

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202833Orig1s000**

**CHEMISTRY REVIEW(S)**

**MEMORANDUM**

**Date:** January 23, 2012

**To:** NDA 202-833

**From:** Terrance Ocheltree, Ph.D., R.Ph.  
Director  
Division of New Drug Quality Assessment II  
ONDQA

**Subject:** Tertiary review of ONDQA recommendation for NDA 202-833, ingenol mebutate gel, 0.05% and 0.015%, Picato™.

I have assessed the ONDQA reviews of NDA 202-833 by Nina Ni, Ph.D., Tapash Ghosh, Ph.D. and Shulin Ding, Ph.D. The initial ONDQA CMC review was entered into DARRTS on November 18, 2011, with a recommendation for a Complete Response due to an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites acceptability and pending labeling issues. A second CMC review was entered into DARRTS on January 23, 2012 by Dr. Ding updating the status of the recommendation from the Office of Compliance. On January 20, 2012 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES.

All CMC related label/labeling issues were satisfactorily resolved through amendments dated Jan. 12, 2012 (labels) and Jan. 13, 2013 (package insert).

The ONDQA Biopharmaceutics review was entered into DARRTS on November 11, 2011. The review focused on the evaluation of the proposed in vitro release method and acceptance of the bridging results from the study conducted to link the formulations manufactured at different stages of development and different sites. Dr. Ghosh determined that the in vitro release data supports the use of both proposed drug product manufacturing sites (DPT Laboratories Ltd., US (DPT) and LEO Laboratories Ltd. (LEO) in Ireland).

The drug substance, manufactured by (b) (4)  
(b) (4) Therefore, the (b) (4)  
recommended storage condition (b) (4)  
A (b) (4) months retest period of is granted based on the submitted stability data.

The proposed drug products, Picato (ingenol mebutate) gel, 0.015% and 0.05% are clear and colorless gel packaged in 1 mL (b) (4) laminated aluminum tubes with HDPE screw caps and a fill weight of 0.47 g. The proposed dose is approximately 0.25 g of gel. Therefore, each tube contains an overfill and should be discarded after a single use.

A method validation was requested by Dr. Ni. On December 13, 2011, Mr. James Allgire, Team Leader, Division of Pharmaceutical Analysis, CDER, FDA entered a summary report, including a cover memo, into DARRTS. The reports states that method AP000459 for ingenol mebutate: Identification, Assay and determination of Organic Impurities by HPLC was acceptable for quality

control and regulatory purposes, but that method AP000449 for PEP005 (Ingenol Mebutate) Gel: Identification, Assay and Determination of Organic Impurities of Ingenol Mebutate by UPLC was not acceptable for the Organic Impurities portion. Comments were generated and sent to the Applicant. The Applicant submitted response on December 12, 2011 and January 10, 2012. Based on these responses, the revised method AP000449, PEP005 (INGENOL MEBUTATE) GEL was determined to be acceptable for quality control and regulatory purposes, as indicated by a memo entered into DARRTS on January 12, 2012, by Mr. Allgire.

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommendation of a drug product shelf life of 24 months for the proposed commercial product when it is stored [REDACTED] <sup>(b) (4)</sup> Excursions are permitted from 0–15 °C (32–59 °F).

Secondary review of the CMC reviews was performed by Moo-Jhong Rhee, Ph.D.

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/s/  
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TERRANCE W OCHELTRIE  
01/23/2012

MEMORANDUM

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

DATE: January 23, 2012  
FROM: Shulin Ding, Ph.D., CMC Lead, DNDQA II/ONDQA  
THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA  
TO: NDA 202-833  
SUBJECT: Addendum to CMC Review #1 for NDA 202-833

In CMC Review #1, dated 11-18-11, this NDA was recommended for “**Not Approval**” due to the following issues:

1. The final recommendation from the Office of Compliance was pending.
2. Label/labeling issues were not satisfactorily resolved.

The issues have been resolved since the filing of CMC Review #1 in DARRTS. An overall “Acceptable” recommendation was issued by the Office of Compliance on Jan. 20, 2012. The FDA CDER Establishment Evaluation Request Summary Report is attached to this memorandum.

Label/labeling issues were satisfactorily resolved through amendments dated Jan. 12, 2012 (labels) and Jan. 13, 2013 (package insert). The final version of carton/container labels agreed upon by the applicant and the Agency is attached to this memorandum.

