

Applicant's Contact Person: U.S. Agent: Cheri Jones, M.S., RAC, FRAPS

Address: 481 haven Point Drive, Treasure Island, Florida 33706

Telephone: 727-940-4535 Fax: [cherijonesrac@gmail.com](mailto:cherijonesrac@gmail.com) (email)/ 970-232-8150

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Date Methods Validation Consult Request Form Received by DPA: 7/8/2011

Date Methods Validation Package Received by DPA: 7/8/2011

Date Samples Received by DPA: 8/8/2011

Date Analytical Completed by DPA: 12/13/2011

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Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.   
2. Methods are acceptable with modifications (as stated in accompanying report).   
3. Methods are unacceptable for regulatory purposes.

Comments:

Cover memo and summary of analysis are attached



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Date: November 10, 2011  
To: Nina Ni, Ph.D., CMC Reviewer, ONDQA/DNDQAI  
Through: B.J.Westenberger, Deputy Director, Division of Pharmaceutical Analysis (HFD-920)  
From: Terry W. Moore, Chemist, Division of Pharmaceutical Analysis (HFD-920)  
Subject: Method Validation for NDA 202833  
Ingenol mebutate gel 0.015%  
LEO Pharma A/S

The following method was evaluated and is acceptable for quality control and regulatory purposes:

- Ingenol Mebutate: Identification, Assay and determination of Organic Impurities by HPLC ( AP\_000459)

The following method was evaluated:

- PEP005 (Ingenol Mebutate) Gel: Identification, Assay and Determination of Organic Impurities of Ingenol Mebutate by UPLC (AP\_000449)

The Identification and Assay are acceptable for quality control and regulatory purposes. The Organic Impurities portion is not acceptable for quality control and regulatory purposes. The impurity peaks, especially (b) (4), could not be reliably identified and several other peaks need better resolution between each other.

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods that should be addressed.

Ingenol Mebutate: Identification, Assay and Determination of Organic Impurities by HPLC (AP\_000459)

(b) (4)

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/s/  
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JAMES F ALLGIRE  
12/13/2011

BENJAMIN J WESTENBERGER  
12/13/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: November 21, 2011

To: Susan Walker, MD, Director  
**Division of Dermatology and Dental Products (DDDP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs (DMPP)**  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs**

Subject: DMPP Review of Patient Labeling (Patient Package Insert  
and Instructions for Use)

Drug Name (established name): PICATO (ingenol mebutate)

Dosage Form and Route: Gel (0.05% and 0.015%)

Application Type/Number: NDA 202-833

Applicant: LEO Pharma AS c/o Jones Regulatory Consulting LLC

OSE RCM #: 2011-1409

## 1 INTRODUCTION

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for PICATO gel (ingenol mebutate).

The purpose of the Applicant's submission is to seek approval of original New Drug Application (NDA) 202-833 for PICATO (ingenol mebutate) gel (0.015% and 0.05%). The proposed indication is for the topical treatment of actinic keratosis on the face and scalp and on the trunk and extremities. Jones Regulatory Consulting is acting as U.S. agent for this NDA on behalf of LEO Pharma AS.

## 2 MATERIAL REVIEWED

- Draft PICATO gel (ingenol mebutate) Patient Package Insert (PPI) received on March 31, 2011 and further revised by the Applicant on November 7, 2011, revised by the Review Division and provided to DMPP on November 11, 2011.
- Draft PICATO gel (ingenol mebutate) Instructions for Use (IFU) received on November 7, 2011 and provided to DMPP on November 10, 2011.
- Draft PICATO gel (ingenol mebutate) Prescribing Information (PI) received March 31, 2011, revised by the Review Division and provided to DMPP on November 10, 2011.
- Approved ZYCLARA (imiquimod) cream 3.75% and 2.5% (NDA 22-483) comparator labeling, dated September 29, 2011.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI and IFUs the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFUs documents using the Verdana font, size 11.

In our review of the PPI and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFUs are consistent with the prescribing information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFUs are consistent with the approved comparator labeling where applicable.
- The enclosed IFU review comments are collaborative DMPP and DMEPA comments.

