

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 202-833/S-05

Trade Name: Picato®

Generic Name: ingenol mebutate

Sponsor: Leo Laboratories LTD

Approval Date: October 6, 2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 202-833/S-05

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 202-833/S-05

APPROVAL LETTER



NDA 202833/S-005

SUPPLEMENT APPROVAL

LEO Pharma A/S
C/o Leo Pharma Inc.
Attention: Ronald L. Dundore, PhD
Consultant, US Regulatory Affairs
1 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Dundore:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 14, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Picato[®] (ingenol mebutate) gel, 0.015% and 0.05%.

We also refer to our letter dated August 21, 2015, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Picato[®] (ingenol mebutate) gel, 0.015% and 0.05%. This information pertains to the risk of severe hypersensitivity reactions, herpes zoster, allergic contact dermatitis and eye injuries.

This supplemental new drug application provides for revisions to the labeling for Picato[®] (ingenol mebutate) gel, 0.015% and 0.05%, consistent with our August 21, 2015 letter.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below/indicated in the enclosed labeling.

1. Subsection 6.2 Postmarketing Experience was added to the Full Prescribing Information: Contents.
2. Throughout the Prescribing Information, “gel” was added after “Picato” for consistency.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the

patient package insert, text for instructions for use), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels **and** carton and immediate-container labels submitted on September 14, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 202833/S-005.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call J. Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

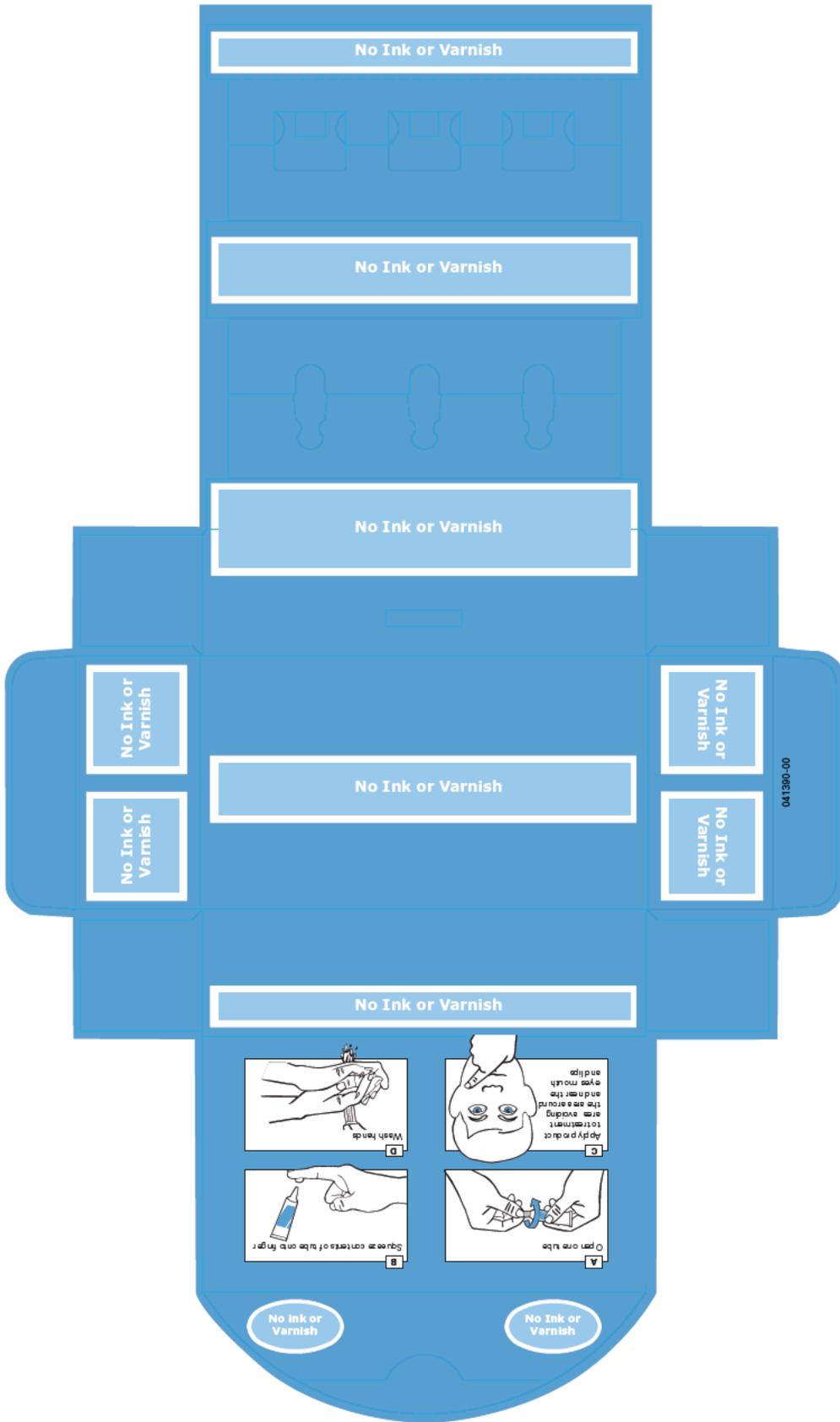
Content of Labeling
Carton and Container Labeling