Additionally, there were two amendments (Dec. 22, 2011 and Jan. 10, 2012) submitted to the NDA to address issues noted by Division of Pharmaceutical Analysis (St. Louis, MO) on the analytical methods during the Method Validation process. Although the issues were deemed not critical enough to hold off the NDA when the CMC Review #1 was previously finalized, they were conveyed to the applicant. The applicant responded by updating the method procedures with more information and submitted the updated procedures through the 12/22/11 and 1/10/12 amendments. Division of Pharmaceutical Analysis has reviewed the two amendments and found the updated procedures as revised are acceptable for quality control and regulatory purpose (See Method Validation Report Reviews dated Dec. 13, 2011 and Jan. 12, 2012).

Therefore, from the ONDQA perspective, the **NDA is recommended for approval.**

\*A typo is noted in the statement of excursion temperatures in CMC Review #1 (pages 10 and 153). It should be 0°-15°C (32°-59°F) instead of 2-15°C (59-86°F).

**Attachments:**

- 1. EER reports**
- 2. Carton and container labels**

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 202833/000	<b>Sponsor:</b>	LEO PHARMA AS
<b>Org. Code:</b>	540		481 HAVEN POINT DR
<b>Priority:</b>	1		TREASURE ISLAND, FL 33708
<b>Stamp Date:</b>	25-MAR-2011	<b>Brand Name:</b>	(ingenol mebutate) Gel 0.015% and 0.05%
<b>PDUFA Date:</b>	25-JAN-2012	<b>Estab. Name:</b>	(ingenol mebutate) Gel 0.015% and 0.05%
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	28-NOV-2011	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
			001; GEL; INGENOL MEBUTATE; .015%
			002; GEL; INGENOL MEBUTATE; .05%
<b>FDA Contacts:</b>	J. DAVID	Project Manager	301-796-4247
	N. NI	Review Chemist	
	S. DING	Team Leader	301-796-1349

---

Overall Recommendation: ACCEPTABLE on 20-JAN-2012 by D. SMITH ()

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Establishment: (b) (4)

DMF No:

Responsibilities:

Profile:

Last Milestone:

Milestone Date:

Decision:

Reason:

---

Establishment: CFN: 1628114 FEI: 1000117884

DPT LABORATORIES INC  
200/307 E JOSEPHINE STREET  
SAN ANTONIO, TX 78215

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Profile: OINTMENT, NONSTERILE (INCLUDES CREAM, JELLY, PASTE) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAY-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

---

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: 3005023061 FEI: 3005023061  
DPT LABORATORIES INC  
3300 RESEARCH PLAZA BROOKS CITY BASE  
SAN ANTONIO, TX 78235

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE RELEASE TESTER

**Profile:** CONTROL TESTING LABORATORIES "ALSO" (DRUGS) OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 26-MAY-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** (b) (4)

**DMF No:**

**Responsibilities:**

**Profile:**

**Last Milestone:**

**Milestone Date:**

**Decision:**

**Reason:**

---

**Establishment:** CFN: 0611012 FEI: 3002807468  
LEO LABORATORIES, LTD.  
285 CASHEL RD  
DUBLIN, IRELAND

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Profile:** OINTMENT, NONSTERILE (INCLUDES CREAM, JELLY, PASTE) OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 31-OCT-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: 9610697 FEI: 3002807496  
LEO PHARMA A/S  
INDUSTRI PARKEN 55  
BALLERUP, . DENMARK

**DMF No:** **ADA:**

**Responsibilities:** DRUG SUBSTANCE STABILITY TESTER  
FINISHED DOSAGE STABILITY TESTER

**Profile:** CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 20-JAN-2012

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** (b) (4)

**DMF No:**

**Responsibilities:**

**Profile:**

**Last Milestone:**

**Milestone Date:**

**Decision:**

**Reason:**

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/s/  
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SHULIN DING  
01/23/2012

MOO JHONG RHEE  
01/23/2012  
Chief, Branch IV



Date: January 12, 2012

To: Shulin Ding, Ph.D., CMC Reviewer, ONDQA/DNDQAI

From: James Allgire, Chemist, Division of Pharmaceutical Analysis (HFD-920)

Subject: Addendum to Method Validation for NDA 202833  
Ingenol mebutate gel 0.015%  
LEO Pharma A/S

The revised method received from Shulin Ding, Ph.D., ONDQA on 1/10/2012 for AP000449, PEP005 (INGENOL MEBUTATE) GEL that is dated 10-Jan-2012 is acceptable for quality control and regulatory purposes.