#### **4 DISCUSSION**

During the review cycle DMPP learned that the Applicant proposed to include figures on the flap of the product cartons, to instruct patients how to correctly apply PICATO gel. Based on discussions between DMPP, DMEPA, and DDDP, it was decided that the figures may be useful; however, if the figures are included on the product cartons, they should also be part of patient labeling. Since there are two different proposed product strengths (0.015 % and 0.05%), which are applied to different parts of the body and used for different lengths of time, DMPP, DMEPA, and DDDP agreed to request that the Applicant develop two separate Instructions for Use, one for each respective product strength. The Instructions for Use are to be approved as part of labeling for PICATO gel. On October 27, 2011, DDDP conveyed comments to the Applicant by email, along with a request for submission of proposed Instructions for Use.

#### **5 CONCLUSIONS**

The PPI and IFUs are acceptable with our recommended changes.

#### **6 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI and IFUs are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFUs.

Please let us know if you have any questions.

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/s/  
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SHARON R MILLS  
11/21/2011

BARBARA A FULLER  
11/21/2011

LASHAWN M GRIFFITHS  
11/22/2011

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

**DATE:** September 30, 2011

**TO:** J. Paul Phillips, Regulatory Project Manager  
Joanna Ku, M.D., Medical Officer  
Division of Dermatologic and Dental Drug Products

**FROM:** Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Lauren Iacono-Connors, Ph.D.  
Team Leader (Acting)  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Jean Mulinde, M.D.  
Branch Chief (Acting)  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections.

**NDA:** 202833

**APPLICANT:** Leo Pharma A/S

**DRUG:** Ingenol mebutate Gel, .015% and 0.05%

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Treatment of actinic keratoses

**CONSULTATION REQUEST DATE:** April 19, 2011

**DIVISION ACTION GOAL DATE:** January 17, 2012

PDUFA DATE: January 25, 2012

**I. BACKGROUND:**

The Applicant submitted this application for the use of Ingenol mebutate Gel, 0.015% and 0.05% to support an indication for the treatment of actinic keratoses. The pivotal studies, Protocol #s PEP005-025, entitled "A Multi-center, Randomized, Parallel Group, Double-blind, Vehicle-controlled Study to Evaluate the Efficacy and Safety of PEP005 (ingenol mebutate) Gel, 0.015% in Patients with Actinic Keratoses on the Head (Face or Scalp)" and PEP005-028, entitled "A Multi-center, Randomized, Parallel-group, Double-blind, Vehicle-controlled Study to Evaluate the Efficacy and Safety of PEP005 (ingenol mebutate) Gel, 0.05%, In Patients with Actinic Keratoses on Non-Head Locations" were submitted in support of the indication.

The conduct of Protocols PEP005-025 and PEP005-028 were inspected. Protocol PEP005-025 was a double-blind, vehicle-controlled study to determine the safety and efficacy of the test article in the treatment of actinic keratoses (AK) lesions on the head. Protocol PEP005-028 was of similar design; however, it assessed the safety and efficacy of the test article in the treatment of AK lesions in non-head locations.

The primary efficacy endpoint for both protocols was the complete clearance rate of AK lesions at Day 57 with no clinically visible AK lesions in the selected treatment area.

These two Clinical Investigator (CI) sites were selected because of the large number of subjects enrolled and the high treatment effect. One site represented the study of the head with the other representing the study of the rest of the body. The sponsor, Leo Pharma A/S, was also inspected because the drug is a New Molecular Entity (NME).

**II. RESULTS (by Site):**

<b>Name of CI, Location</b>	<b>Protocol #/ # of Subjects/</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Site # 06 Karl G. Heine, M.D. Solutions...A Clinical Trial Company, LLC 880 Seven Hills Drive, Suite 150 Henderson, NV 89052-4380	PEP005-025/ 16/	27 Jun-8 Jul 2011	VAI.
Site #62 Suzanne Bruce, M.D. Suzanne Bruce and Associates, PA The Center for Skin Research 1900 St. James Place, Suite 650 Houston, TX 77056	PEP005-028/ 16/	15-23 Aug 2011	NAI. Pending final classification.
Leo Pharma (sponsor) Industriparken, 2750 Ballerup, Denmark.	PEP005-025 and PEP005-028/	11-15 Jul 2011	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Site # 06

Karl G. Heine, M.D.

