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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	15 December 2011
From	Jill Lindstrom, MD FAAD
Subject	Cross-Discipline Team Leader Review
NDA #	202833
Applicant	LEO Pharma A/S
Date of Submission	25 March 2011
PDUFA Goal Date	25 January 2012
Proprietary Name / Established (USAN) names	Picato (ingenol mebutate)
Dosage forms	gel
Strengths	0.015% and 0.05%
Proposed Indication(s)	Topical treatment of actinic keratosis on the face and scalp and on the trunk and extremities
Recommended:	*Approval*

1. Introduction

Picato (ingenol mebutate) gel, 0.015% or 0.05%, is a topical drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the topical treatment of actinic keratoses (AK) on the face or scalp (0.015% strength) or trunk and extremities (0.05% strength). This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

Ingenol mebutate, a new molecular entity, is an ingenol derivative that is extracted from *Euphorbia peplus L.*, a member of the Spurge family. Ingenol is a cell death inducer that causes cellular necrosis in vitro and in vivo. Picato (ingenol mebutate) gel is formulated in two concentrations: 0.015% and 0.05%. Two dose regimens are proposed, based on anatomic location: for the treatment of AKs on the face and scalp, Picato gel 0.015% is to be applied once daily for three days, and for the treatment of AKs of the trunk and extremities, Picato gel 0.05% is to be applied once daily for two days. Picato gel is not marketed in the US or in any other jurisdiction.

AKs are dysplastic lesions of the epidermis that are thought to be induced by chronic ultraviolet radiation exposure. They are commonly found on the sun-exposed skin of fair-complected older adults. Clinically-typical AK lesions are yellow-to-red papules with a rough surface which may be more easily palpated than visualized. They may be tender or asymptomatic. Although AKs can progress to squamous cell carcinoma, the rate of malignant transformation is low. AKs may also resolve spontaneously.

3. CMC

The drug substance, ingenol mebutate, is a new chemical entity with the molecular formula $C_{25}H_{34}O_6$ that is derived from the plant *Euphorbia peplus* L (*E. peplus)*, or petty spurge. Although derived from plant material, ingenol mebutate is not a botanical drug because it is highly purified through extraction, purification, and crystallization steps during manufacture. It is a white to yellow powder that is soluble in isopropyl alcohol but not in water. (b) (4)

The drug product, Picato (ingenol mebutate) gel, is a clear, colorless gel containing either 0.015% (150 mcg/gm) or 0.05% (500 mcg/gm) of ingenol mebutate. The composition is described in the following table:

Ingredient	Function	% w/w
Ingenol mebutate	Drug substance	0.015 or 0.05
Isopropyl alcohol	(b) (4)	
Hydroxyethyl cellulose		
Benzyl alcohol		
Citric acid monohydrate		
Sodium citrate		
Purified water		

Source: adapted from NDA 202833 section 2.3.P.1

None of the excipients are novel; all are listed in the FDA Inactive Ingredients database and are contained in marketed products at concentrations equal to or greater than those in Picato gel. (b) (4)

The drug product is packaged into unit-dose laminate aluminum tubes with (b) (4) and an HDPE shoulder/nozzle/screw cap closure system. The applicant proposes to market both strengths in unit-dose tubes of 0.47gms, which provide 0.25gms for application, packed in cartons of three tubes of the 0.015% strength or two tubes of the 0.05% strength. Stability data support an expiry of 24 months.

Because the product is an aqueous gel containing approximately (b) (4) water, it is formulated with benzyl alcohol as a (b) (4) Antimicrobial effectiveness testing performed according to <USP 51> at the beginning and end of the stability study was found acceptable. These results, as well as the presence of (b) (4) isopropyl alcohol and (b) (4) benzyl alcohol in the formulation (b) (4) support the absence of AET from release specifications. (b) (4)

Facilities inspections for the drug substance and drug product were completed, but the final report is pending at the time of close of this review.