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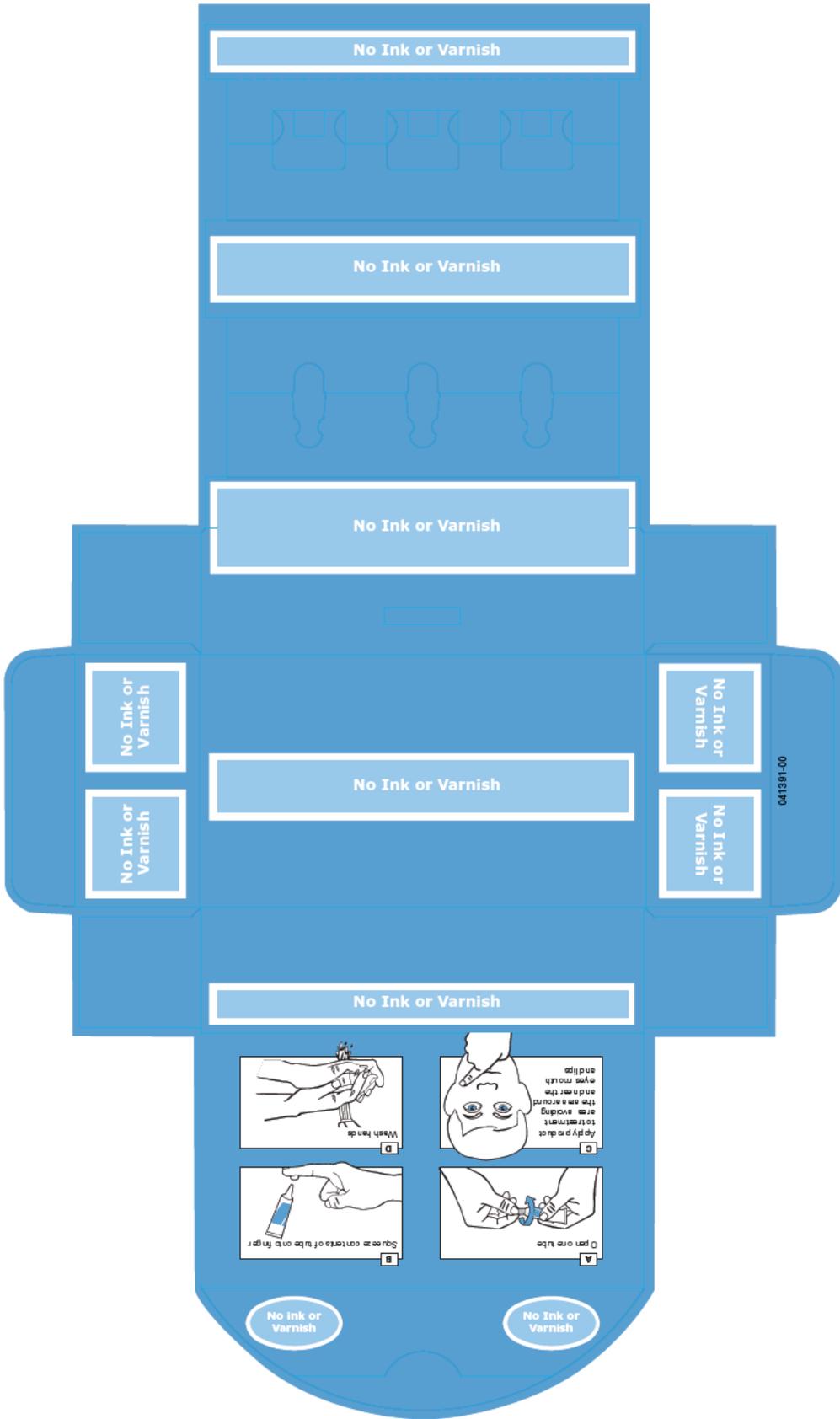
/s/

TATIANA OUSSOVA
10/06/2015





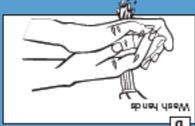
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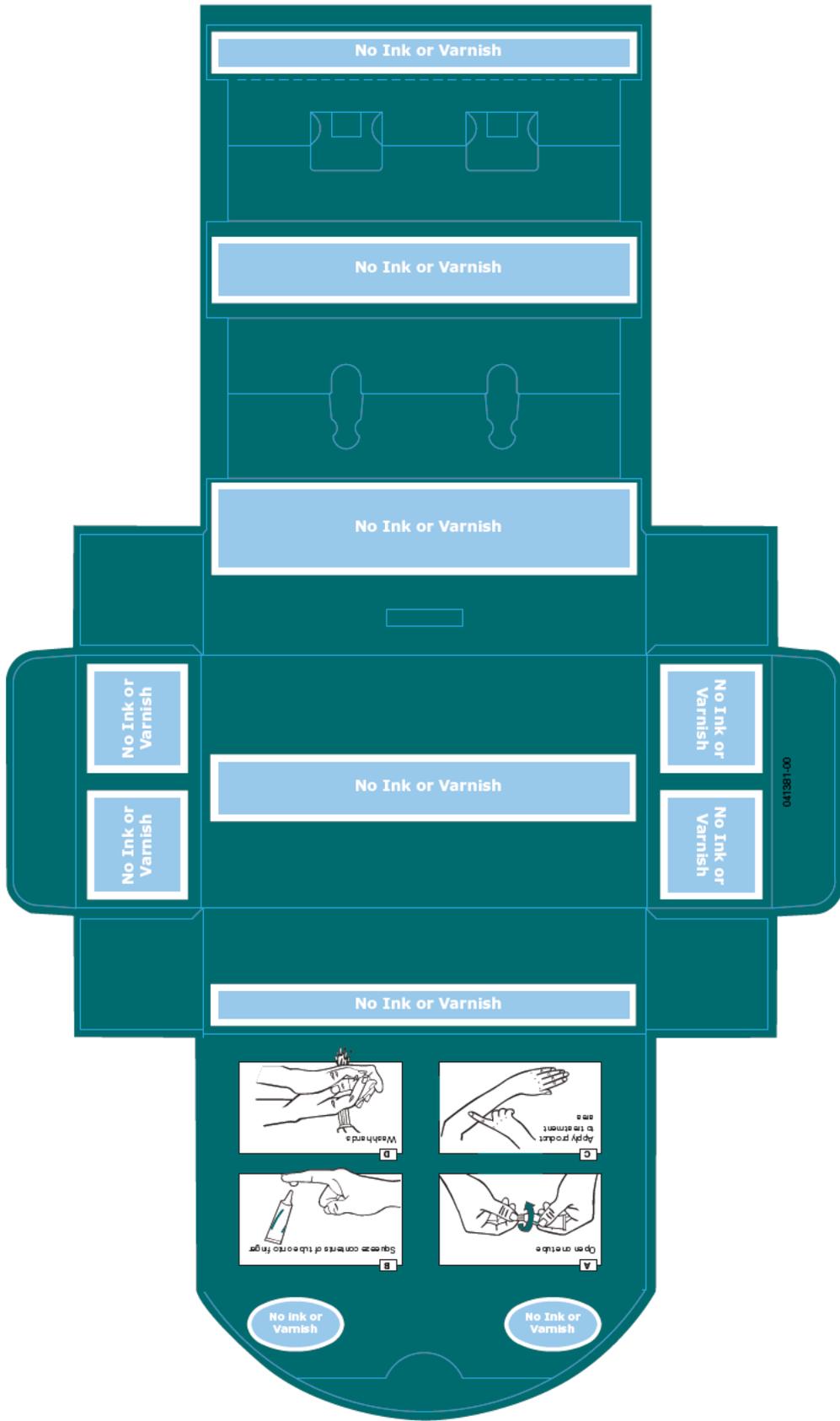
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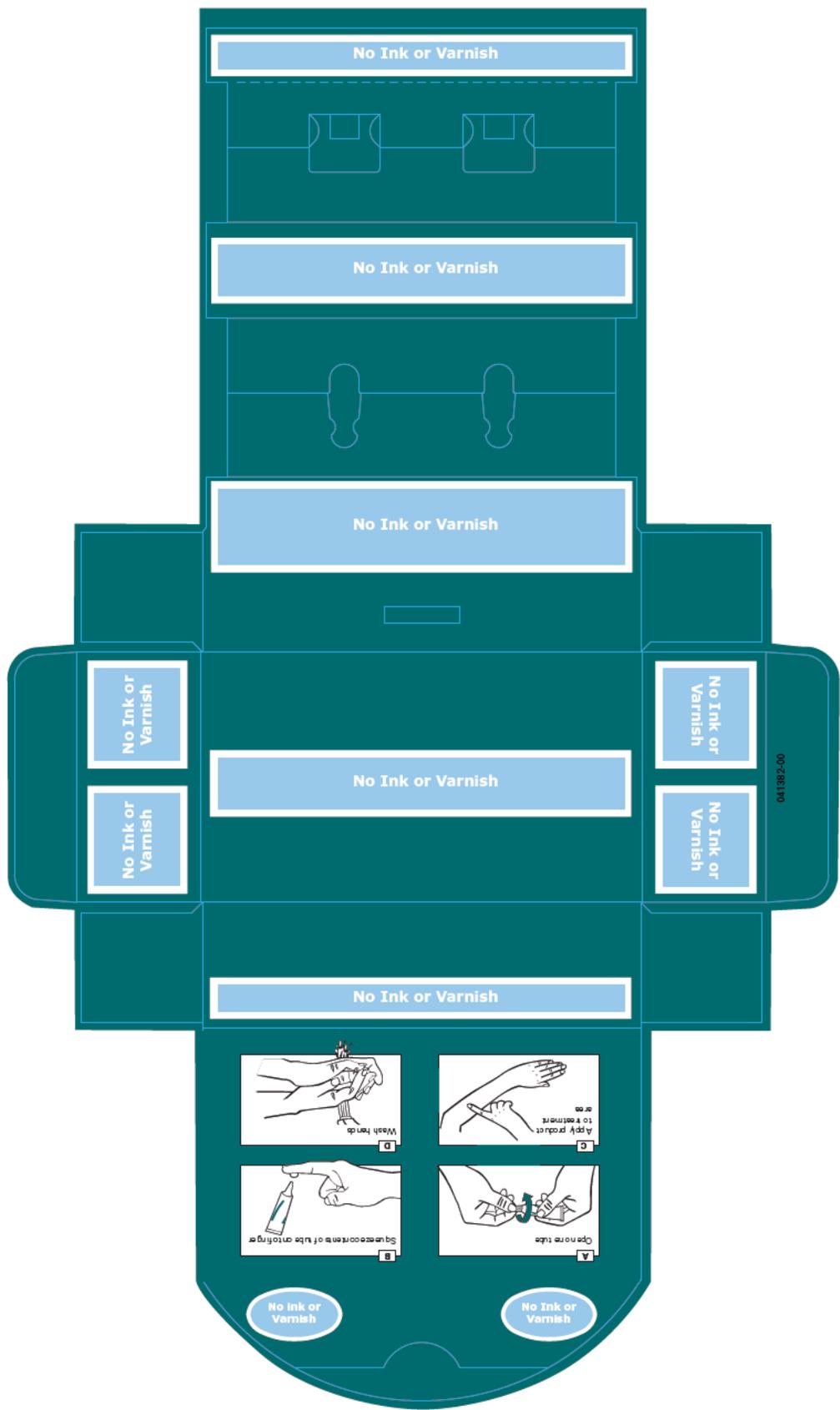
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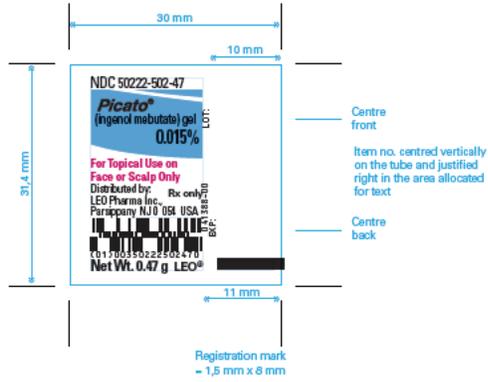
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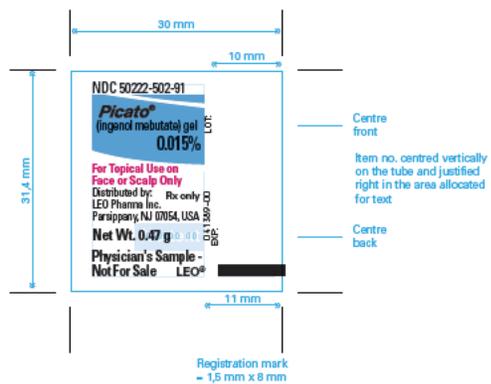