Solutions...A Clinical Trial Company, LLC

880 Seven Hills Drive, Suite 150

Henderson, NV 89052-4380

**a. What was inspected:** At this site, 23 subjects were screened and 16 completed the study. The records of eight enrolled subjects were reviewed. The records reviewed included, but were not limited to, randomization, ECGs, vital signs, number, location and photographic documentation of skin lesions, concomitant medications, medical histories, and test article storage conditions and accountability.

**b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Observations included, but were not necessarily limited to, the following:

- Subject 001 met an exclusion criterion by taking methotrexate at the screening visit but remained in the study.
- Subjects 001, 004, 006, 010, 012, 014, 017, and 023 had their Fitzpatrick skin type determined by the study coordinator rather than the clinical investigator, a violation of the protocol
- Subjects 001, 014, 017, and 023 did not have screening photographs delineating the treatment area, a protocol violation
- Subjects 001, 004, 010, 012 and 014 had baseline photographs that did not include photographs where the treatment areas were marked and labeled, a protocol violation.
- Subjects 004, 006, 012, and 014 had study transparencies that did not map and label at least three anatomical landmarks in the vicinity of the selected treatment area. Transparencies for these four subjects noted only two anatomical landmarks each, a protocol violation.
- Subjects 001, 004, 006, 010, 012, 014, 017, and 023 had study transparencies in which none of the selected lesions were numerically designated, a protocol violation.
- Subject 010 was randomized to the study and received study medication prior to an evaluation of the subject's AST and LDH levels, a protocol violation.
- Subject 001 was taking methotrexate and using Clobex 0.05% shampoo, Clobex, 0.05% spray, Nizoral 2% shampoo, and 2% Nizoral lotion, but these concomitant medications were not listed in the CRFs as required by protocol.
- Subject 004 was treated with Altanax ointment but this concomitant medication was not listed in the CRF as required by protocol.

- Subject 004 was treated with lidocaine HCl 1% during the study but this concomitant medication was not listed in the CRF as required by protocol.
- Subject 001 had Charcot-Marie-Tooth polyneuropathy; however, this medical condition was not reported in the CRF as required by protocol.

OSI Reviewer's Comment:

The review division medical officer, after extensive discussion regarding missing photographs/transparencies, advised that they would still consider endpoint data usable because the primary efficacy endpoint was based on an objective count of the complete clearance of lesions; because the determination of clearance of such lesions could be easily made; because existing clinical notes described the location of the treatment area and the presence/absence of lesions; and because the drop-out rate was less than 4% whereas one might expect a greater drop-out in the vehicle arm if the study were blinded. Other deviations noted above appear to be isolated in nature and unlikely to significantly impact primary safety or efficacy analyses, or to compromise the rights, safety, or welfare of study subjects.

**Additional notable inspectional observations:**

During the inspection, based on site staff comments, it was revealed that staff believed that they knew which treatment subjects were taking based on occurrence of local site reactions (i.e. that subject's receiving active drug developed reactions). Both Dr. Heine and his study coordinator confirmed this observation in discussion with FDA's investigator.

**c. Assessment of data integrity:**

Though OSI cannot determine the extent of unblinding at this or other sites, the review division may wish to query the sponsor regarding the extent to which sites believed they were able to ascertain treatment arm based on local skin reactions and if broadly present consider the impact of such functional unblinding may have had on safety and efficacy analyses.

