

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202833Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 30 th , 2011
From	Susan J. Walker, M.D., F.A.A.D
Subject	Division Director Summary Review
NDA	202833
Applicant Name	LEO Pharma A/S
Date of Submission	March 25 th , 2011
PDUFA Goal Date	January 25 th , 2012
Proprietary Name / Established (USAN) Name	PICATO [®] / ingenol mebutate
Dosage Forms / Strength	Gel/ 0.015% and 0.05%
Proposed Indication(s)	1. Actinic keratoses of face and scalp 2. Actinic keratoses of trunk and extremities
Recommended Action	<i>Approval –Pending CMC Inspection Approvals</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Joanna Ku, M.D. / Jill Lindstrom, M.D.
Statistical Review	Yuqing Tang, Ph.D., Carin Kim, Ph.D. / Mohamed Alesh, Ph.D.
Pharmacology Toxicology Review	Jiaqin Yao, Ph.D. / Barbara Hill, Ph.D.
CMC Review	Nina Ni, Ph.D. / Shulin Ding, Ph.D.
CMC Biopharm	Tapash K. Gosh, Ph.D. / Angelica Dorantes, Ph.D.
Clinical Pharmacology Review	Abimbola Adebawale, Ph.D. / Doanh Tran, Ph.D.
DDMAC	Lynn Panholzer, Pharm.D.
DSI	Roy Blay, Ph.D. / Lauren Iacono-Connors, Ph.D.
CDTL Review	Jill Lindstrom, M.D.
DCRP	CDER DCRP QT Interdisciplinary Review Team / Norman Stockbridge, M.D., Ph.D.
OSE/DMEPA	Lubna Merchant, M.S. / Melina Griffis, R.Ph.
OMP/PLT	Sharon R. Mills, B.S.N., R.N., C.C.R.P. / Barbara Fuller, R.N., M.S.N., C.W.O.C.N.

Division Director Summary Review

1. Introduction

This application provides for the approval of a new molecular entity, ingenol mebutate, to be used for the topical treatment of actinic keratoses. The development program for this product included meetings and agreements with the agency at major milestones. I am in agreement with the recommendations of the review team for approval of this application. My review will summarize the major areas of the submission and documents my concurrence with the review team's recommendation for approval.

2. Background

This application proposes use of ingenol mebutate gel (0.015% and 0.05 %) for the topical treatment of actinic keratosis (AK) on the face and scalp and on the trunk and extremities, respectively, with two different dosing regimens, in adults 18 years and older. The proposed dosing regimens include:

- For the treatment of AK lesions on the head (face and scalp) locations, ingenol mebutate gel, 0.015% is to be applied topically to a 25 cm² treatment area once daily for 3 consecutive days.
- For the treatment of AK lesions on the non-head (trunk and extremities) locations, ingenol mebutate gel, 0.05%, is to be applied topically to a 25 cm² treatment area once daily for 2 consecutive days

3. CMC/Device

The identity, strength, purity and quality of the drug product have been reviewed by the CMC review team and determined to be acceptable, pending final inspection results. A final recommendation from Compliance regarding inspections is pending at the time of signoff for this review.

The drug substance, ingenol mebutate, is a new molecular entity consisting of a small molecule extracted/purified from the (b) (4) of the plant *Euphorbia peplus* L. (*E. peplus*).

(b) (4)
Further processing steps, detailed in the CMC review, result in isolation of the ingenol mebutate crystals, identified as the drug substance. This is sufficiently purified to be regarded as a non-botanical substance. The drug substance is controlled by a proposed specification, which has

been deemed adequate by the CMC review team to assure the identity, strength, purity and quality of the drug substance.

The drug products are ingenol mebutate gels, in two strengths, 0.015% and 0.05%. The to-be-marketed formula is the same as those used in all clinical trials and stability batches. Stability data indicate that the drug product is physically and chemically stable, with stability data up to 24 months when stored at 5° C, with minor excursions. Stability testing supports an expiry of 24 months.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance, however, approval of this application is dependent upon the outcome of final inspections. The Office of Compliance final recommendation is PENDING.