The CMC reviewer, Dr. Nina Ni, concluded that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product, and did not recommend any postmarketing commitments. She identified the absence of a final recommendation on facilities from the Office of Compliance (pending at the time of close of this review) and unresolved labeling issues (pending at the time of close of this review) which would preclude a recommendation for *Approval*.

4. Nonclinical Pharmacology/Toxicology

Repeat dose dermal toxicology studies in rats, and minipigs revealed local irritation but no significant systemic toxicity. Ingenol mebutate appears to induce local cell necrosis, although the exact mechanism by which cell necrosis is induced is not clear. Safety pharmacology studies, including hERG channel and anesthetized beagle studies, did not identify a signal for prolongation of cardiac repolarization. Ingenol mebutate was negative for mutagenicity 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. Carcinogenicity studies were not conducted because the clinical dosing regimen is $\leq$ 3 days. Fertility and pre- and post-natal development studies were not conducted because of the negligible systemic exposure. Embryofetal effects seen in rabbits support a pregnancy category rating of C, although the clinical relevance of the findings is unclear in the absence of demonstrable systemic exposure in subjects with actinic keratoses treated with Picato gel.

The reader is referred to the comprehensive review by Dr. Jianyong Wang for a full discussion of the nonclinical pharmacology/toxicology data. Dr. Wang and Dr. Barbara Hill did not recommend further nonclinical studies or phase 4 commitments, and recommended an *Approval* action from a pharmacological/toxicological perspective.

5. Clinical Pharmacology/Biopharmaceutics

Picato (ingenol mebutate) gel, 0.015% or 0.05%, is a topical product for the treatment of actinic keratoses. It is applied once daily to up to 25cm^2 of involved skin for three consecutive days on the head (0.015%) or for two consecutive days or the trunk or extremities (0.05%).

The applicant conducted study PEP005-017 to assess pharmacokinetics and systemic exposure under maximum usage conditions. Fourteen subjects with a similar density of AKs to that required for enrollment in the pivotal trials (4 to 8 AKs within a 25 cm^2 area on the dorsal forearm) received treatment to a 100cm^2 treatment area on the dorsal forearm, once daily for two days; thirteen subjects received ingenol mebutate gel, 0.05% and one subject received vehicle gel. All pharmacokinetic samples were below the limit of detection (LLOQ $\leq$0.1ng/mL) for ingenol mebutate and two metabolites (PEP015 and PEP025). Ten of 13 subjects in the active arm and no subject in the vehicle arm had complete clearance of their AKs in the 25cm^2 assessment area within the larger 100cm^2 treatment area. Pharmacokinetic samples were obtained in three other studies, none of which represented maximum use conditions; serum levels of ingenol mebutate and the two metabolites were all below the limit of detection.

The applicant did not conduct a thorough QT/QT_c study. Although ingenol mebutate is a new molecular entity, systemic exposure following topical application to 100cm^2 of skin with actinic keratoses was below the level of detection. Hence systemic exposure from topical administration (used according to proposed labeling) for treatment of actinic keratoses would be expected to be in the subnanomolar range. Consultation was obtained from the QT Interdisciplinary Review Team, who concurred that a TQT study was not needed.

The applicant conducted in vitro studies using human hepatocytes and hepatic microsomal protein to evaluate the effect of ingenol mebutate on CYP isoforms; no notable induction or inhibition was identified. Formal in vivo drug interaction studies were not performed. The results of the in vitro hepatic and in vivo PK studies suggest that clinical drug interactions will be unlikely.

Dr. Adebowale found that the applicant met the requirements for approval from a clinical pharmacology perspective, and recommended *Approval* from a clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

To establish the effectiveness of their product, the applicant submitted data from four pivotal trials: two for the head location (Study 016 and Study 025), and two for the non-head location (Study 014 and Study 028). The dosage regimen of study drug for the head location was Picato gel 0.015% or vehicle applied once daily for three days, and for the non-head location was Picato gel 0.05% or vehicle applied once daily for two days. All four trials were multi-center, prospective, randomized, double-blind, parallel group studies with two arms. Studies 016 and 025 enrolled adult subjects with 4 to 8 clinically typical actinic keratoses within a contiguous 25cm^2 of skin on the head (face or scalp), and studies 014 and 028 enrolled adult subjects with 4 to 8 clinically typical actinic keratoses within a contiguous 25cm^2 of skin on non-head location (trunk or extremities).