The review division may also wish to consider excluding data from Subject 001 who took an excluded medication (methotrexate) from per protocol analyses. Except as noted above, the study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

2. Site #62

Suzanne Bruce, M.D.  
Suzanne Bruce and Associates, PA  
The Center for Skin Research  
1900 St. James Place, Suite 650  
Houston, TX 77056

- a. What was inspected:** At this site, 16 subjects were enrolled in the study. The records of all 16 enrolled subjects were reviewed. Records reviewed included, but were not limited to, all informed consent documents, screening logs, medical/dermatologic histories, inclusion/exclusion criteria, subject diaries, source documents, laboratory results, photographs, Case Report Forms (CRFs), visit schedules, adverse events, concomitant medications, drug accountability, and sponsor correspondence

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

3. Leo Pharma (sponsor)  
Industriparken, 2750  
Ballerup, Denmark.

- a. What was inspected:** Review included, but was not limited to, the following parameters: sponsor organization and oversight, selection and monitoring of clinical investigators, site monitoring practices, data collection and handling, test article accountability, primary efficacy endpoints, adverse event evaluation and reporting, delegation of responsibilities, and contractual agreements. The inspector also compared selected subject CRFs with the firm's data listings.
- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. The observations included the sponsor's failure to ensure proper monitoring of the study and to ensure that the study was conducted in accordance with the protocol and/or investigational plan. The Standard Operating procedure (SOP) for conducting monitoring visits stated that source documentation was to be checked for 100% of enrolled subjects and for 100% of the data entered into the Case Report Forms (CRFs); however, for Interim Monitoring Visits (IMVs) 1-4 at Dr. Bruce's site, not all available CRFs and accompanying source documents were reviewed. Per the same SOP, follow-up correspondence to the monitoring visit was to be sent to the clinical investigator within two weeks of conclusion of the visit. For IMVs 1 and 2 at Dr. Bruce's site, these letters were issued more than two weeks after the conclusion of the visits. The sponsor responded satisfactorily to the observations listed on the Form FDA 483 in a letter dated August 1, 2011.
- c. Assessment of data integrity:** The observations noted above appear to be isolated in nature and are unlikely to affect primary safety or efficacy analyses in any significant manner. The rights, safety, or welfare of subjects does not appear to have been compromised. With the exception of issues noted above, the studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Heine and Bruce were inspected in support of this NDA. Regulatory violations were noted at Dr. Heine's site though not at Dr. Bruce's site. Dr. Heine noted that he believed study unblinding occurred because of the test article's propensity to induce local site reactions. The review division may wish to query the sponsor regarding the extent to which such unblinding may have occurred and resulted in biased interpretation of the study results. Dr. Heine's site did not perform all protocol-required photography, nor were appropriate transparencies generated marking

the number and site of lesions to be treated. These deviations were discussed at length with the reviewing medical officer who determined that the lack of completion of some photographs and transparencies did not render the data unusable for the reasons cited above. Other deficiencies noted at Dr. Heine's site appear to have been isolated in nature and unlikely to affect the primary safety or efficacy analyses or to affect the rights safety, or welfare of subjects. Overall, other than the issues noted above, the studies conducted at these clinical sites appear to have been conducted adequately, and the data generated appear acceptable in support of the respective indication.

A sponsor inspection of Leo Pharma A/S was also conducted. Regulatory violations included inadequate monitoring at Dr. Bruce's site because of a lack of review of 100% of data entered into the CRFs as required in the firm's SOPs and a delay in the issuance of follow up correspondence after monitoring visits. These observations, however, appear isolated in nature and are unlikely to affect the safety and/or efficacy analyses. Otherwise, the studies appear to have been conducted adequately (other than the issue of potential study unblinding as addressed above), and the data generated appear acceptable in support of the respective indication.

**Note:** The observations noted above for Dr. Bruce are based on the preliminary communications provided by the FDA field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIR.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

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Jean Mulinde, M.D.  
Branch Chief (Acting)  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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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.**  
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/s/  
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ROY A BLAY  
09/30/2011