The revision included adding the UV spectrum of (b) (4) and giving a RRT range.

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/s/  
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JAMES F ALLGIRE  
01/12/2012

# **NDA 202-833**

**Picato (ingenol mebutate) Gel  
0.05% and 0.015%**

**LEO Pharma A/S**

**Nina Ni, Ph. D.**

**Review Chemist**

**Branch IV**

**Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment**

**CMC REVIEW**

**For the Division of Dermatology & Dental**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 202-833
2. REVIEW #: 1
3. REVIEW DATE: 11/18/2011
4. REVIEWER: Nina Ni, Ph.D.
5. PREVIOUS DOCUMENTS:
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	03/31/2011
Correspondence (C): 0000	
Amendment (BC): 0003	04/05/2011
Amendment (BC): 0004	04/29/2011
Amendment (BC): 0008	06/21/2011
Amendment (BC): 0009	06/27/2011
Amendment (BC): 0010	07/06/2011
Amendment (BC): 0011	07/25/2011
Amendment (BC): 0015	09/06/2011
Amendment (BC): 0017	09/16/2011
Amendment (BC): 0018	09/30/2011
Amendment (BC): 0021	10/21/2011
Amendment (BC): 0024	11/14/2011

7. NAME & ADDRESS OF APPLICANT:

Name: LEO Pharma A/S  
Address: Industriparken 55, DK-2750 Ballerup, Denmark  
Representative: Cheri Jones, US Agent  
Telephone: +45 7226 3288

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Picato<sup>®</sup> Gel
- b) Non-Proprietary Name (USAN): Ingenol Mebutate
- c) Code Name/# (ONDQA only): PEP005
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1

## CMC Review Data Sheet

- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Topical treatment of actinic keratosis on the face and scalp and on the trunk and extremities.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 0.015% and 0.05%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Ingenol mebutate

CHEMICAL NAME: 2-Butenoic acid, 2-methyl-, (1aR,2S,5R,5aS,6S,8aS,9R,10aR)-1a,2,5,5a,6,9,10,10a-octahydro-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1H-2,8-methanocyclopenta[a]cyclopropa[e]cyclodecen-6-yl ester, (2Z)- (Chemical Abstracts Index Name)  
or

(1aR,2S,5R,5aS,6S,8aS,9R,10aR)-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1H-2,8-methanocyclopenta[a]cyclopropa[e]cyclodecen-6-yl (2Z)-2-methylbut-2-enoate

STRUCTURAL FORMULA:

CMC Review Data Sheet

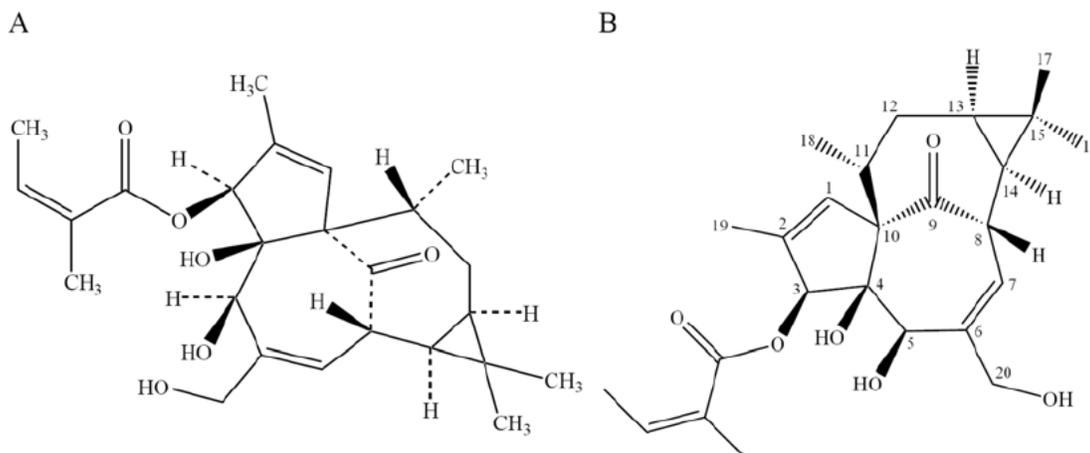


Figure 1A presents the molecular structure of ingenol mebutate (as adopted by USAN). Figure 1B is an alternative presentation of the same molecule. As the depiction and numbering used in Figure 1B is commonly used in the literature, this convention is used in the current submission for ingenol mebutate and related impurities.