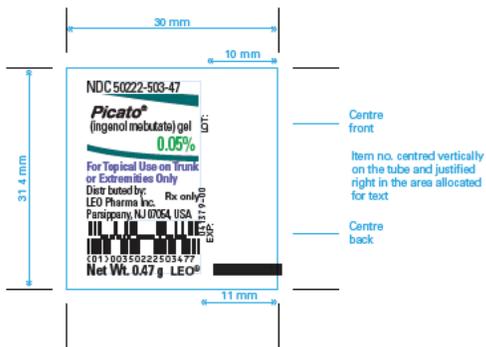
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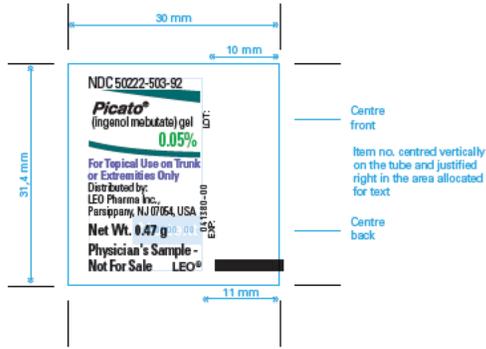


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/s/

TATIANA OUSSOVA
10/06/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 202-833/S-05

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PICATO® gel safely and effectively. See full prescribing information for PICATO® gel.

PICATO® (ingenol mebutate) gel, 0.015% for topical use
PICATO® (ingenol mebutate) gel, 0.05% for topical use
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

- Dosage and Administration (2).....10/2015
- Contraindications (4).....10/2015
- Warnings and Precautions, Ophthalmic Adverse Reactions (5.1).....10/2015
- Warnings and Precautions, Hypersensitivity Reactions (5.2).....10/2015

INDICATIONS AND USAGE

Picato® gel is an inducer of cell death indicated for the topical treatment of actinic keratosis. (1)

DOSAGE AND ADMINISTRATION

- For topical use only; not for oral, ophthalmic, or intravaginal use. (2)
- Avoid transfer of Picato gel to periocular area. (2)
- Avoid application near and around the mouth and lips. (2)
- For application of up to one contiguous skin area of approximately 25 cm² (5 cm x 5 cm) using one unit dose tube. (2)
- Actinic keratosis on the face or scalp: Apply Picato® gel, 0.015% to the affected area once daily for 3 consecutive days. (2)
- Actinic keratosis on the trunk or extremities: Apply Picato® gel, 0.05% to the affected area once daily for 2 consecutive days. (2)

DOSAGE FORMS AND STRENGTHS

Gel containing ingenol mebutate, 0.015% or 0.05% (3)

CONTRAINDICATIONS

Known hypersensitivity to ingenol mebutate or any component of the formulation. (4)

WARNINGS AND PRECAUTIONS

Avoid treatment in the periocular area. Eye disorders, including severe eye pain, chemical conjunctivitis, corneal burn, eyelid edema, eyelid ptosis, periorbital edema can occur after exposure. Avoid accidental transfer of the drug into the eyes and to the periocular area. If accidental exposure occurs, flush eyes with water and seek medical care. (5.1)

Local skin reactions can occur including severe reactions (e.g., vesiculation/pustulation, erosion/ulceration). Administration of Picato® gel is not recommended until skin is healed from any previous drug or surgical treatment. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥2 %) are local skin reactions, application site pain, application site pruritus, application site irritation, application site infection, periorbital edema, nasopharyngitis and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LEO Pharma Inc. at 1-877-494-4536 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2015

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*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Picato[®] gel is indicated for the topical treatment of actinic keratosis.