LAUREN C IACONO-CONNORS  
10/03/2011

JEAN M MULINDE  
10/03/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 202833	NDA Supplement #:S- 000	Efficacy Supplement Type SE- n/a
Proprietary Name: (undetermined at time of filing) Established/Proper Name: ingenol mebutate Dosage Form: Gel Strengths: 0.015% and 0.05%		
Applicant: Leo Pharma A/S Agent for Applicant (if applicable): Cheri Jones		
Date of Application: 03/25/2011 Date of Receipt: 03/25/2011 Date clock started after UN: n/a		
PDUFA Goal Date: 01/25/2012		Action Goal Date (if different): 01/17/2012
Filing Date: 05/24/2011		Date of Filing Meeting: 05/13/2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) : Type 1		
Proposed indication(s): Topical treatment of actinic keratosis on the face and scalp and on the trunk and extremities.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ): n/a				
List referenced IND Number(s): IND 070114; IND 070155				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			Originally listed as Priority Review; correction made so date is correct
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			Corrected to remove "PEP005" leaving only the established name, dosage form, and strength.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Corrected from priority to standard. Added the proper Division Classification codes.
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				n/a
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				n/a
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Dated 2/4/2011

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at:  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			Section 1.3.5.3
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			U.S. Agent signed electronically
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			Some sites are new and do not yet have registration numbers.
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			Not in original NDA submission; requested in acknowledgement letter and received as amendment on 4/5/11
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with				

authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FDCA 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...”</i>	X			Incorrect signatures in original submission; 5/2/11 IR requesting that both foreign applicant signed <u>and</u> U.S. Agent sign document. Corrected certificate received in amendment on 5/4/11
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<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			Scheduled to go to PeRC on 8/10/11

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Full waiver request
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			Full waiver request
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			Section 1.9.1
<b>BPCA (NDAs/NDA efficacy supplements only):</b> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Separate submission
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Consult dated 5/2/11
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Consult dated 5/2/11
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Consult dated 5/2/11
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	X			QT consult sent on 5/13/11
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 06/03/2009	X			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 12/15/2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> Clinical—06/02/2008; 05/13/2009 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			Nonclinical SPA: Exec CAC minutes faxed on 07/12/2006

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** May 13, 2011

**NDA #:** 202833

**PROPRIETARY NAME:** (undetermined at time of filing)

**ESTABLISHED/PROPER NAME:** ingenol mebutate

**DOSAGE FORM/STRENGTH:** Gel, 0.015% and 0.05%

**APPLICANT:** Leo Pharma

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of AK on face & scalp and trunk & extremities

**BACKGROUND:** The Agency has held two Guidance, one Pre-Phase 2, one End-of-Phase 2, one CMC, and one Pre-NDA meeting with the sponsor. The Agency has provided comments for both a Clinical and Nonclinical SPA, as well as ten advice/ information request letters.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Paul Phillips	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	Jill Lindstrom		Y
Clinical	Reviewer:	Joanna Ku	Y
	TL:	Jill Lindstrom	Y
Clinical Pharmacology	Reviewer:	Abi Adebawale	Y
	TL:	Donny Tran	Y
Biostatistics	Reviewer:	Yuqing Tang/ Carin Kim	Y
	TL:	Mohamed Alosh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jiaqin Yao	Y

	TL:	Barbara Hill	Y
Product Quality (CMC)	Reviewer:	Nina Ni	Y
	TL:	Shulin Ding	Y
CMC Biopharm	Reviewer:	Taposh Gosh	N
	TL:	Patrick Marroum	N
Facility Review/Inspection (DMPQ)	Reviewer:	Shawn Gould	Y
	TL:	Tara Gooen	N
OSE/DMEPA (proprietary name)	Reviewer:	Lubna Merchant	N
	TL:	Melina Griffis	N
OSE/DRISK (PPI)	Reviewer:	Sharon Mills	N
	TL:	Barbara Fuller	N

Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	Y
	TL:	Tejashri Purohit-Sheth	N
DDMAC	Reviewer:	Lynn Panholzer	N
	TL:	Sheetal Patel	N
Other attendees	Julie Beitz, M.D., Director, ODEIII Giuseppe Randazzo, M.S., Regulatory, ODEIII		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>If no, explain:</b>	
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> Application in order</p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>Comments:</b> No review issues, but some information requests for the 74-day letter.</p>	
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: There are multiple other drugs for AK (i.e. not first in class) and the application does not raise significant safety or efficacy concerns.
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b> No review issues, but some information requests for the 74-day letter.	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b> No review issues, but some information requests for the 74-day letter.	<input type="checkbox"/> Review issues for 74-day letter
<b><u>Environmental Assessment</u></b>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>If no</b> , was a complete EA submitted?	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>If EA submitted</b> , consulted to EA officer (OPS)?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b> CMC sent consult (5/13/11) for EA review	