4. Nonclinical Pharmacology/Toxicology

I have considered the pharmacology/toxicology reviews by the primary reviewer, Dr. Jiaqin Yao, and supervisory reviews by Dr. Barbara Hill and Dr. Abigail Jacobs. I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

Ingenol mebutate was negative in the Ames test, in vitro mouse lymphoma assay, and in vivo rat micronucleus test, but positive in the Syrian hamster embryo (SHE) cell transformation assay. Ingenol mebutate was tested for acute and chronic toxicity in multiple animal models. Local topical irritation was noted to increase with dose and duration of treatment.

Considering available information, including the proposed short treatment period of 3 days and the local toxicity of the product, the Executive CAC recommended that a carcinogenicity study was not necessary to support the short treatment regimen. However, the need for a carcinogenicity study may change in the future if the clinical use changes, such as longer application or retreatment.

A hERG assay was conducted with an appropriate positive control to validate the study. Ingenol did not cause any inhibition of the hERG channel in this assay. Human Embryonic Kidney cells (HEK293 cells) stably transfected with hERG (human ether-a-go-go related gene) were exposed to PEP005 and currents were recorded at the completion of a 5-minute exposure equilibration period. There was no statistically significant inhibition of hERG tail current density for I+15 (n = 7) following sequential exposure to PEP005 at concentrations of 0.5, 1.0, 2.5, and 5.0 µg/mL. No IC50 value could be calculated. In this study, the positive control, E-4031 (a potent and selective IKr inhibitor) induced a significant decrease (71.6%) in average tail current for I+15 compared to the baseline current.

There are no adequate and well controlled studies of ingenol mebutate gel in pregnant women. A category C designation is appropriate for this product, indicating that PICATO® gel should

be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Human systemic exposure is anticipated to be minimal, as systemic exposure of ingenol mebutate was not detected in subjects with actinic keratoses treated with the higher strength (0.05%) gel applied to a 100 cm² treatment area.

5. Clinical Pharmacology/Biopharmaceutics

I have considered the clinical pharmacology reviews by the primary reviewer Dr. Abimbola Adebowale with concurrence by team leader Dr. Doanh Tran. I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

Ingenol mebutate is a new molecular entity that induces cell death when applied topically to actinic keratoses. The mechanism of action is not fully understood. In vivo and in vitro models have supported a dual mechanism of action for the effects of ingenol mebutate: 1) induction of local lesional cell death and 2) promoting an inflammatory response characterized as infiltration of neutrophils and other immunocompetent cells. Preclinical review indicates that it is difficult to determine which effect of either cytokine induction or associated inflammatory response noted for ingenol mebutate in vitro translates to the in vivo efficacy for the treatment of actinic keratoses demonstrated for PICATO® gel.

Pharmacokinetic studies in 16 subjects evaluated the systemic bioavailability of ingenol mebutate 0.05% gel following application of approximately 1mL to a 100cm² (5cm x 20cm) contiguous area of skin on the dorsal aspect of 1 forearm daily for 2 consecutive days. Blood samples were collected on an appropriate schedule. Levels of ingenol mebutate or its metabolites (acyl isomers) were not detected, with a lower limit of quantification (LLOQ) at 0.1ng/ml.

Based on the lack of quantifiable systemic levels, a thorough QT/QTc (TQT) study was not conducted. EKG analysis was conducted in phase 3 and a combined cardiac EKG safety report was submitted, and the clinical reviewer notes that there were no significant EKG abnormalities that changed the safety profile of the drug. A nonclinical HERG study was negative.

6. Clinical Microbiology

This application did not contain clinical microbiology information.

7. Clinical/Statistical-Efficacy

I have considered the biostatistical reviews of Drs. Kim and Tang (Dr. Alesh, Team Leader) and the clinical review by Dr. Ku (Dr. Lindstrom, Clinical Team Leader and Cross Discipline Team Leader). The applicant has provided adequate information to demonstrate the efficacy of PICATO® gel for the treatment of actinic keratoses on both the face/scalp and the extremities/trunk. The development program included independent studies in each anatomic area, and these studies were replicated. The development program was discussed extensively with the agency, and agreements on study design, endpoints, and statistical analysis plan were reached during the IND phase. Successful interactions included an EP2 meeting, SPA agreements, and a preNDA meeting.