2 DOSAGE AND ADMINISTRATION

For topical use only; Picato[®] gel is not for oral, ophthalmic, or intravaginal use.

Avoid transfer of Picato[®] gel to periocular area [*see Warnings and Precautions (5.1)*].

Avoid application near and around the mouth and lips.

For the treatment of actinic keratosis on the face or scalp Picato[®] gel, 0.015% should be applied to the affected area once daily for 3 consecutive days.

For the treatment of actinic keratosis on the trunk or extremities Picato[®] gel, 0.05% should be applied to the affected area once daily for 2 consecutive days.

Picato[®] gel may be applied to the affected area, up to one contiguous skin area of approximately 25 cm² (e.g., 5 cm x 5 cm) using one unit dose tube. After spreading evenly over the treatment area, the gel should be allowed to dry for 15 minutes. Patients should wash their hands immediately after applying Picato[®] gel and take care not to transfer the applied drug to other areas, including the eye. Patients should avoid washing and touching the treated area for a period of 6 hours after application of Picato[®] gel. Following this time, patients may wash the area with a mild soap.

3 DOSAGE FORMS AND STRENGTHS

Gel, 0.015% or 0.05%, in a clear colorless gel base.

4 CONTRAINDICATIONS

Picato[®] gel is contraindicated in patients with known hypersensitivity to ingenol mebutate or any component of the formulation. Anaphylaxis, as well as allergic reactions leading to hospitalization have been reported in postmarketing use with Picato[®] gel [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Ophthalmic Adverse Reactions

Avoid treatment in the periocular area. Eye disorders, including severe eye pain, chemical conjunctivitis, corneal burn, eyelid edema, eyelid ptosis, periorbital edema can occur after exposure [*see Adverse Reactions (6)*].

To avoid transfer of the drug into the eyes and to the periocular area during and after application, patients should wash hands well after applying Picato[®] gel . If accidental exposure occurs, the area should be flushed with water and the patient should seek medical care as soon as possible.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and allergic contact dermatitis, have been reported post-marketing [*see Adverse Reactions (6.2)*]. If anaphylactic or other clinically significant hypersensitivity reactions occur, discontinue Picato[®] gel immediately and institute appropriate medical therapy.

5.3 Local Skin Reactions

Severe skin reactions in the treated area, including erythema, crusting, swelling, vesiculation/postulation, and erosion/ulceration, can occur after topical application of Picato[®] gel [*see Adverse Reactions (6)*]. Administration of Picato[®] gel is not recommended until the skin is healed from any previous drug or surgical treatment.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of the labeling:

- Ophthalmic Adverse Reaction [*see Warnings and Precautions (5.1)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

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.

The data described below reflect exposure to Picato[®] gel in 499 subjects with actinic keratosis, including 274 subjects exposed to Picato[®] gel field treatment (skin area of 25 cm² in the face or scalp regions) 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 in the trunk or extremities regions) at a concentration of 0.05% once daily for 2 consecutive days.

Local skin reactions, including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration were assessed within the selected treatment area and graded by the investigator on a scale of 0 to 4. A grade of 0 represented no reaction present in the treated area, and a grade of 4 indicated a marked and severe skin reaction that extended beyond the treated area.

Table 1 Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (face/scalp trials)

| | | |
|--|-----------------------------------|---------|
| Face and Scalp (n=545) Picato[®] gel, 0.015% once daily for 3 days | | |
| Skin reactions | Any Grade ^a > Baseline | Grade 4 |

| | Picato [®] gel (n=274) | Vehicle (n=271) | Picato [®] gel (n=274) | Vehicle (n=271) |
|--------------------------|------------------------------------|--------------------|------------------------------------|--------------------|
| Erythema | 258 (94%) | 69 (25%) | 66 (24%) | 0 (0%) |
| Flaking/Scaling | 233 (85%) | 67 (25%) | 25 (9%) | 0 (0%) |
| Crusting | 220 (80%) | 46 (17%) | 16 (6%) | 0 (0%) |
| Swelling | 217 (79%) | 11 (4%) | 14 (5%) | 0 (0%) |
| Vesiculation/Pustulation | 154 (56%) | 1 (0%) | 15 (5%) | 0 (0%) |
| Erosion/Ulceration | 87 (32%) | 3 (1%) | 1 (0%) | 0 (0%) |

^aMild (grade 1), Moderate (grade 2-3) or Severe (grade 4).

Table 2 Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (trunk/extremities trials)

| Trunk and Extremities (n=457) | | | | |
|--|------------------------------------|--------------------|------------------------------------|--------------------|
| Picato[®] gel, 0.05% once daily for 2 days | | | | |
| Skin reactions | Any Grade ^a > Baseline | | Grade 4 | |
| | Picato [®] gel (n=225) | Vehicle (n=232) | Picato [®] gel (n=225) | Vehicle (n=232) |
| Erythema | 207 (92%) | 43 (19%) | 34 (15%) | 0 (0%) |
| Flaking/Scaling | 203 (90%) | 44 (19%) | 18 (8%) | 0 (0%) |
| Crusting | 167 (74%) | 23 (10%) | 8 (4%) | 0 (0%) |
| Swelling | 143 (64%) | 13 (6%) | 7 (3%) | 0 (0%) |
| Vesiculation/Pustulation | 98 (44%) | 2 (1%) | 3 (1%) | 0 (0%) |
| Erosion/Ulceration | 58 (26%) | 6 (3%) | 2 (1%) | 0 (0%) |

^aMild (grade 1), Moderate (grade 2-3) or Severe (grade 4).

Local skin reactions 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.

Adverse reactions that occurred in $\geq 2\%$ of subjects treated with Picato[®] gel and at a higher frequency than the vehicle are presented in Table 3 and Table 4.