MOLECULAR FORMULA:  $C_{25}H_{34}O_6$   
 MOLECULAR WEIGHT: 430.53 g/mol  
 CAS NUMBER: [75567-37-2]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
							(b) (4)

<sup>1</sup> Action codes for DMF Table:  
 1 – DMF Reviewed.  
 Other codes indicate why the DMF was not reviewed, as follows:  
 2 – Type 1 DMF  
 3 – Reviewed previously and no revision since last review

CMC Review Data Sheet

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,114	

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	Acceptable	11/11/2011	Tapash Ghosh, Ph. D.
LNC	NA		
Methods Validation	Submitted		
DMEPA	NA		
EA	Acceptable	09/15/2011	Raanan A. Bloom, Ph. D.
Microbiology	NA		

# The CMC Review for NDA 202-833

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has not made a final recommendation for the facilities involved in this NDA.

Issues on label/labeling also have not been resolved.

Therefore, from the ONDQA's perspective, this NDA is not recommended for approval in its present form per 21 CFR 314.125 (b)(6)&(13) until all the pending issues are satisfactorily resolved.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

The proposed drug substance, ingenol mebutate, is a small molecule and a new molecular entity which is extracted/purified from the <sup>(b) (4)</sup> of plant Euphorbia peplus L. (E. peplus) cultivated in Australia. <sup>(b) (4)</sup>

The subsequent manufacturing process consists of the following steps: <sup>(b) (4)</sup>

## CMC Assessment Section

(b) (4)

During these manufacturing steps, adequate in-process and controls are in place for each intermediate to provide assurance for the purity and batch to batch consistency. The final crystalline drug substance was subject to structural elucidation using elemental analysis (EA) and a combination of spectroscopic techniques including infrared (IR), ultraviolet (UV), nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), and single crystal x-ray crystallography.

The drug substance is controlled by a proposed specification, which is deemed adequate for assuring the identity, strength, purity, and quality of the drug substance.

Satisfactory batch data based on the specification were provided for the drug substance, which were used during the drug development including toxicological studies, phase 2 and phase 3 clinical trials, and stability studies. Also submitted were the batch data used in the process validation and stability studies.

The drug substance is [REDACTED] (b) (4)  
The proposed retest period of [REDACTED] (b) (4) is granted based on the submitted stability data.

## (2) Drug Product

The proposed drug products, Picato (ingenol mebutate) gel, 0.015% and 0.05% are clear and colorless gel packaged in [REDACTED] (b) (4) laminated aluminum tubes with HDPE screw caps. The capacity of the tube is 1 mL and the fill weight is 0.47 g. However, the deliverable amount for a single dose is approximately 0.25 g. Therefore, the tube should be discarded after a single use.

The to-be-marketed formulation is the same as those used in all clinical trials and registration stability batches. The formulation consists of ingenol mebutate, isopropyl alcohol, hydroxyethyl cellulose, benzyl alcohol, citric acid monohydrate, sodium citrate, and water. All excipients are compendial grades.

The commercial drug product is to be manufactured through the following manufacturing steps: [REDACTED] (b) (4)

The proposed commercial manufacturing scale is [REDACTED] (b) (4) and its manufacturing processes are relatively straightforward and well developed. Adequate in-process controls are also in place. Two commercial manufacturing sites, DPT Laboratories in Texas and Leo Laboratories in Ireland, are proposed, and the same manufacturing processes are used at both sites. DPT manufactured the phase 3 clinical batches as well as the registration stability batches, while Leo has not manufactured any clinical batches. Therefore, Leo's batches were bridged to DPT's phase 3 clinical batches through an in-vitro drug release

## CMC Assessment Section

study. The in-vitro study was reviewed and found adequate by the Biopharm Reviewer, Tapash Ghosh, Ph. D.

The proposed drug product specification includes description/appearance, identification (UV spectrum and UPLC retention time), ingenol mebutate assay (UPLC), organic impurities (UPLC), benzyl alcohol assay (HPLC), pH (USP <791>), viscosity, minimum fill (USP <755>), and microbial limits (USP <61> and USP <62>). The specification is deemed adequately justified for assuring the identity, strength, purity, and quality of drug product. All non compendial analytical methods were also adequately validated and considered to be suitable for their intended use.

All registration batches met the proposed specification.