The applicant was granted a Special Protocol Assessment (SPA) for the non-head location, and an Agreement letter was issued on 2 June 2008. Agreements included:

- the general study design
- treatment area of 25cm^2 with 4 to 8 AKs
- dose regimen of once daily for two consecutive days
- primary efficacy endpoint of proportion of subjects with complete clearance of AK lesions in the treatment area at day 57
- primary timepoint for assessment at day 57
- secondary endpoint of proportion of subjects with 75% or greater reduction in number of AK lesions at day 57
- primary analysis based on intent to treat (ITT) population with missing data imputed using last observation carried forward

The applicant attended and End of Phase 2 meeting for the head location on 3 June 2009. The importance of long-term follow-up for recurrence was conveyed at that time. The applicant did not request a SPA for the head location.

Efficacy assessment was the same in the four pivotal trials. The primary efficacy measure was AK lesion counts. The primary efficacy timepoint was day 57. The primary efficacy endpoint was the proportion of subjects with complete clearance, defined as no clinically visible AK lesions in the selected treatment area. The efficacy results for the ITT populations in the head locations (Study 016 and Study 025) and the non-head locations (Study 014 and Study 028) are presented in the following tables.

Complete Clearance Rates at Day 57, ITT Population, Head locations

	Study 016		Study 025	
	Picato gel, 0.015% (N=135)	Vehicle (N=134)	Picato gel, 0.015% (N=142)	Vehicle (N=136)
Complete clearance	50 (37%)	3 (2.2%)	67 (47.2%)	7 (5.2%)
p-value	<0.0001		<0.0001	

Source: adapted from Statistical Review and Evaluation NDA 202833; Yuqing Tang, PhD, archived 11.17.2011, p 11.

Complete Clearance Rates at Day 57, ITT Population, Non-head locations

	Study 014		Study 028	
	Picato gel, 0.05% (N=126)	Vehicle (N=129)	Picato gel, 0.05% (N=100)	Vehicle (N=103)
Complete clearance	35 (27.8%)	6 (4.7%)	42 (42.0%)	5 (4.9%)
p-value	<0.001		<0.001	

Source: adapted from Statistical Review and Evaluation NDA 202833; Carin Kim, PhD, archived 11.16.2011, p 10.

Picato gel 0.015% was superior to vehicle in the proportion of subjects that achieved complete clearance of their AK lesions on the face or scalp (head), and Picato gel 0.05% was superior to vehicle in the proportion of subjects that achieved complete clearance of their AK lesions on the trunk or extremities (non-head).

The reader is referred to the reviews of Drs. Joanna Ku, Carin Kim and Dr. Yuqing Tang for detailed review of the pivotal trials and additional analyses, including post hoc explorations of the data and sensitivity analyses.

I concur with Drs. Joanna Ku, Carin Kim and Yuqing Tang, that the data support a determination of efficacy.

8. Safety

The safety database is adequate. Four hundred ninety nine subjects were exposed to Picato gel in the pivotal trials (274 subjects at 0.015% concentration in the head location trials, and 225 subjects at 0.05% concentration in the non-head location trials), and 1165 subjects with AKs were exposed to Picato gel used as field treatment during the development program.

There was one death reported in the development program: a 57 year-old male subject with hypertension enrolled in the phase 2 study PEP005-015, was found dead on the sidewalk on study day 34, one month after completion of study drug administration. The investigator considered this event unrelated to the study drug, with which I agree.