Table 3 Adverse reactions occurring in $\geq 2\%$ of subjects treated with Picato[®] gel and at higher frequency than vehicle (face/scalp trials)

| Adverse Reactions | Face/Scalp | |
|----------------------------|--|--------------------|
| | Picato [®] gel, 0.015% (N=274) | Vehicle (N=271) |
| Application Site Pain | 42 (15%) | 1 (0%) |
| Application Site Pruritus | 22 (8%) | 3 (1%) |
| Application Site Infection | 7 (3%) | 0 (0%) |
| Periorbital Edema | 7 (3%) | 0 (0%) |
| Headache | 6 (2%) | 3 (1%) |

Table 4 Adverse reactions occurring in $\geq 2\%$ of subjects treated with Picato[®] gel and at higher frequency than vehicle (trunk/extremities trials)

| Adverse Reactions | Trunk/Extremities | |
|-----------------------------|---|--------------------|
| | Picato [®] gel, 0.05% (N=225) | Vehicle (N=232) |
| Application Site Pruritus | 18 (8%) | 0 (0%) |
| Application Site Irritation | 8 (4%) | 1 (0%) |
| Nasopharyngitis | 4 (2%) | 2 (1%) |
| Application Site Pain | 5 (2%) | 0 (0%) |

Less common adverse reactions in subjects treated with Picato[®] gel included: eyelid edema, eye pain, conjunctivitis.

A total of 108 subjects treated with Picato[®] gel on the face/scalp and 38 subjects treated on the trunk/extremities were followed for 12 months. Results from these studies did not change the safety profile of Picato[®] gel.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Picato (ingenol mebutate) gel, 0.015% and 0.05%: hypersensitivity, allergic contact dermatitis, herpes zoster, chemical conjunctivitis, and corneal burn.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Picato[®] gel in pregnant women. Picato[®] gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted with ingenol mebutate in rats and rabbits. Intravenous doses of 1.5, 3, and 5 µg/kg/day (9, 18, and 30 µg/m²/day) ingenol mebutate were administered during the period of organogenesis (gestational days 6 – 16) to pregnant female rats. No treatment related effects on embryofetal toxicity or teratogenicity were noted at doses up to 5 µg/kg/day (30 µg/m²/day). Intravenous doses of 1, 2, and 4 µg/kg/day (12, 24, and 48 µg/m²/day) ingenol mebutate were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. An increase in embryo-fetal mortality was noted at 4 µg/kg/day (48 µg/m²/day). An increased incidence of fetal visceral and skeletal variations was noted in all three ingenol mebutate dose groups. The clinical relevance of these findings is unclear since systemic exposure of ingenol mebutate was not detected in subjects with actinic keratosis treated with Picato[®] gel, 0.05% applied to a 100 cm² treatment area [see *Clinical Pharmacology* ([12.3](#))].

8.4 Pediatric Use

Actinic keratosis is not a condition generally seen within the pediatric population.

The safety and effectiveness of Picato[®] gel for actinic keratosis in patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the 1165 subjects treated with Picato[®] gel in the clinical trials, 56% were 65 years and older and, 21% were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

10 OVERDOSAGE

Topical overdosing of Picato[®] gel could result in an increased incidence of local skin reactions.

11 DESCRIPTION

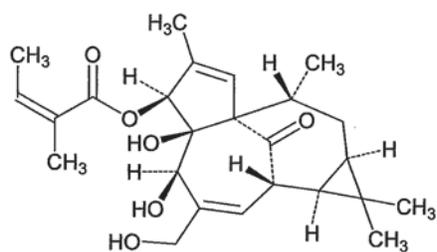
Picato[®] (ingenol mebutate) gel, 0.015% or 0.05% is a clear colorless gel for topical administration, which contains the active substance ingenol mebutate, an inducer of cell death.

The chemical name of ingenol mebutate is:

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-2,8a-methanocyclopenta[a]cyclopropano[cyclodecen-6-yl] ester, (2Z) -
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-2,8a-methanocyclopenta[a]cyclopropano[cyclodecen-6-yl] (2Z) 2-methylbut-2-enoate.

The molecular formula is C₂₅H₃₄O₆ and molecular weight is 430.5. Ingenol mebutate is represented by the following structural formula:



Ingenol mebutate is a white to pale yellow crystalline powder.

Picato[®] gel, 0.015% and 0.05% contains 150 mcg and 500 mcg of ingenol mebutate, respectively in each gram of gel consisting of isopropyl alcohol, hydroxyethyl cellulose, citric acid monohydrate, sodium citrate, benzyl alcohol and purified water.

Picato[®] gel is clear colorless gel and supplied in unit dose laminate tubes, for single use, containing a nominal fill weight of 0.47 g, with a deliverable weight of 0.25 g. The tubes should be discarded after single use.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action by which Picato[®] gel induces cell death in treating AK lesions is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of Picato[®] gel is unknown.

12.3 Pharmacokinetics

Absorption

The systemic exposure to Picato[®] gel, 0.05% was assessed in two studies in a total of 16 subjects with AK, following application of approximately 1 g of Picato[®] gel, 0.05% to an area of 100 cm² of the dorsal forearm once daily for two consecutive days. In these studies, the blood levels of ingenol mebutate and two of its metabolites (acyl isomers of ingenol mebutate) were measured. Blood levels of ingenol mebutate and the two metabolites were below the lower limit of quantification (0.1 ng/mL) in all the blood samples of the subjects evaluated.

Drug Interactions

In vitro studies demonstrated that [³H]-ingenol mebutate undergoes extensive metabolism in human hepatocytes.

In vitro studies to assess the potential of ingenol mebutate to inhibit or induce human cytochrome P450 (CYP) enzymes demonstrated that ingenol mebutate does not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 or induce CYP 1A2, 2C9, and 3A4. The estimated expected systemic exposure (< 0.1 ng/mL) following topical application of Picato[®] gel, 0.05% to AK subjects in the pharmacokinetic studies described above is negligible compared to the concentrations of ingenol mebutate evaluated in the in vitro studies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Picato[®] gel or ingenol mebutate. The effects of ingenol mebutate on fertility have not been evaluated.

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.

14 CLINICAL STUDIES

14.1 Actinic Keratosis of the Face and Scalp

In two double-blind, vehicle-controlled, clinical trials, 547 adult subjects with AK on the face or scalp were randomized to treatment with either Picato[®] gel, 0.015% or vehicle gel for 3 consecutive days, followed by an 8 week follow-up period. The studies enrolled subjects with 4 to 8 clinically typical, visible, discrete AK lesions within a 25 cm² contiguous treatment area. Hypertrophic and hyperkeratotic lesions were excluded from treatment. On each scheduled dosing day, the study gel was applied to the entire treatment area. A total of 536 subjects (98%) completed these studies. Study subjects ranged from 34 to 89 years of age (mean 64 years) and 94% had Fitzpatrick skin type I, II, or III. Approximately 85% of subjects were male, and all Picato[®] gel-treated subjects were Caucasian.