Stability data (accelerated and long term) are provided for a total of 6 primary stability batches (3 batches of each strength, 0.05% and 0.015%) as well as 12 process validation batches, which consist of 6 batches from each proposed commercial manufacturing site, DPT and LEO. The stability data indicate that the drug product is physically and chemically stable, and based on the real time stability data up to 24 months, the proposed expiration dating period of 24 months, when stored (b) (4) excursions permitted to 2 - 15°C (59 - 86°F), is granted.

**B. Description of How the Drug Product is Intended to be Used**

Picato gel, 0.015% topically applies to the affected area once daily for 3 consecutive days for the treatment of actinic keratosis lesions on the face and scalp.

Picato gel, 0.05% topically applies to the affected area once daily for 2 consecutive days for the treatment of actinic keratosis lesions on the trunk and extremities.

**B. Basis for Not-Approval Recommendation**

- 21 CFR 314.125(b)(13)

The Office of Compliance has *not* made a final recommendation for the manufacturing facilities.

- 21 CFR 314.125(b)(6)

Issues on labels and labeling have *not* been resolved yet (see the List of the Deficiencies on p.184).

## CMC Assessment Section

**III. Administrative****A. Reviewer's Signature:**

*(See appended electronic signature page)*

Nina Ni, Ph.D., CMC Reviewer, Branch IV, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, ONDQA

**C. CC Block:** entered electronically in DFS

Shulin Ding, Ph.D., CMC Lead, Branch IV, ONDQA

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/s/  
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NINA NI  
11/18/2011

MOO JHONG RHEE  
11/18/2011  
Chief, Branch IV

Initial Quality Assessment  
Branch IV  
Division of New Drug Quality Assessment II

**OND Division:** Division of Dermatology and Dental Products  
**NDA:** 202833  
**Applicant:** Leo Pharma A/S  
**Stamp Date:** March 31, 2011  
**PDUFA Date:** Jan. 25, 2012  
**Trademark:** Picato  
**Established Name:** Ingenol Mebutate  
**Dosage Form:** Gel  
**Route of Administration:** Topical  
**Indication:** Actinic keratosis on the face and scalp and on the trunk and extremities

**CMC Lead:** Shulin Ding

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

**Summary and Critical Issues:**

A. Summary

Leo Pharma A/S is submitting a 505(b)(1) New Drug Application (NDA) for the prescription use of Picato (ingenol mebutate). Two strengths are proposed: 0.015% for the treatment of actinic keratosis on the face and scalp and 0.05% for actinic keratosis on the trunk and extremities.

The proposed drug substance, ingenol mebutate, is a small molecule and a new molecular entity extracted/purified from the <sup>(b) (4)</sup> of plant *Euphorbia peplus* L. (*E. peplus*) cultivated in Australia. <sup>(b) (4)</sup>

The subsequent drug substance manufacturing process consists of the following steps:

<sup>(b) (4)</sup>

[REDACTED] (b) (4)

The proposed retest period for drug substance is [REDACTED] (b) (4)

The proposed drug products, Picato (ingenol mebutate) gel, 0.015% and 0.05% are clear, colorless gel packaged in [REDACTED] (b) (4) aluminum tubes with high-density-polyethylene screw caps. The capacity of the tubes is 1 mL, the fill weight is 0.47 g, and the deliverable is approximately 0.25 g. Each tube should be discarded after one use.

The to-be-marketed formulation is the same formulation used in all clinical trials and registration stability batches. The formulation contains the following excipients: hydroxyethyl cellulose, NF; isopropyl alcohol, USP; benzyl alcohol, USP; citric acid monohydrate, USP, sodium citrate (b) (4) [REDACTED] (b) (4), USP; and purified water, USP. There are no novel excipients. .

The proposed commercial manufacturing scale is (b) (4) . Two commercial drug product sites, DPT Laboratories in Texas and Leo Laboratories in Ireland, are proposed. DPT was the manufacturing site of Phase 3 supplies and registration stability batches. Leo has not manufactured any clinical batches. Leo's batches are bridged to DPT Phase 3 batches through an in-vitro drug release study. The commercial drug product manufacturing process consists of the following steps: [REDACTED] (b) (4)

[REDACTED] The manufacturing process evolved throughout the product development, and in-vitro drug release studies were conducted to bridge different processes.

Stability data provided in the initial submission to support an expiry period of 24 months [REDACTED] (b) (4) include up to 18 months of long term (5°C ) data from 18 batches (9 for each strength), and up to 6 months of accelerated (25°C/60% RH) data from the same 18 batches. Additionally, temperature cycling and photostability studies were conducted to support the storage/handling of the product.

