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APPLICATION NUMBER:
202833Orig1s000

OFFICE DIRECTOR MEMO

Date: January 17, 2012
To: NDA 202833
Picato (ingenol mebutate) gel, 0.015% and 0.05%
Leo Pharma A/S

From: Victoria Kusiak, M.D.
Deputy Director, Office of Drug Evaluation III

Subject: Approval Action

Picato (ingenol mebutate) gel, 0.015% and 0.05% is a topical formulation of ingenol mebutate (a new molecular entity), isopropyl alcohol, hydroxyethyl cellulose, benzyl alcohol, citric acid monohydrate, sodium citrate and water. Ingenol mebutate is extracted/purified from the aerial parts of a plant (*Euphorbia peplus* L.) cultivated in Australia. Picato is a cell death inducer (mechanism unknown) that has been evaluated as a treatment for actinic keratosis (AK) on the face and scalp (0.015%) and on the trunk and extremities (0.05%).

This memorandum documents my concurrence with the Division of Dermatology and Dental Products (DDDP's) recommendation to approve Picato (ingenol mebutate) gel, 0.015% and 0.05% for the treatment of actinic keratosis when applied to the affected area on the face and scalp (0.015%) once daily for 3 consecutive days, and on the trunk and extremities (0.05%) once daily for 2 consecutive days in adults 18 years of age or older.

REGULATORY HISTORY

Leo Pharma A/S submitted IND 070114 on June 28, 2004, received on June 30, 2004. IND 070114 was for PE005 Gel for the topical treatment of actinic keratosis.

Subsequent to the submission of the IND, the Agency has held 3 Guidance (3/7/05; 4/10/06; 9/16/09), 1 End-of Phase 2 (6/3/09), 1 CMC (5/24/10), and 1 Pre-NDA (12/15/10) meeting with the Sponsor. In addition the Agency provided comments for both a Clinical (6/2/08) and a Nonclinical SPA (7/12/06), and issued 10 advice/information request letters.

The clinical SPA agreement letter provided four major points:

1. The primary endpoint was agreed to be percent of subjects with complete clearance at a pre-specified time point.
2. The selected treatment area was to be 25 cm² (4-8 clinically typical, visible, and discrete AK lesions within the 25 cm² treatment area).
3. Efficacy was to be measured at day 57.
4. Recurrence of lesions that were cleared with treatment was to be evaluated at 12 months after successful treatment.

Leo Pharma A/S submitted a 505 (b) (1) NDA (202833) on March 25, 2011 (stamped March 31, 2011) for the prescription use of Picato (ingenol mebutate) for the treatment of actinic keratosis of the face and scalp and of the trunk and extremities. Two strengths were

proposed: 0.015% ng/mL for the treatment of actinic keratosis of the face and scalp and 0.05% ng/mL for actinic keratosis of the trunk and extremities.

No initial review issues were identified. Requests for information were largely referable to CMC and included:

1. Drug substance issues: with manufacturing process control and storage/handling; Manufacturing process information (primarily Master Batch Records and Executed Batch Records).
2. Drug product manufacturing issues with multiple site use of different equipment
3. Drug product stability issues
4. Drug assay issues
5. Method validation issues

All of these issues were adequately addressed in Sponsor responses to requests for information.

The application was not discussed at an FDA advisory committee because the application did not raise any significant safety or efficacy issues in the intended population.

Drug Product:

The drug substance, ingenol mebutate, is a new chemical entity that is derived from the plant *Euphorbia peplus* L. It is not a botanical drug because it undergoes extensive purification through extraction, purification, and crystallization during manufacture. None of the excipients are novel; all are listed in the FDA Inactive Ingredients database and are contained in marketed products at concentrations equal or greater than those in Picato gel. The CMC reviewer has determined that the Sponsor provided sufficient information to assure the identity, strength, purity and quality of the drug product and did not recommend any post marketing commitments.

EFFICACY

Four phase 3 vehicle controlled studies were conducted, two for each indication. In two of the studies subjects received “field treatment” (i.e., treatment over a selected area of skin) of AKs on the face and scalp, and in two studies subjects received field treatment of AKs on the trunk and extremities. Subjects were recruited from the US (the majority) and from Australia. All subjects were Caucasian, approximately 60% were male and subjects had a mean age of approximately 60 years.

In Studies 016 and 025 (face/scalp) 547 subjects were randomized 1:1 to Picato or vehicle. Complete clearance at day 57 was observed in 42% of the Picato treated group compared to 4% of vehicle treated subjects ($p < 0.0001$). Partial clearance, defined as the proportion of subjects with 75% or greater reduction in the number of AK lesions at baseline in the selected treatment area, was 64% in the Picato treated group compared to 7.5% in the vehicle treated group. The result was statistically significant.

In Studies 014 and 028 (trunk/extremities) 458 subjects were randomized 1:1 to Picato or vehicle. Complete clearance at day 57 was seen in 34% of the Picato subjects compared to 5% of the vehicle treated subjects ($p < 0.001$). Partial clearance, defined as the proportion of patients with 75% or greater reduction in the number of AK lesions present at baseline in the selected treatment area was 50% compared to 7% in the vehicle treated group. The result was statistically significant.

About half of the successfully treated subjects had recurrence of at least one AK lesion in the treated area at 12 months. The recurrence rate at 12 months was 54% for the face/scalp subjects and 50% for the trunk/extremity subjects.