Adverse events were reported more frequently for subjects receiving active than vehicle: 36% versus 25% in the pooled pivotal trials, and 43% versus 24% in the pooled AK field treatment trials. The most frequently reported adverse events in the pivotal trials were application site pain (9% vs <1%), application site pruritus (8% vs 1%), and application site irritation (3% vs <1%). In the pooled pivotal trials, serious adverse events were reported for 14 subjects treated with active and 17 subjects treated with vehicle. In three subjects, all of whom received Picato 0.05% gel, the investigator considered the SAE to be possibly related to study drug: Bowen's disease with in the treatment area diagnosed on day 29, squamous cell carcinoma (SCC) within the treatment area diagnosed on day 29, and SCC within the treatment area diagnosed on day 57. The brevity of the treatment duration (3 day) and of the interval between treatment and diagnosis (29 or 57 days) do not support a determination of causality by study drug in these subjects.

Local skin reactions, which were actively assessed, were frequent. Post hoc analysis showed correlation of local skin reaction intensity with AK clearance. Local skin reactions peaked in intensity in the first week, and generally resolved within a month of completion of therapy. Ocular adverse events, primarily periorbital edema and eyelid edema, were reported in the head location trials, and may have resulted from the proximity of the treatment area or inadvertent transfer of the drug.

The reader is referred to the clinical review by Dr. Joanna Ku for a full discussion of the safety database.

No postmarketing commitments or requirements to address safety signals are needed.

9. Advisory Committee Meeting

Not applicable, as no Advisory Committee meeting was held for this application. Although ingenol mebutate is a new molecular entity, the application did not raise controversial issues that would benefit from outside discussion.

10. Pediatrics

Actinic keratoses are caused by chronic ultraviolet radiation exposure and occur almost exclusively in adults. Actinic keratoses are seen in children with xeroderma pigmentosa, a condition caused by defective DNA repair mechanisms, but this genodermatosis is rare. The applicant requested a waiver for all pediatric age groups on the grounds that pediatric studies would be impossible or highly impracticable because there are too few children with the disease/condition to study. The Pediatric Review Committee (PeRC) agreed with the Division's recommendation to grant a complete pediatric waiver for ages 0 to 16 because the disease is rare in children.

11. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.

One of the study investigators inspected by DSI (Dr. Heine) raised concern that the propensity of the active study drug to induce local skin reactions resulted in functional unblinding. Although possible, the low dropout rate, the non-subjective nature of the primary efficacy endpoint (complete clearance of all AKs from the treatment area), and active assessment of safety parameters mitigate any potential impact.

12. Labeling

All components of labeling were reviewed. Labeling negotiations with the applicant are ongoing at the time of close of this review.

Dr. Teresa McMilan of Division of Medication Error Prevention and Analysis found the proposed proprietary name, Picato, to be acceptable.

The applicant proposed, "(b) (4) cell-death inducer (b) (4) as the established pharmacologic class for ingenol mebutate. Review of nonclinical information supported "cell death inducer" (b) (4) Although Dr. Ku did not find the term, "cell death inducer" to be clinically meaningful, I do. Physical modalities used for treatment of actinic keratoses such as liquid nitrogen and electrodessication are known to cause cellular necrosis and employed to this end. I find the find the pharmacology-toxicology reviewer's modification of the applicant's proposal for the established pharmacologic class, "cell death inducer," to be acceptable from a scientific, regulatory and clinical perspective.

Professional labeling conforms to the standards of the Physician Labeling Rule. Patient labeling, which includes both a Patient Package Insert and a separate Instructions for Use document, contains text and diagrams to inform patients about proper application and use of the product, the risk for local skin and eye reactions, and measures to reduce the risks. These risks are self-limited and commensurate with those of other products for this indication, and a Medication Guide is not recommended.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Approval.*

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 202833 Picato (ingenol mebutate) gel for the treatment of actinic keratoses, pending satisfactory final facilities inspection report and resolution of labeling negotiations.

The applicant established the efficacy and safety of Picato gel in the treatment of actinic keratoses of the head and non-head regions in two adequate and well-controlled trials, and provided sufficient information in their application to support product labeling.

Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not recommended.

No postmarketing requirements or commitments are recommended.

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/s/

JILL A LINDSTROM
12/16/2011