Efficacy was assessed at Day 57. Complete clearance rate was defined as the proportion of subjects with no (zero) clinically visible AK lesions in the treatment area. Partial clearance rate was defined as the proportion of subjects with 75% or greater reduction in the number of AK lesions at baseline in the selected treatment area. Table 5 presents the efficacy results for each trial.

| | Study 1 | | Study 2 | |
|--------------------------------|--|--------------------|--|--------------------|
| | Picato [®] gel, 0.015% (N=135) | Vehicle (N=134) | Picato [®] gel, 0.015% (N=142) | Vehicle (N=136) |
| Complete Clearance Rate | 50 (37%) | 3 (2%) | 67 (47%) | 7 (5%) |
| Partial Clearance Rate (≥ 75%) | 81 (60%) | 9 (7%) | 96 (68%) | 11 (8%) |

Table 6 presents the response rates by anatomical location for each trial.

| | Study 1 | | Study 2 | |
|--|--|--------------------|--|--------------------|
| | Picato [®] gel, 0.015% (N=135) | Vehicle (N=134) | Picato [®] gel, 0.015% (N=142) | Vehicle (N=136) |

| | | | | |
|-------|--------------|------------|--------------|------------|
| Scalp | 4/26 (15%) | 0/25 (0%) | 9/31 (29%) | 1/25 (4%) |
| Face | 46/109 (42%) | 3/109 (2%) | 58/111 (52%) | 6/111 (5%) |

Subjects who achieved complete clearance at Day 57 in Study 1 and Study 2 entered a 12-month follow-up period. Based on 108 Picato[®] gel-treated subjects who achieved complete clearance in Study 1 and Study 2, the recurrence rate at 12 months was 54% where recurrence was defined as the percentage of subjects with any identified AK lesion in the previously treated area who achieved complete clearance at Day 57.

14.2 Actinic Keratosis of the Trunk and Extremities

In two double-blind, vehicle-controlled clinical trials, 458 adult subjects with AK on the trunk or extremities were randomized to treatment with either Picato[®] gel, 0.05% or vehicle gel for 2 consecutive days, followed by an 8 week follow-up period. The studies enrolled subjects with 4 to 8 clinically typical, visible, discrete AK lesions within a 25 cm² contiguous treatment area. Hypertrophic and hyperkeratotic lesions were excluded from treatment. On each scheduled dosing day, the study gel was applied to the entire treatment area. A total of 447 subjects (98%) completed these studies. Study subjects ranged from 34 to 89 years of age (mean 66 years) and 94% had Fitzpatrick skin type I, II, or III. Approximately 62% of subjects were male, and all Picato[®] gel-treated subjects were Caucasian.

Efficacy was assessed at Day 57. Complete clearance rate was defined as the proportion of subjects with no (zero) clinically visible AK lesions in the treatment area. The partial clearance rate was defined as the proportion of subjects with 75% or greater reduction in the number of AK lesions at baseline in the selected treatment area. Table 7 presents the efficacy results for each study.

| | Study 3 | | Study 4 | |
|-----------------------------------|---|--------------------|---|--------------------|
| | Picato [®] gel, 0.05% (N=126) | Vehicle (N=129) | Picato [®] gel, 0.05% (N=100) | Vehicle (N=103) |
| Complete Clearance Rate | 35 (28%) | 6 (5%) | 42 (42%) | 5 (5%) |
| Partial Clearance Rate (≥ 75%) | 56 (44 %) | 9 (7 %) | 55 (55 %) | 7 (7 %) |

Table 8 presents the response rates by anatomical location for each study.

| | Study 3 | | Study 4 | |
|-----|---|--------------------|---|--------------------|
| | Picato [®] gel, 0.05% (N=126) | Vehicle (N=129) | Picato [®] gel, 0.05% (N=100) | Vehicle (N=103) |
| 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 (13 %) | 3/5 (60 %) | 1/3 (33 %) |
| Other ^a | 1/8 (13 %) | 1/10 (10 %) | 6/8 (75 %) | 1/6 (17 %) |

^aOther includes shoulder, back, leg.

Subjects who achieved complete clearance at Day 57 in Study 4 entered a 12-month follow-up period. Based on 38 Picato[®] gel-treated subjects who achieved complete clearance in Study 4, the recurrence rate at 12 months was 50% where recurrence was defined as the percentage of subjects with any identified AK lesion in the previously treated area who achieved complete clearance at Day 57.

16 HOW SUPPLIED/STORAGE AND HANDLING

Picato[®] gel is a clear colorless gel and is supplied in unit dose laminate tubes containing a nominal fill weight of 0.47 g, with a deliverable weight of 0.25 g. The tubes should be discarded after single use.

Picato[®] gel is available in 2 dosage strengths: 0.015% and 0.05%.

| Dosage Strength | Number of unit dose tubes per carton | NDC# |
|-----------------|--------------------------------------|--------------|
| 0.015 % | 3 | 50222-502-47 |
| 0.05 % | 2 | 50222-503-47 |

Store Picato[®] gel in a refrigerator at 36°F – 46°F (2°C – 8°C); excursions permitted between 32°F – 59°F (0°C – 15°C) (see USP for controlled cold temperature). Protect from freezing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions can occur with Picato[®] gel. Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur [*see Warnings and Precautions (5.2)*].

Ophthalmic Adverse Reactions

Inform patients that severe eye injury can occur with Picato[®] gel. Advise patients that Picato[®] gel is not for ophthalmic use. Advise patients to avoid application around the eyes. If severe eye pain or other symptoms of accidental exposure occur, advise patients to flush eyes with water and seek medical care [*see Warnings and Precautions (5.1)*].

Local Skin Reactions

Inform patients that treatment with Picato[®] gel may lead to local skin reactions [*see Warnings and Precautions (5.3)*].

Important Administration Instructions

Advise patients that Picato[®] gel is for external use only. Advise patients to avoid application near and around the eyes, mouth and lips.

Patients should avoid inadvertent transfer of Picato[®] gel to other areas, or to another person.

Instruct patients to:

- allow the treated area to dry for 15 minutes after application.
- avoid washing and touching the treated area, or participating in activities that cause excessive sweating, for 6 hours after treatment. Following this time, patients may wash the area with a mild soap and water.
- keep out of the reach of children.

Patient Information
PICATO[®] (Pih-KAY-toe)
(ingenol mebutate)
gel, 0.015%, 0.05%

Important: For use on the skin only (topical). Do not use Picato[®] gel in, around, or near your eyes, lips, mouth, or vagina.

What is Picato[®] gel?

- Picato[®] gel, 0.015% is a prescription medicine used on the skin to treat actinic keratosis on the face or scalp.
 - Picato[®] gel, 0.05% is a prescription medicine used on the skin to treat actinic keratosis on the body or arms and legs.
- It is not known if Picato[®] gel is safe and effective for the treatment of actinic keratosis in children less than 18 years of age.

Who should not use Picato gel?

Do not use Picato gel if you are allergic to ingenol mebutate or any of the ingredients in Picato gel. See the end of this leaflet for a list of the ingredients in Picato gel.

What should I tell my healthcare provider before using Picato[®] gel?

Before using Picato[®] gel, tell your healthcare provider about all of your medical conditions, including if you:

- are being treated or have been treated for actinic keratosis with other medicines or surgery. You should not use Picato[®] gel until your skin has healed from other treatments.
- have other skin problems or sunburn in the treatment area.
- are pregnant or plan to become pregnant. It is not known if Picato[®] gel can harm your unborn baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

How should I use Picato[®] gel?