even though categorical exclusion was requested.	
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p>Comments: CMC RPM submitted EERs</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Julie Beitz, M.D., Director, ODEIII</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p>Comments: Filing Mtg. 5/13/11                      Discipline reviews due 11/18/11  Mid-Cycle Mtg. 9/6/11                      Clinical review due 11/29/11  Wrap-Up Mtg. 11/14/11                      CDTL review due 12/6/11  DD summary review due 12/27/11  OD summary review due 1/17/12</p> <p>Target Sign-off 1/17/12</p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.

	<p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

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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.**  
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/s/  
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J P PHILLIPS  
05/31/2011

BARBARA J GOULD  
05/31/2011

**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Medication Error Prevention and Risk Management**

Date: May 16, 2011

Application Type/Number: NDA 202833

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

Through: Melina Griffis, RPh, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Lubna Merchant, M.S., Pharm.D, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name and Strengths: (b) (4) (Ingenol Mebutate) Gel, 0.015% and 0.05%.

Applicant/sponsor: Leo Pharma.

OSE RCM #: 2011-1233

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4. CONCLUSION AND RECOMMENDATIONS.....	3
4.1 Comments to the Applicant.....	3

## 1. INTRODUCTION

This review evaluates the proposed labels and labeling for (b) (4) (Ingenol Mebutate) Gel (NDA 202833) for areas of vulnerabilities that could lead to medication errors. The proposed proprietary name is evaluated under separate review (OSE # 2011-1192).

## 2. METHODS AND MATERIALS

Using Failure Mode and Effects Analysis (FMEA)<sup>1</sup>, the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the container labels, carton labeling and insert labeling. This review focuses on labels and labeling submitted as part of the March 31, 2011 original NDA submission. See Appendix A-B for images of the proposed container labels and carton labeling.

## 3. RESULTS

The following section describes the results of our label and labeling review.

### 3.1 LABELS AND LABELING

Our evaluation finds the proposed label and labeling noted the following deficiencies:

- The labels and labeling for the two proposed strengths appear similar
- Prominence of the company name and distributor information on the container label
- Absence of route of administration on the container labels
- Decreased readability of the carton labeling
- The graphic on the bottom right side of the top panel is very distracting

We provide labeling recommendations in section 4 to address these deficiencies.

## 4. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations in Section 4.1 Comments to the Applicant for the container labels and carton labeling. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Janet Anderson at 301-796-0675.

### 4.1 COMMENTS TO THE APPLICANT:

#### A. Proposed Container Label (0.015% and 0.05%)

1. The proposed labels for the two strengths utilize similar colors (aqua green and blue) on the principal display panel making it difficult to differentiate between the different strengths. To avoid section errors, revise the labels to ensure that the color selected to highlight each strength presentation is unique and different from each other.

2. Increase the prominence of the strength and relocate it to appear after the established name as shown below:

TRADEMARK<sup>TM</sup>  
(Ingenol Mebutate) Gel  
0.05%

3. Revise the proprietary name presentation so that it is presented in title case and not in capital letters
4. Remove the RX Only statement from the box to decrease its prominence.
5. Revise the proprietary name presentation so that the symbol ‘TM’ is superscripted as follows: TRADEMARK<sup>TM</sup>
6. The company name and distributor information is more prominent than the established name. Decrease the size of the company name and distributor information.
7. Add a statement “For Topical Use on Face and Scalp Only” on the principal display panel the 0.015% container label.
8. Add a statement “For Topical Use on Trunk and Extremities Only” on the principal display panel the 0.05% container label.