CLINICAL PHARMACOLOGY

Two pivotal maximal use pharmacokinetic studies were conducted that demonstrated that blood levels of ingenol mebutate were below the lower limit of quantification (0.1 ng/mL) in all samples collected.

The systemic exposure to Picato gel 0.05% was assessed in two studies in a total of 16 subjects with AK. Studies PEP005-017 and PEP005-013 indicated that treatment of a 100 cm² area of skin with ingenol mebutate gel, 0.05% once daily for 2 consecutive days demonstrated minimal systemic exposure of the parent compound or its acyl isomers. The blood levels of ingenol mebutate and its 2 acyl isomers were below the lower limit of quantification (0.1 ng/mL) in all samples collected.

In vitro studies demonstrated that ingenol mebutate does not inhibit cytochrome P450 (CYP) enzymes. The estimated expected systemic exposure (< 0.1 ng/mL) following topical application of Picato gel, 0.05% to AK subjects is negligible compared to the concentration of ingenol mebutate evaluated in the in vitro studies.

NONCLINICAL

Long term animal studies have not been performed to evaluate the carcinogenic potential of Picato gel or ingenol mebutate nor have their potential effects on fertility been studied.

In genetic testing, ingenol mebutate was negative in the Ames test, the in vitro mouse lymphoma assay, and in the in vivo rat micronucleus test, but positive in the Syrian hamster embryo (SHE) cell transformation assay.

In in vivo studies of pregnant rabbits given intravenous ingenol mebutate, an increase in the incidence of embryo-fetal mortality and an increased incidence of fetal visceral and skeletal variations were seen, supporting a Pregnancy Category C classification.

SAFETY

In the applicant's phase 3 clinical development program, of 1006 subjects treated for AK with either Picato or vehicle, 1002 were available for safety evaluation for local reactions. Of the 1002 subjects evaluated, 503 were exposed to vehicle and 499 were exposed to Picato including 274 subjects exposed to Picato gel field treatment (skin area of 25 cm²) on the face and scalp at a concentration of 0.015% once daily for 3 consecutive days, and 225 subjects exposed to Picato gel field treatment (skin area of 25 cm²) on the trunk and extremities at a concentration of 0.05% once daily for 2 consecutive days. All 1002 subjects were evaluated by the investigator for local skin reactions.

Local skin reactions within the selected treatment area including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration were assessed by the investigator and graded on a 0-4 scale with 0 being no reaction, and 4 representing a marked and severe reaction extending beyond the treated area.

In the subjects exposed to Picato gel 0.015%, 94% of subjects experienced erythema (24% grade 4) compared to 25% (0% grade 4) of vehicle treated subjects. 79-85% (5-9% grade 4) of Picato treated subjects experienced flaking/scaling, and crusting or swelling compared to 17-25% (0% grade four) of vehicle treated subjects (only 4% of vehicle treated subjects experienced swelling). Vesiculation/pustulation was seen in 56% (5% grade 4) of Picato treated subjects vs. 0% of vehicle treated subjects and erosion/ulceration was seen in 32% (0% grade 4) of Picato treated subjects vs. 1% (0% grade 4) of vehicle treated subjects. Results for the Picato gel 0.05% treatment were similar in extent and in comparison to vehicle.

Local skin reactions typically occurred within 1 day of treatment, peaked at 1 week after treatment and resolved within 2 weeks when the reaction occurred on the face and within 4 weeks when the reaction occurred on the trunk or extremities.

Application site pain occurred in approximately 8-15% of Picato treated patients and application site pruritus and application site infection was seen in 3-8%. The incidence of these events in vehicle treated subjects was negligible.

Periorbital edema, headache, eyelid swelling, eye pain, conjunctivitis, nasopharyngitis, and application site pain were also reported in <3% of Picato treated subjects.

Twelve month follow-up did not alter the safety profile of Picato gel.

The WARNINGS AND PRECAUTIONS section of the product label will advise that eye disorders including severe eye pain, eyelid edema, eyelid ptosis and periorbital edema can occur after eye exposure. Hand washing and avoidance of accidental transfer of the drug to the eye will be emphasized.

The potential for severe skin reactions in the treated area including erythema, crusting, swelling, vesiculation/pustulation, and erosion/ulceration will also be noted.

USE IN SPECIFIC POPULATIONS

Picato gel has not been studied in pregnant women, and therefore it should be used in pregnancy only if the potential benefits outweigh the potential risk to the fetus.

Actinic keratosis is not a condition generally seen in children and Picato has not been studied in subjects less than 18 years of age. Because actinic keratosis is so rarely seen in children, the pediatric study requirement for this application is waived.

Because actinic keratosis is a disease whose incidence increases with age, more than 50% of subjects treated in clinical trials were 65 or older. Of the 1165 subjects treated with Picato gel in clinical trials, 56% were 65 years and older and 21% were 75 years and older. No differences in safety or effectiveness were noted in older subjects compared to younger subjects.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

No postmarketing requirements other than those for an approved NDA (21 CFR 314.80 and 314.81) are attached to this approval.

TRADENAME REVIEW

On May 30, 2011, Leo Pharma A/S requested withdrawal of its initial request for review of the proprietary name of [REDACTED]^{(b) (4)} which was withdrawn on May 31, 2011. At that time, a request for review of the proprietary name “Picato” was made.

Subsequently, on August 8, 2011 the Division of Medication Error Prevention and Analysis found the proprietary name “Picato” to be acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA KUSIAK
01/23/2012