- Use Picato[®] gel exactly as your healthcare provider tells you. **Picato[®] gel is for skin use only.**
- Your healthcare provider will tell you where to apply Picato[®] gel, and how often, and how long to apply it. **Do not apply Picato[®] gel to other areas.**
- Do not use more Picato[®] gel than you need to cover the treatment area. Using too much Picato[®] gel, or using it too often, or for too long can increase your chances for having a severe skin reaction or other side effects.
- **Do not get Picato[®] gel in, around, or near your eyes. Do not touch your eyes while you are applying Picato[®] gel.**
 - Wash your hands well with soap and water after applying Picato[®] gel. After applying Picato[®] gel, be careful to keep Picato[®] gel on the treated area from coming into contact with your eyes. Irritation may happen if you get Picato[®] gel in your eyes.
 - **If you accidentally get Picato[®] gel in your eyes**, flush them with large amounts of water and get medical care as soon as possible. Also see "What are the possible side effects of Picato[®] gel?"
- Do not get Picato[®] gel in, around, or near your mouth or lips.
- To help prevent accidental transfer of Picato gel to other areas of your body or to another person:
 - allow the treated area to dry for 15 minutes after you apply Picato gel.
 - avoid washing and touching the treated area, or doing activities that cause a lot of sweating, for **6 hours** after treatment. After 6 hours, you may wash the area with a mild soap and water.
- Only use a tube of Picato[®] gel **1** time. Throw away any open tube of Picato[®] gel after use even if there is medicine still left in it.
- See the Instructions for Use that comes with your Picato[®] gel for information about the right way to apply it.

What are the possible side effects of Picato[®] gel?

PICATO[®] gel may cause serious or severe side effects including:

- **Serious allergic reactions.** Serious allergic reactions have happened with Picato gel, and in some cases have required treatment in a hospital. See “Who should not use Picato Gel?” **Get medical help right away** if you get any of the following symptoms of a serious allergic reaction:
 - swelling of the lips or tongue
 - chest tightness
 - trouble breathing or wheezing
 - dizziness or passing out
- **Eye problems** can happen if Picato[®] gel gets in your eyes. Eye problems may include severe eye pain, swelling or drooping of your eyelids, or swelling around your eyes. **If you accidentally get Picato[®] gel in your eyes**, flush them with large amounts of water and get medical care as soon as possible.
- **Local skin reactions.** Skin reactions in the treatment area are common with Picato[®] gel. You may get a skin reaction such as mild redness, flaking or scaling, crusting, or swelling. Call your healthcare provider if you get skin redness, flaking or scaling, crusting, or swelling that is more severe, or if you get blisters, pus, ulcers or breakdown of your skin.

The most common side effects with Picato[®] gel include:

- local skin reactions, see “Local skin reactions” above
- pain, itching, or skin irritation at the treatment area
- infection at the treatment area
- swelling around the eyes
- nose and throat irritation
- headache

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Picato[®] gel. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to LEO Pharma Inc. at 1-877-494-4536.

How should I store Picato[®] gel?

- Store Picato[®] gel in a refrigerator at 36°F to 46°F (2°C to 8°C). Do not freeze.
- Picato[®] gel has an expiration date (exp) marked on the end of the tube. Do not use the gel after this date.
- Safely throw away used Picato[®] gel tubes in household trash.

Keep Picato[®] gel and all medicines out of the reach of children.

General information about the safe and effective use of Picato[®] gel.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Picato[®] gel for a condition for which it was not prescribed. Do not give Picato[®] gel to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Picato[®] gel that is written for health professionals.

What are the ingredients in Picato[®] gel?

Active ingredient: ingenol mebutate.

Inactive ingredients: isopropyl alcohol, hydroxyethyl cellulose, citric acid monohydrate, sodium citrate, benzyl alcohol and purified water.

Manufactured by: LEO Laboratories Ltd. (LEO Pharma) 285 Cashel Road, Dublin 12 Ireland or
DPT Laboratories, Ltd. 307 E. Josephine Street San Antonio, TX 78215, USA
Distributed by: LEO Pharma Inc. 1 Sylvan Way, Parsippany, NJ 07054, USA. For more information call 1-877-494-4536.
US Patent Nos. US6432452, US6787161
Copyright LEO Laboratories Ltd., January 2012

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: October 2015

Instructions for Use
PICATO[®] (Pih-KAY-toe)
(ingenol mebutate)
gel, 0.015%

Be sure that you read, understand, and follow these Instructions for Use before you use Picato[®] gel for the first time. Also read the Patient Information leaflet that comes with Picato[®] gel.

Important:

- **Always use Picato[®] gel exactly as your healthcare provider tells you.** Check with your healthcare provider or pharmacist if you are not sure.
- Only use **Picato[®] gel, 0.015%** to treat actinic keratosis on your **face or scalp**.
- Apply Picato[®] gel, 0.015% to the skin area to be treated **1** time each day for 3 days in a row. Use a new tube for each day of treatment.
- Avoid touching the treatment area or doing activities that cause a lot of sweating for 6 hours after applying Picato[®] gel. After 6 hours you may wash the treatment area with a mild soap and water.

Do not:

- apply right after taking a shower or less than **2** hours before bedtime.
- **get Picato[®] gel in, around, or near your eyes. Do not touch your eyes while you are applying Picato[®] gel.**
 - Wash your hands well with soap and water after applying it. After applying Picato[®] gel, be careful to keep Picato[®] gel on the treated area from coming into contact with your eyes. Irritation may happen if you get Picato[®] gel in your eyes.
 - **If you accidentally get Picato[®] gel in your eyes**, flush them with large amounts of water and get medical care as soon as possible. Also see the section of Patient Information leaflet section called “What are the possible side effects of Picato[®] gel?”
- **get Picato gel in, around, or near your lips and mouth.**

Applying Picato[®] gel.

Step 1. Open a new tube each time you use Picato[®] gel.

Step 2. Remove cap from tube just before use. (See Figure A.)

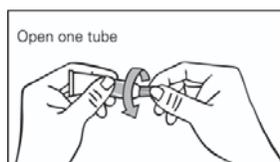


Figure A

Step 3. Squeeze the gel from the tube onto a fingertip. (See Figure B.) Only use enough gel needed to cover the affected area, as directed by your healthcare provider. One tube contains enough gel to cover a skin area of about 2 inches by 2 inches.

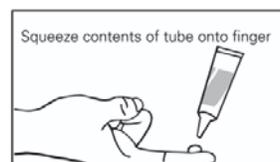


Figure B

Step 4. Spread the gel evenly over only the skin area to be treated. Do not get in, around or near the eyes, lips, and mouth. Allow the treated area to dry for 15 minutes. (See Figure C.)



Figure C

Step 5. Wash your hands right away after applying Picato[®] gel. (See Figure D.)

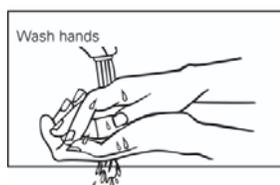


Figure D

Step 6. Safely throw away (dispose of) the tube after use.