**B. Proposed Carton Labeling (0.015% and 0.05%)**

1. See comment A1, A2, A3, A4, A5
2. The graphic on the bottom right side of the top panel is very distracting and makes the labeling for both strengths appear similar. Delete this graphic.
3. We note the established name is ½ the size of the proprietary name, but it lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
4. Revise the (b) (4) statement as follows “For Topical Use on Face and Scalp Only” for the 0.015% carton labeling and “For Topical Use on Trunk and Extremities Only” for the 0.05% carton labeling. This statement should be more prominent than the (b) (4).
5. Relocate the (b) (4) statement to appear after the route and revise as follows: 2 Unit Dose Tubes each containing 0.47 gm. Present this information in unbolded text.
6. Delete the (b) (4) statements that appear above the company logo.
7. Decrease the size of the company logo and relocate it to the side panel.
8. The information on the back panel of the carton labeling is difficult to read, increase the font size and the contrast to increase the readability.

9. Revise the dosage statement on the back panel to read as follows:

**For the 0.015 %**

Dosage: Apply one tube per day to the treatment area on the face and scalp. See insert for complete information.

**For the 0.05 %**

Dosage: Apply one tube per day to the treatment area on the trunk and extremities. See insert for complete information.

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

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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.**  
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/s/  
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LUBNA A MERCHANT  
05/16/2011

MELINA N GRIFFIS  
05/16/2011

CAROL A HOLQUIST  
05/16/2011

# **REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW**

**Application:** NDA 202833

**Name of Drug:** (ingenol mebutate) Gel, 0.015% and 0.05%

**Applicant:** Leo Pharma

## **Labeling Reviewed**

**Submission Date:** 03/25/2011

**Receipt Date:** 03/25/2011

## **Background and Summary Description**

This New Drug Application (NDA) provides information in support of the use of a New Molecular Entity (NME), ingenol mebutate, to be used for the topical treatment of actinic keratosis on the face and scalp (0.015%) and on the trunk and extremities (0.05%). The sponsor has included proposed labeling in the PLR format.

## **Review**

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages of the Selected Requirements for Prescribing Information (SRPI) with an "X."

The labeling issues are also described below:

1. The required highlights limitation statement (i.e. "These highlights do not include...") is duplicated at the beginning of the Highlights section. One of the occurrences should be deleted.
2. The required adverse reactions reporting statement (i.e. "To report SUSPECTED ADVERSE REACTIONS...") is duplicated at the end of the Highlights section. One of the occurrences should be deleted.
3. Capitalize "Full Prescribing Information" in the asterisk statement at the end of the Contents.
4. Remove the subsection 17.4 (FDA approved patient labeling) from section 17 (Patient Counseling Information) in the Contents. The patient labeling is appended to

label as separate document, and is not a subsection of section 17 (see labeling comment #8 below).

5. Add an “s” to the title of section 1 “INDICATIONS AND USAGE” where it appears in both the Contents and the Full Prescribing Information (FPI).
6. Under section 6 (Adverse Reactions) of the FPI, revise the standard disclaimer statement to read verbatim as follows:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
7. Under section 17 (Patient Counseling Information) on the line immediately following the section header, revise the reference to patient approved labeling to read as follows:

“See FDA-approved patient labeling (Patient Information)”
8. Remove the subsection number 17.4 from the header for patient labeling (currently under section 17) and start patient labeling on a new page. This information is not included as a subsection to section 17, but rather is a stand alone piece of labeling that is appended to the package insert.

### **Recommendations**

All labeling issues identified on the following pages with an “X” and described above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by June 21, 2011. The resubmitted labeling will be used for further labeling discussions.

J. Paul Phillips, MS	05/10/2011
Regulatory Project Manager	Date
Barbara J. Gould, M.B.A.H.C.M.	05/25/2011
Chief, Project Management Staff	Date

## Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

### Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)

- |  |
|--|
| <ul style="list-style-type: none"><li>• <b>Patient Counseling Information Statement</b> (required statement)</li></ul> |
| <ul style="list-style-type: none"><li>• <b>Revision Date</b> (required information)</li></ul>                          |

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

**Contents: Table of Contents (TOC)**

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

### **Full Prescribing Information (FPI)**

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

This section is required and cannot be omitted.

Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/  
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J P PHILLIPS  
05/26/2011

BARBARA J GOULD  
05/26/2011