Head and Face

Two multi-centered, double blind, randomized, vehicle controlled parallel group studies enrolled patients at least 18 yrs old with 4-8 clinically typical, visible, and discrete actinic keratosis lesions within a contiguous 25cm² treatment area on the head. Subjects were randomized in a 1:1 ration to PICATO® gel 0.015% or vehicle. Subjects were instructed to apply study medication once daily for 3 consecutive day, allowing the gel to dry for 15 minutes and washing off with mild soap at 6 hrs. Follow-up visits were scheduled on days 4, 8, 15, 29, and 57, with efficacy evaluation at day 57. The primary efficacy endpoint was complete clearance of AK lesions at the day 57 visit. Partial clearance was considered to be a reduction of at least 75% of clinically visible lesions in the treatment area. PICATO® gel demonstrated efficacy superior to vehicle gel in both pivotal trials, with p-value <0.0001.

Study 16 enrolled 269 subjects with 135 randomized to active, and Study 25 enrolled 278 subjects with 142 randomized to active. The drop-out rates were small, 98% and 100% on active respectively in studies 16 and 25. PICATO® gel demonstrated efficacy superior to vehicle gel in both studies, with p-values for comparisons with vehicle less than 0.0001. Results were consistent across age, genders, skin types, and baseline lesion counts.

	Study 025		Study 016	
	PICATO® gel 0.015%	Vehicle	PICATO® gel 0.015%	Vehicle
Complete Clearance (ITT)	67/142 (47.2%)	7/136 (5.2%)	50/135 (37%)	3/134 (2.2%)
Partial Clearance	96/142 (67.6%)	11/136 (8.1%)	81/135 (60%)	9/134 (6.7%)
Face	58/111 (52%)	6/111 (5%)	46/109 (42%)	3/109 (3%)
Scalp	9/31 (29%)	1/25 (4%)	4/26 (15%)	0/25 (0%)

Trunk and Extremities

The application includes information from studies 014 and 028 to support approval for treatment of actinic keratoses on the trunk and extremities.

Two multi-centered, double blind, randomized, vehicle controlled parallel group studies enrolled a total of 255 patients at least 18 yrs old with 4-8 clinically typical, visible, and

discrete actinic keratosis lesions within a contiguous 25cm² treatment area on a non- head area, i.e. trunk or extremities. Subjects were randomized in a 1:1 ration to PICATO® gel 0.05% or vehicle. Subjects were instructed to apply study medication once daily for 2 consecutive days. Follow-up visits were scheduled on days 3, 8, 15, 29, and 57, with efficacy evaluation at day 57. The primary efficacy endpoint was complete clearance of AK lesions at the day 57 visit. Partial clearance was considered to be a reduction of at least 75% of clinically visible lesions. No interim efficacy information was collected. The applicant also included evaluations at 12 months following treatment to evaluate durability of response. PICATO® gel demonstrated efficacy superior to vehicle gel in both trials, with p-value <0.0001.

Study 14 enrolled 255 subjects with 126 randomized to active, and Study 28 enrolled 203 subjects with 100 randomized to active. The drop-out rates were small, 3% and 2% on active respectively in studies 14 and 28. PICATO® gel demonstrated efficacy superior to vehicle gel in both studies, with p-values for comparisons with vehicle less than 0.001. Results were consistent across ages, genders, skin types, and baseline lesion counts.

	Study 014		Study 28	
	PICATO® gel 0.05%	Vehicle	PICATO® gel 0.05%	Vehicle
Complete Clearance (ITT)	35/126 (28%)	6/129 (5%)	42/100 (42%)	5/103 (5%)
Partial Clearance	56/126 (44%)	9/129 (7%)	55/100 (55%)	7/103 (7%)
Arm	22/84 (26%)	4/82 (5%)	27/59 (46%)	3/67 (5%)
Back of hand	4/25 (16%)	0/29 (0%)	6/28 (21%)	0/27 (0%)
Chest	8/9 (89%)	1/8 (12%)	3/5 (60%)	1/3 (33%)
Back	0/2 (0%)	0/3 (0%)	3/3 (100%)	-
Leg	1/6 (17%)	1/5 (20%)	1/3 (33%)	0/5 (0%)
Shoulder	-	0/2 (0%)	2/2 (100%)	1/1 (100%)

I concur with the recommendations of the review team that the application has provided adequate evidence of efficacy for the treatment of actinic keratoses of the head and non-head areas.

8. Safety

The clinical development program consisted of 25 trials/studies, with a total of 1774 subjects exposed to ingenol mebutate for at least 1 treatment.