Repeat the above steps for each day of treatment.

To help prevent transfer of Picato gel to other areas of your body or to another person, allow the treated area to dry for 15 minutes after you apply Picato gel.

How should I store Picato[®] gel?

- Store Picato[®] gel in a refrigerator at 36°F to 46°F (2°C to 8°C). Do not freeze.
- Picato[®] gel has an expiration date (exp) marked on the end of the tube. Do not use the gel after this date.
- Safely throw away used Picato[®] gel tubes in household trash.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: LEO Laboratories Ltd. (LEO Pharma), 285 Cashel Road, Dublin 12, Ireland or
DPT Laboratories, Ltd., 307 E. Josephine Street, San Antonio, TX 78215, USA

Distributed by: LEO Pharma Inc., 1 Sylvan Way, Parsippany, NJ 07054, USA

For more information call 1-877-494-4536

Revised: October 2015

**Instructions for Use
PICATO[®] (Pih-KAY-toe)
(ingenol mebutate)
gel, 0.05%**

Be sure that you read, understand, and follow these Instructions for Use before you use Picato[®] gel for the first time. Also read the Patient Information leaflet that comes with Picato[®] gel.

Important:

- **Always use Picato[®] gel exactly as your healthcare provider tells you.** Check with your healthcare provider or pharmacist if you are not sure.
- Only use **Picato[®] gel, 0.05%** to treat actinic keratosis on your **body, arms, hands or legs.**
- Apply Picato[®] gel, 0.05% to the skin area to be treated **1** time each day for 2 days in a row. Use a new tube for each day of treatment.
- Avoid touching the treatment area or doing activities that cause a lot of sweating for 6 hours after applying Picato[®] gel. After 6 hours you may wash the treatment area with a mild soap and water.

Do not:

- apply right after taking a shower or less than **2** hours before bedtime.
- **get Picato[®] gel in, around, or near your eyes. Do not touch your eyes while you are applying Picato[®] gel.**
 - Wash your hands well with soap and water after applying it. After applying Picato[®] gel, be careful to keep Picato[®] gel on treated area from coming into contact with your eyes. Irritation may happen if you get Picato[®] gel in your eyes.
 - **If you accidentally get Picato[®] gel in your eyes,** flush them with large amounts of water and get medical care as soon as possible. Also see the section of Patient Information leaflet section called “What are the possible side effects of Picato[®] gel?”
- **get Picato gel in, around, or near your lips and mouth**

Applying Picato[®] gel.

Step 1. Open a new tube each time you use Picato[®] gel.

Step 2. Remove cap from tube just before use. (See Figure A.)

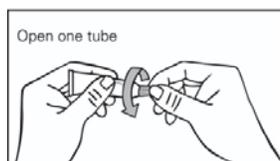


Figure A

Step 3. Squeeze the gel from the tube onto a fingertip. (See Figure B.) Only use enough gel needed to cover the affected area, as directed by your healthcare provider. One tube contains enough gel to cover a skin area of about 2 inches by 2 inches.

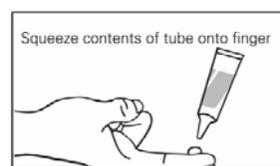


Figure B

Step 4. Spread the gel evenly over only the skin area to be treated. Do not get in, around or near the eyes, lips, and mouth. Allow the treated area to dry for 15 minutes. (See Figure C.)



Figure C

Step 5. Wash your hands right away after applying Picato[®] gel. (See Figure D.) If you are treating your hands you should only wash the fingertip which you used for applying the gel.

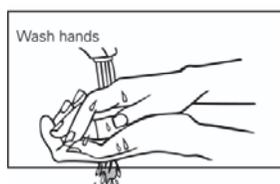


Figure D

Step 6. Safely throw away (dispose of) the tube after use.

Repeat the above steps for each day of treatment.

To help prevent transfer of Picato gel to other areas of your body or to another person, allow the treated area to dry for 15 minutes after you apply Picato gel.

How should I store Picato[®] gel?

- Store Picato[®] gel in a refrigerator at 36°F to 46°F (2°C to 8°C). Do not freeze.
- Picato[®] gel has an expiration date (exp) marked on the end of the tube. Do not use the gel after this date.
- Safely throw away used Picato[®] gel tubes in household trash.

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Revised: October 2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 202-833/S-05

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 202,833

Labeling Supplement –CBE 150

| | | |
|---|---------|--|
| NDA: 202,833-S2 | SD: 150 | Sponsor: Leo Pharma, Inc |
| Established name: ingenol mebutate 0.05% | | Trade name: Picato® gel, 0.015% and 0.05% |
| Route of administration: topical | | Indications: actinic keratosis |
| Stamp date: September 14, 2015 | | Review completed: October 5, 2015 |
| Clinical reviewer: Milena Lolic, M.D., M.S. | | Clinical team leader: David Kettl, M.D. |
| Project manager: Paul Phillips; Dawn Williams | | |

Regulatory Background:

Picato® (ingenol mebutate) Gel, 0.015% and 0.05% was approved on January 23, 2012 for the treatment of actinic keratosis. Per current labeling, dosage and administration are as follows:

- Actinic keratosis on the face and scalp: Apply Picato® gel, 0.015% to the affected area once daily for 3 consecutive days.
- Actinic keratosis on the trunk and extremities: Apply Picato® gel, 0.05% to the affected area once daily for 2 consecutive days.

During 2014, a collaborative post market safety assessment for Picato ® Gel was conducted by OSE, DDDP, OTS and OC in accordance with Title IX, section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA).

In brief, three major areas of concern were detected:

- Medication errors and use inconsistent with labeling resulting in severe skin reactions and eye injuries
- Hypersensitivity reactions
- Herpes zoster reactivation

The Agency concluded that the safety review provided sufficient new information about medication errors to proceed with recommendations for mandated safety labeling changes.

The Agency issued a Drug Safety Communication on August 21 2015 regarding Severe Adverse Events requiring safety labeling changes.

In this submission, the sponsor submits final revised labeling that is “in alignment with the recommendations made by the FDA.” The sponsor accepted the proposed changes to the approved labeling for Picato as well as changes to the carton and container labeling “in accordance with Section 505(o)(4) of the Food Drug and Cosmetic Act (FDCA).” Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

As Dr. Lolic, the primary clinical reviewer for Picato [REDACTED] ^{(b) (6)}, and Agency action on these labeling changes is required within 30 days, this memorandum serves as the clinical review for this labeling/CBE supplement.

Review:

The sponsor has accepted the safety labeling changes conveyed in the letter signed by Dr. Tatiana Oussova dated August 21, 2015, and did not suggest edits or additions. Line by line review of the label has been completed by project management. There is no sponsor proposed change to the mandated labeling changes.

Recommended Regulatory Action:

This supplement can be approved. There are no comments to be conveyed. Final labeling will be attached to the action letter.

David Kettl, MD, FAAP

Clinical Team Leader

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

/s/

DAVID L KETTL
10/05/2015