## B. Critical issues for review

### Drug Substance

- Although the Agency agreed in the response to the CMC guidance meeting dated May 24, 2010 that [REDACTED] (b) (4) is the starting material for the manufacture of ingenol mebutate, the adequacy of controls over the manufacturing process of [REDACTED] (b) (4) and its storage/handling will still need to be critically reviewed.
- Manufacturing process information described in Module 3 from starting material onward is not sufficient. Many potentially important process parameters and steps are not identified and described. Neither is there any risk assessment. This is a major issue since

the applicant informed the Agency in the CMC guidance meeting that they did not plan to submit Master Batch Record and Executed Batch Records to the NDA. The records would be available at the sites. By excluding the records from the NDA, process changes may not be reported to the NDA. Due to the reluctance of the applicant to provide Master and Executed Batch Records, and the complexity of the manufacturing process, reviewer's participation in the GMP inspection is highly recommended.

- A comparability protocol is provided for recovering ingenol mebutate from (b) (4). (b) (4) The protocol needs to be critically reviewed and concurrence should be sought from the post-marketing branch supporting HFD 540.

#### Drug Product Manufacturing

- Since Leo site and DPT site use different equipment, and process adjustments have been made because of equipment difference, the reviewer should evaluate whether the batches made by these two sites have the same stability/impurity profile.

- The significance of the process difference between (b) (4) (b) (4)

#### Drug Product Stability and Post-approval Stability Protocol

- The applicant proposes to (b) (4) (b) (4) The proposal needs to be carefully reviewed because the limited data provided seem to suggest batch-to-batch inconsistency.
- The proposed language is inconsistent between package insert and container/carton labels. The package insert has (b) (4) (b) (4)

#### Drug Product method for assay and related substances

- The method should be critically reviewed. If necessary, the reviewer may want to consider to send the method to the lab for evaluation.

#### Deliverable

- The applicant claims a deliverable of 0.25 g per tube without data. Additionally, the CMC reviewer should consult with the clinical division to determine whether the deliverable of 0.25 g should be included in label/labeling

#### Biopharm Issues

- The applicant bridges multiple processes and multiple sites using In-vitro-Drug-Release studies. The studies need to be reviewed by Biopharm reviewer.

#### Environmental Assessment

- Although the drug substance is extracted/purified from cultivated plants, a consult to the Environmental Assessment group is still recommended.

C. Comments for 74-Day Letter:

- Provide drug product samples with lower viscosity for dosage form evaluation. The viscosity of the samples is preferred to be near the lower limit of the proposed viscosity acceptance criterion. The samples should be accompanied with their certificates of analysis.

D. Comments/Recommendation:

The application is acceptable for filing from CMC perspective. The major CMC review issues with this NDA are drug substance manufacturing, drug product manufacturing, and method validation.

Drug substance manufacturing sites (b) (4) Drug product manufacturing sites are located in U.S. and Ireland. GMP inspection requests have been requested. **Reviewer's participation in the inspection is recommended.**

The CMC review of this NDA is recommended to be a team-review. Nina Ni is the primary CMC reviewer, and Tapash Ghosh is the BioPharm reviewer.

An Environmental Assessment consult is to be sent.

Master Batch Records for each of the two proposed drug product manufacturing sites were not provided in the initial submission but provided in the 4/29/11 amendment upon the Agency's request.

Shulin Ding, Ph.D.  
CMC Lead

Moo-Jhong Rhee, Ph.D.  
Chief, Branch IV

NDA Number: 202833 Supplement Number and Type: Established/Proper Name:  
 Ingenol mebutate/Picato

Applicant: Leo Letter Date: March 31, 2011 Stamp Date: March 31, 2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	x		

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		In Form 356h.

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorically exclusion is claimed. EA consult is recommended.

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	x		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		Master batch records for DPT and Leo are provided in the 4/29/11 amendment.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	n/a
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)					

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			n/a
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	x		See pages 2 and 3

*{See appended electronic signature page}*

Shulin Ding, Ph.D.  
 CMC Lead  
 Division of New Drug Quality Assessment II  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
 Branch Chief  
 Division of New Drug Quality Assessment II  
 Office of New Drug Quality Assessment

Date

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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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SHULIN DING  
05/13/2011

MOO JHONG RHEE  
05/13/2011  
Chief, Branch IV