Subjects in the pivotal vehicle controlled studies applied the topical drug gel at home. Study medication was not to be applied immediately following a shower or less than two hours before going to bed. The treatment area was to dry for 15 minutes before any further activity. For 6 hours after medication application, the subject was to avoid touching or washing the treatment area, or engaging in activities that cause excessive sweating. When washing the area after the 6 hour wait period, the area was to be washed gently using a mild, nonabrasive,

non-medicated soap. The treatment area was not to be covered with tight clothing. Caution was given that the drug is a “severe eye irritant” and that contact with eyes should be avoided, and if contact were to occur, the subject was to rinse the eyes thoroughly with plenty of water and proceed immediately to the nearest Emergency Room or Urgent Care Center for treatment.

One death was reported in the clinical development program. The subject, a 58 year old Caucasian male with a history of hypertension (taking irbesartan 300mg daily), impaired fasting hyperglycemia and insulin resistance, applied a low strength ingenol mebutate gel (0.005%) to the face for 3 days. On the morning of the event, 4 weeks after application of the study medication, the subject was out for a walk or run and was found dead on the sidewalk. The death certificate listed coronary atherosclerosis and hypertension as the cause of death. I concur with the conclusion that this death was unrelated to the study drug. The clinical review has found no trend towards increased cardiac risk with the use of topical ingenol mebutate.

The clinical review by Dr. Ku notes that specific safety concerns for this topical product are 1) ocular and peri-ocular disorders and 2) local skin reactions/application site reactions.

Ocular

Ocular and peri-ocular disorders occurred more frequently in the PICATO® gel treatment groups than in vehicle. Of the 39 local ocular adverse events that occurred in the ingenol treated subjects in the actinic keratosis field application studies, eyelid edema and periorbital edema were the most frequently reported eye related disorders. Most events were graded as mild or moderate. Five events were graded as severe. All these AE’s resolved without sequelae. There were no AE’s that resulted in permanent visual loss or other catastrophic medical consequences. Directions for managing eye related adverse events should be included in product labeling.

Local Skin Reactions

PICATO® gel may produce robust local skin reactions. 1774 subjects were treated with topical ingenol mebutate in the development program - 26 subjects received treatment for adverse reactions related to application of the study drug in the local treatment area. The most frequent necessary treatments for local skin reactions were analgesics for application site pain (9 subjects), antibiotics (9 subjects) for application site skin infection, and topical steroids (4 subjects) and oral steroids (1 subject) for edema. Local skin reactions were actively assessed in the phase 3 program. Patient safety evaluations included a scoring scale for “local skin reactions” and an accompanying photographic scale. Local skin responses typically occurred within 1 day of treatment initiation, peaked in intensity up to 1 week following completion of treatment, and resolved within 2 weeks for areas treated on the face and scalp and within 4 weeks for areas treated on the trunk and extremities. The majority of local skin reactions occurred on days 3 and 4, with resolution by day 57. I concur that these local skin reactions can be adequately described in labeling.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application. The application did not raise issues of safety or efficacy that would require discussion before an advisory committee.

10. Pediatrics

Actinic keratoses are not generally diagnosed in the pediatric population. The Pediatric Review Committee (PeRC) concurs with the recommendation for a complete pediatric waiver for ages 0 to 16 years because the disease is rare in children.

11. Other Relevant Regulatory Issues

The Office of Compliance final recommendations are pending.

12. Labeling

The proprietary name, PICATO®, was cleared by DMEPA within 90 days of the PDUFA date of January 25th, 2012. Final product labeling is currently under discussion. The application has provided sufficient information to demonstrate that PICATO® gel is safe and effective for treatment of the full spectrum of clinically relevant locations affected by actinic keratosis. The indication “treatment of actinic keratosis” is appropriate, without anatomic restriction.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – This product is recommended for approval following:
 - receipt of appropriate inspection reports from Office of Compliance
 - acceptance of final labeling
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None
- Recommendation for other Postmarketing Requirements and Commitments – None
- Risk Benefit Assessment – The risks associated with use of this product are essentially limited to local adverse reactions, that is, a robust effect which is also likely to lead to the desired product performance. Inadvertent application of the product to the ocular area may result in significant irritation, but these reactions have been shown to resolve and labeling should adequately warn patients and providers regarding these events.

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/s/

SUSAN J WALKER
12/30/2011